Hepatic and Biliary Ascariasis

Anup K Das

Department of Medicine and I/C Hepatology Clinic, Assam Medical College, Dibrugarh, Assam, India

ABSTRACT

Ascariasis mainly contributes to the global helminthic burden by infesting a large number of children in the tropical countries. Hepato-biliary ascariasis (HBA) is becoming a common entity now than in the past owing to the frequent usage of ultrasonograms and endoscopic diagnostic procedures in the clinical practice. There are a variety of manifestations in HBA and diagnosis depends on a high index of suspicion in endemic areas coupled with subsequent confirmation by sonographic or endoscopic demonstration of the worm. Most of them present with acute abdomen and jaundice. Oriental or recurrent pyogenic cholangiopathy is possibly the result of HBA, commonly encountered in South-East Asian countries. Conservative treatment with anthelminthic agents is used in the majority. Failure to respond to medical therapy usually indicates the need for endoscopic or surgical interventions. Overall, mortality is low and prognosis is good, but many epidemiological and immunological aspects of *Ascaris* infection are unclear, meaning our understanding the disease and infection still remains incomplete. Therefore, it is difficult to definitely put down a fixed modality of treatment for HBA. This underscores the need for further studies as ascariasis has the potential to adversely affect the national socio-economy by compromising the health of children and adults alike with its sheer number.

Key words: *Ascaris lumbricoides*, Biliary ductal ascariasis, Clinical manifestations, Complications and principles of treatment Hepatobiliary ascariasis, Pathophysiology, Recurrent pyogenic cholangitis, Review of pathogenesis, Roundworm infestation

INTRODUCTION

Ascaris lumbricoides is the largest common nematode causing human ascariasis[1] and 33% of the world population are estimated to be infested with it.[2] It is mentioned in ancient Greko-Roman and Chinese texts, making it probably the earliest record of helminthic infection of mankind. The first scientific description of the genus *Ascaris* was given by Linnaeus in 1758, followed a century later by Epstan and Grassi who showed that the infection is preceded by ingestion of eggs.[3]

Ascarias is common in tropical countries with low standards of hygiene, malnutrition, heavy rainfall and where untreated sewage is discharged into rivers, lakes and agricultural land or is used as fertilizer. The clinical disease spectrum comprise of pulmonary, intestinal (including intestinal obstruction), appendicular, hepatobiliary and pancreatic ascariasis. However human ascariasis is silent in the majority of infected persons or only associated with vague abdominal symptoms. In children, it can lead to stunted growth, impaired learning, protein-energy and vitamin deficiencies.[4,5]

It is estimated that about 60 million of those infected are at risk of developing some form of morbid disease.[6] However, clinical disease occurs with heavy worm loads (13-40 worms) and around 10,000-20,000 deaths occur annually globally due to severe disease.[6-8] Epidemics of ascariasis can occur.[9] It is important to separate "infection" from "disease" and recognize the magnitude of the problem especially while formulating control and eradication strategies.

LIFE CYCLE

Man is infected by ingesting food, raw vegetables or water contaminated by mature ova. Children are mostly infected by contaminated fingers, toys and soil. To complete their life cycle, the worms leave the human body as eggs and re-infect

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Address for correspondence:
Prof. Anup K Das, E-mail: anupkrdas5@gmail.com

it as larvae. The eggs hatch in the duodenum after being stimulated by gastric juice and the resultant rhabditiform larvae migrate to the cecum. They penetrate the epithelium to reach the portal vein and then the liver. Some will migrate through the hepatic veins or the lymphatics to be carried to heart and lungs. There they cross the capillary wall into the alveolar space and reach the bronchial tree. They molt twice during this journey and ascend to the larynx and hypopharynx before being swallowed.[10,11] In the upper gastrointestinal tract, they attain sexual maturity by 2-3 months and molt again to become adult worms. The adult worm resides in the jejunum as a facultative anaerobic organism, with a life-span of 6-18 months. Since adult worms do not multiply inside their host, manifestation of clinical disease depends on their absolute number. Female worms are bigger; approximately 20-40 cm and can produce a large number of eggs daily (~240,000/female) which pass out in the feces.[3] In the soil the fertilized eggs require 10-15 days to become infectious. Clay soil favors their survival. The eggs are resistant to cold weather, chemical water purifiers, disinfectants and can remain viable and infectious for up to 10 years[12] making eradication difficult.

EPIDEMIOLOGICAL CONSIDERATIONS

The world-wide distribution of *A. lumbricoides* has resulted in 1.4 billion people being infected with it[13] and most of them belong to South East Asia. However, it has acquired the character of a global disease due to increases in international travel.[6] Still the major burden is felt by the tropical countries which have moist soil and good rain. In the tropics, up to 70% of the children are found to be infected.[14] South-East Asian countries and China show prevalence rates of 41-92%[15] while in parts of Africa, it is about 95%.[16] Bangladesh is also highly endemic with a prevalence rate of 82%. In India, high prevalence rates are found in Tamil Nadu (85%)[17] and Kashmir (70%).[12] Table 1 shows the prevalence of roundworm infection as reported by some workers from different parts of India.[18-26]

Table 1: Prevalence of Ascariasis in different Indian Studies

Author of Studies	Prevalence in %	Place
Mani *et al.*	91.3	Andhra Pradesh
Ramesh *et al.*	8.3	Chandigarh
Saha *et al.*	34.8	Rural Darjeeling
Baveja and Kaur	1.4	Delhi
Subbannayya *et al.*	8.4	Karnataka
Nagoba *et al.*	1.2	Rural Maharashtra
Raghunathan L *et al.*	43.21	Urban Pondicherry
	10.1	Rural Pondicherry
Saha *et al.*	7.2	Puri
Sharma and Mahadik	0.9	Rajasthan

According to a World Health Organization report, advanced countries have the lowest rate of infection, and immigrants from endemic countries contribute to the bulk of infection there.[27] Still in some rural parts of Europe, the prevalence may reach as high as 52%.[12] This may be due to the so called "stratified" distribution[28] because the infection rates are found to be highly segregated in certain population within the same region.

PREVALENCE AND PROPAGATION OF INFECTION

Prevalence of ascariasis is directly proportional to the population density in a region (overcrowding), sanitation status, educational level, use of untreated sewage/human excreta as manure for vegetable production, dietary and personal hygiene (e.g., eating unwashed food). 30% of adults and 60-70% of children harbor the adult worm in high endemic areas. In general, socio-economic improvement is associated with a falling prevalence. For example, Japan had prevalence of 80% after World War II which drastically fell to 0.04% in 1992; whereas the high endemicity in lesser developed Latin American countries over the same period remained almost unchanged.[29] This indicates that improvement in living standards, which is inversely proportional to the prevalence and infection rates in the society, is an important factor in control strategy. One way of propagating the infection is by "seeding" of the soil through eggs present in the feces of small children, who are re-infected by the eggs while playing in the contaminated soil.[3,13] There seems to be an age related change in the intensity of infection in the same individual.[30] In endemic areas, the prevalence rises at 2-3 years of age becoming maximum by the age of 8-14 years. Then it declines to a much lower level in the adult.[31]

Intensity of infection and reinfection

The observation, that clinically manifest diseases are restricted to a relatively small segment of those infected (1.2-2 million per annum in endemic zones worldwide)[12,32] with only a heavy worm load, means that there exists an uneven, "stratified" distribution of the infection demonstrating a negative binomial distribution.[33] This may be partly due to an increased susceptibility (genetic, behavioral or spatial) to acquire heavy infection in some than in others.[33-36] However, the reasons for such individual susceptibility is not definitely known.[30] Immunity is an important determinant of heavy infection serving as a regulatory mechanism in natural infection[16] although protective immunity is incomplete.[37] Studies are exploring the possible contribution of the host immunological reactions in influencing the global helminth burden.[38,39] Continuous exposure to infective eggs leading

to progressive accumulation of worms over years also plays a major part in producing heavy infection. In endemic areas children are more likely to show heavy infection than adults (70% vs. 49%).[12] Of these, 80% get re-infected within 6 months of eradication therapy. This is found to be commoner in those who had prior heavy infection, implying individual susceptibility.[36]

HEPATO-BILIARY ASCARIASIS (HBA)

This is one type of human ascariasis, which is seen more commonly now in the endemic zones and in the earlier days the diagnosis was made either at autopsy or at laparotomy. Even then, the magnitude of the problem was probably underestimated because the worms move in and out of the bile ducts actively from the duodenum and therefore many would have been absent from the biliary tree at the time of surgery.[12] Since the late 80's and early 90's increasing number of reports from several parts of the world has drawn attention to this entity[40-43] especially as a cause for common bile duct (CBD) obstruction and stricture.[44,45] In Indian studies from Kashmir, at highly endemic area, ascariasis was found to be the cause in 36.7% cases of 109 patients with proven biliary and pancreatic disorders.[46,47] HBA is quite frequently seen in children in South Africa while in Philippines, 20% of all biliary diseases are reported to be due to dead or live worms.[48] However in one series from Middle-East, there were only two cases of biliary ascariasis found in 668 Jordanian patients evaluated by endoscopic retrograde cholangiopancreatography (ERCP) for biliary/pancreatic disease and unexplained upper abdominal pain.[49]

A. lumbricoides has a natural inclination to migrate and seek small orifices.[50] Heavy worm infestation or other intestinal infections of viral, bacterial or parasitic origin (leading to altered gut motility) are the usual pre-requisites to reach the duodenum from their natural habitat-the jejunum. However, host reaction to an adult worm can by itself alter the vasomotor reflexes and secretory responses which in turn affect the intestinal tone and motility.[51] From the duodenum, it can enter the ampulla of Vater to lodge: (a) In the ampulla itself (b) the CBD or (c) the hepatic ducts or anywhere in the biliary tree. It can also enter the orifice of the cystic duct and block it while traversing the CBD, but relatively rarely enters the gall-bladder or the pancreatic duct.

CLINICAL FEATURES

There is a female preponderance (F:M ratio of 3:1) in HBA as studies have shown higher prevalence of roundworm infestation in females.[21,52] HBA is commonly seen in the mid-thirties with a range of 4-70 years.[53] It is less common in children because they tend to present more with intestinal rather than biliary obstruction. This may partly be due to very small caliber of the biliary system in children.[54] Persons who may be at a greater risk of developing HBA include:

a) Those who had prior biliary surgery (cholecystectomy, choledocholithotomy, sphincteroplasty, endoscopic sphincterotomy.[44,45,55]
b) Pregnant when compared with non-pregnant women[56] probably owing to hormonal effects on the ampula during the pregnancy.
c) Disturbance of the environment around the worm e.g., fever, anesthetics and tetrachlorethylene.[16]

Modes of presentation

1. Biliary colic in HBA presents as acute onset right hypochondrial pain which may be recurrent or continuous lasting a few days. It occurs due to entry of the worm into the ampullary orifice from the duodenum. Cholangitic features such as shaking chills, fever and mild jaundice are seen only occasionally.
2. Acute cholangitis in HBA is an emergency[53], presenting with high grade fever, chill, icterus and upper abdominal pain. On examination, there is hypotension, tender hepatomegaly, leucocytosis, raised bilirubin (mostly conjugated) and raised liver enzymes – especially serum alanine aminotransferase and alkaline phosphatase. Those going on to develop pyogenic cholangitis, pus forms, which may be seen at the ampullary orifice or can be aspirated by ERCP.
3. Acute cholecystitis is suspected by right hypochondrial pain and guarding, vomiting and fever. The pain may be referred to the interscapular area or the tip of the right shoulder. Tenderness and a palpable mass in the right hypochondrium may be present. The temperature is usually of low grade and there is no shock. The gall-bladder reveals thickened wall with distension and biliary sludge is usually found.[57]
4. Hepatic abscess may be solitary or multiple and contains pus. There is tender hepatomegaly, high fever, intercostal tenderness and edema along with right hypochondrial pain. These abscesses may result from dead ova released by female worms migrating up the CBD, producing a granulomatous inflammatory reaction with subsequent breakdown with eosinophil infiltration. It may be commoner in children.[16]

Hemobilia can very rarely occur as a result of biliary ascariasis.[58]

DIAGNOSIS

The diagnosis depends upon demonstrating the worm in the biliary tree in a clinical set-up compatible with the conditions described above, especially in an endemic zone. This is not always easy because frequently most of the worms move in and out of the ducts within 7 days.[12] Ultrasonography is a highly sensitive and specific in visualizing a worm in the biliary system, as well as monitoring its mobility to and from the ducts over time.[12,45,59,60] A worm, which has not changed its position after 10 days in the duct system, is usually a dead and macerated one. The drawback of ultrasonography is in not being able to detect worms in the duodenum or the ampullary orifice and thereby has been reported to miss up to 50% cases of HBA.[53] ERCP is helpful in these situations both for diagnostic and therapeutic aspects.[42,61,62] The worms appear commonly as linear, smooth filling defects with or without characteristic movements but without distal acoustic shadowing, and may also be seen as parallel filling defects "Railway tract" sign,[63] curved defects or transverse loops across the ducts.[40,64] Worms in the gall-bladder appear as long tubular coiled echogenic structure which may be rapidly mobile and is easier to diagnose than biliary ductal ascariasis.[56] Computed tomography (CT) will reveal the worms as cylindrical structures.[62] Sometimes CT may be used for better visualization of the dilated ductal system.[59]

Stool examination may show *Ascaris* eggs in stool. Many a times the patient passes an adult worm with vomitus or with stool.

Peripheral eosinophilia, due to larval invasion of the blood, is very common.[1,10,11] Aspiration of the pus from hepatic abscesses may reveal *Ascaris* ova[53,65] because larval stages or the ovas are more likely to produce inflammation leading to granulomatous necrosis than adult worms.[51]

Although antibodies against ascariasis develop in infected persons, they are not of much help in the immuno-diagnosis, owing to extensive cross-reactivity with other helminthic antigen.[16]

RELATIONSHIP OF BILIARY LITHIASIS AND ASCARIASIS

In general, only brown pigment stones are associated to some extent with infections of the gall-bladder.[66] In the tropics gall-stones were considered to be relatively rare due to higher dietary fiber, compared to the western diet.[67] However, in Asian population, gall-stones are now increasingly being found to be of either the cholesterol or the black (rather than brown) pigment variety, a pattern similar to that in the West.[68] It is well-known that any biliary obstruction (complete, incomplete or recurrent) leads to impaired bile drainage with secondary bacterial infection and bacterial infection has been reported in about 66% cases of CBD stones.[69] The common offending organism is usually *Escherichia coli* which (and also other bacteria) produce beta-glucoronidase and it deconjugates the bilirubin glucoronides in bile.[70,71] The resultant unconjugated bilirubin precipitates with calcium to form calcium bilirubinate stones in the future. In addition, it also serves as a nidus for cholesterol stones.[70] As already mentioned, biliary sludge is often seen in HBA presenting with acute acalculous cholecystitis. The biliary sludge is composed of cholesterol crystals, mucin and calcium bilirubinate granules.[72] This provides an appropriate milieu for future gall-stone formation[73] and adult worm, ova and larvae can all initiate bile duct stones.[74] Indeed, part of macerated dead worms were found to form nidus of such stones in patients with HBA when followed-up for several years, and these stones usually were composed of calcium bilirubinate layers[53,55] although the eggs of the worm can also serve as a nidus.[43] But gall-bladder and CBD stones were rarely found in patients with previous HBA and instead tended to occur in the intrahepatic biliary ducts, as reported in one large study from India involving 500 patients of HBA.[12] This may in part be due to the relative lack of propensity of the worm to enter the gall-bladder as mentioned earlier. In contrast, in the far east, primary CBD stone are seen quite frequently to follow bacterial infection secondary to biliary ascariasis.[75] Strong epidemiologic correlations between ascariasis and the entity of recurrent pyogenic cholangitis (RPC) exist.[43]

Relationship with RPC

This condition was first described in 1954 in Hong Kong and is also called "Asiatic or Oriental cholangio-hepatitis" and is seen commonly in Hong Kong, Taiwan, South China, Korea and South East Asia.[75] It is also increasingly being seen in the west, and is probably a result of the migration of Oriental Nationals to these countries.[76] It is characterized by biliary sludge, intrahepatic bile duct stones and chronic secondary bacterial infection. The subjects are thin, young and occasionally malnourished. Recurrent upper abdominal pain, cholestatic jaundice and fever with chill are characteristic and the frequency of such recurrent attacks increase over time. Cholangiograms will demonstrate both the intra and extra hepatic biliary tree to be filled with soft "biliary mud". The biliary radicles

are dilated with excessive branching and single or multiple biliary strictures of variable length.[12] In many patients with severe distortion of biliary ducts, recurrent episodes of cholangitis appear to be self-perpetuating in absence of active ascariasis. In longstanding cases, hepatic abscess and scarring may result.[75] This is exacerbated by recurrent biliary sepsis as a result of papillitis and sphincter of Oddi motor dysfunction which is probably related to the mechanical injury of the papilla caused by the worm invading the orifice.[77] In addition, there is a breakdown of normal defense mechanisms and the enteric bacterial flora may reach the intrahepatic bile tree via the portal system.[76] RPC and ascariasis shows similar geographical distribution[78,79] and over 5% of HBA develop RPC after 2 or more years. Stones are common in RPC (90% cases) and 50% occur in CBD or common hepatic ducts whereas 15% of them have stones in the gall-bladder.[76] Conversely 10% of RPC have a definite evidence of ascariasis.[43]

The stones in RPC are pigment stones with layers of bilirubinates deposited on top of a nidus. More importantly, the nidus of biliary stones in 72% of RPC is formed by part or whole of *Ascaris* worm which confirms the significant role of this helminth in cholelithiasis.[43,80] All these strongly imply that hepatic duct stones found in RPC may be an aftermath of biliary damage by biliary ascariasis especially recurrent, frequent in endemic zones.

TREATMENT OF HBA

The patients with HBA are to be hospitalized without delay because in them the worm load is usually high. In addition, co-existing mechanical intestinal obstruction are common (especially in young children) but may also follow deworming during or after institution of treatment. It must be remembered that excretion products of the worms can cause marked bowel contraction.[81] Similarly, associated acute pancreatitis may complicate the clinical course and there is a definite mortality risk in those with hemorrhagic pancreatitis.[41]

Pure biliary ascariasis have a negligible mortality <2%.[82] The principles of treatment of biliary ascariasis are:[83]

1. Treatment of cholangitis or cholecystitis by conservative means.
2. Oral administration of anthelminthics, which allows the paralyzed worms to be expelled by normal intestinal activity.
3. Endoscopic and Surgical treatment.

Coexistent obstructive jaundice and intestinal obstruction in documented cases of HBA is usually an indication for surgery.[4]

Conservative treatment includes broad-spectrum antibiotics, analgesics, intravenous fluid and electrolytes and most of the acute acalculous cholecystitis patients recover without any complications.[47,53,61] However in acute pyogenic cholangitis, more specific antibiotics are indicated depending on the biliary pus culture and sensitivity results. The pus is obtained by duodenoscopy or ERCP from the pus points in the papillary orifice or bile aspiration respectively. Other common therapeutic measures to treat endotoxic shock are also to be instituted including correction of metabolic acidosis. However most of them require some form of interventional treatment to improve morbidity and mortality.

Chemotherapy: An ideal antihelminth should be:[30]

- Safe at high therapeutic dosage,
- Inexpensive, easily available and easy to administer orally,
- Stable and effective for a long time in different climatic conditions.

Oral anthelminths act by paralyzing the adult worm but none can affect the larval stage. They are administered only if the patient has passed flatus or feces. The worm clearance is usually completed by 3 days in most cases depending on the gut transit time, pre-existing diarrhea and worm load.[84] Preferably a soluble preparation is given.[85] Direct instillation of anthelminthic e.g., piperazine citrate in the biliary tree surgico-endoscopically is not helpful and is not recommended.[12] Treatment failure may occasionally occur and persistent eosinophilia should alert one to this possibility.[86] The names, dosage and important contraindications are mentioned in Table 2.[87-89]

Recently, an oriental study involving 50 cases of infected biliary ascariasis has claimed 96% efficacy using Chinese herbal medicine and acupuncture.[90]

Endoscopic and surgical interventions are indicated when patients do not respond to energetic conservative treatment within few days after hospitalization or when the worm is not expelled from the biliary tree after 3 weeks despite vermifuge.[12,91] Acute pyogenic cholangitis needs biliary decompression or drainage in most cases.[47,61,77,92,93] According to some, cholangitis with biliary strictures or with worms in the gall-bladder are also indications for surgery.[94] Endoscopic worm extraction from ampullary orifice rapidly relieves the symptoms in biliary colic.[47,53,61] This may also be necessary in acute pyogenic cholangitis as an urgent measure. In almost 100% cases, endoscopic worm extraction from the ampulla is successful and from the bile ducts in 90% cases by using the endoscopic

Table 2: Efficacy of anti-ascarial drugs with their mode of action

Drug (dose)	Contra-indications	Efficacy against *Ascaris lumbricoides* %	Mode of action
Single dose			
Pyrantel pamoate (11 mg/kg, maximum 1 g)	Pregnancy, age <2 years	90-100	Spastic paralysis (depolarizing neuro muscular junction)
Albendazole (400 mg [200 mg for <2years age])	Pregnancy	100	Inhibits glucose uptake
Levamisole (2.5 mg/kg)	Pregnancy renal disorders	90	Spasitc, followed flaccid paralysis
Multiple dose			
Mebendazole (100 mg bd×3 days)	Pregnancy age <2 years	100	Immobilization by inhibiting the glucose uptake and acetylcholine esterase
Piperazine citrate (75 mg/kg/dose×2 days)	Convulsive disorders	90-100	Flaccid paralysis by blocking acetylcholine
Thiabendazole (25 mg bd×2 days)	Pregnancy, age <2 years	-	Inhibits fumerase reductase

basket. The complications of endoscopic procedures in such cases are low (6%) consisting mainly of hypotension and cholangitis.[61] Therefore endoscopic extraction of the worms by snares, dormia basket or biopsy forceps is becoming the treatment of choice in biliary ascariasis.[94]

Percutaneous needle drainage under ultrasound guidance or rarely surgically is necessary in hepatic abscesses which are large.

Gall-bladder ascariasis usually requires cholecystectomy; but as a whole it is encountered less frequently than bile duct ascariasis.[95] Laparotomy is indicated if ERCP is not available for worm extraction in the patients who deteriorate during hospitalization. It must be remembered that acute pancreatitis, intestinal obstruction with complications (like volvulus, gangrene or perforation) may be present alongwith HBA which can be identified on hospitalization by ultrasonographic and biochemical studies.

In RPC, recurrent cholangitis with obstructing stones may be managed by placing a Roux-en-Y jejunal conduit for biliary access.[96]

CONCLUSION

HBA common in endemic zone and mostly presents with acute pain abdomen and they are diagnosed by ultrasonography or ERCP, but many cases are probably missed because of active migration of the worm to and from the biliary tree. They carry a good prognosis and respond to conservative therapy with oral anthelminthics. In non-responders (acute pyogenic cholangitis, worm in gall-bladder), endoscopic and surgical removal of the worm is necessary. Associated intestinal obstruction and acute pancreatitis should be looked for especially in children. Long-term effects of HBA include RPC and in some cases liver abscesses. There may be an association with biliary lithiasis/gall-stones with HBA in our region but it needs confirmation.

There is still lack in understanding of some epidemiological aspects of ascariasis namely a non-uniform mode of infection in the same community and the unknown genetic or environmental factors which make an individual more susceptible to heavier infection than others. Questions regarding the universal mode of management of certain sub-groups of HBA (e.g., in acalculous cholecystitis) remain to be answered whether urgent surgical intervention should be resorted to or not, or how long should one wait in such a patient who does not improve with conservative management. In our country (high endemic zone), finding a patient with g all-bladder sludge, ascariasis and/or symptoms suggestive of HBA pose another problem regarding their future mode of management should cholecystectomy be done or is vermifuge only needed if the patient responds to medical treatment? If cholecystectomy is contemplated in view of the possibility of future development RPC, then should it be an elective procedure? How often should they be followed-up? Cost factors, the degree of potential disability, risks and benefit of surgical interventions in these situations need further probing. More pointed indications of conservative versus operative procedures should be formulated and works in this direction needs to be carried out in well controlled studies in future.

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