

Intestinal Schistosomiasis Caused by *Schistosoma japonicum*: A Literature Review

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Abstract

Intestinal schistosomiasis caused by the *Schistosoma japonicum* is located mainly in the East Asian region. Schistosomiasis is part of the neglected tropical diseases that affects mostly the poor population; although its incidence has dropped in these years, schistosomiasis caused by *S. japonicum* still is a prevalent disease. Adult worms reside in the mesenteric veins and excrete eggs that migrate through the intestinal wall and pass out with the stool. The clinical manifestations depend on the stage of the disease, the intestinal schistosomiasis mostly affects the colon, but it can also affect the small intestine. This review's purpose is to highlight the background and importance of the intestinal manifestations caused by *Schistosoma japonicum*.

Keywords: *Schistosoma japonicum*, Intestinal schistosomiasis, Parasite egg, Endemic, Neglected tropical disease

Introduction

Neglected tropical diseases (NTD) primarily affect the poorest and most vulnerable populations in the world, they are caused by infectious and parasitic agents¹. Currently the NTD are affecting 41.4 billion people, causing approximately 35,000 deaths per day worldwide². These "neglected" diseases are due to under-financing and low recognition by the pharmaceutical industries³.

Schistosomiasis is a NTD caused by infection with parasitic blood flukes. It is also known as "bilharziasis" after Theodor Bilharz, who first identified the parasite in 1852⁴. The WHO reported that 258 million people worldwide were infected with trematodes of the genus schistosoma, and required treatment and preventive regime⁵.

The distribution of *Schistosoma japonicum* (discovered in Japan) is mainly in China, the Philippines and Indonesia. China is endemic for *S. japonicum* with the *oncomelania* snail as an intermediate; the invasive snail *Biomphalaria straminea* is an intermediate host of *S. mansoni* that was first discovered in 1981 in Southern China⁶.

Epidemiology

Schistosomiasis is a prevalent infection in tropical and subtropical areas, especially in communities without adequate sanitation and safe drinking water⁷. In Asia the agricultural, fishing, and domestic activities in infested water are the main source of exposure; and introduction of this disease in urban areas is secondary to migration and the rise in eco-tourism⁸.

Schistosoma mansoni and *S. haematobium* are found in Africa and Middle East, *S. japonicum* and *S. mekongi* are found in the East

Hemisphere, and *S. intercalatum* is found in parts of central Africa⁹. Schistosomiasis is considered the third most devastating tropical disease in Africa, South America, the Caribbean, Middle East and Asia¹⁰.

S. japonicum has been found along the Yangtze River Basin in China, the southern and eastern islands of the Philippines, and in central Sulawesi, Indonesia. According to a Chinese report for the World Health Organization, "*S. japonicum* infected 45 species of animals and remained endemic in seven provinces"¹¹ and after decades of intensive control this disease still remains a public health problem. China is among the target countries to eliminate schistosomiasis according to the Regional Action Plan for Neglected Tropical Diseases in the Western Pacific (2012-2016), and in 2011 according to the Ministry of Health a decrease of 3.4% was reported compared to the number of cases in 2010¹². The death estimates due to schistosomiasis need to be re-assessed, as it varies between 24,067 and 200,000 globally per year⁸.

Pathogenesis

There are five schistosome species that can cause infection in humans, but the ones that affect the intestinal tract are: *S. mansoni* found in Africa and South America, *S. japonicum* in East Asia, *S. mekongi* in Laos, Cambodia; and *S. intercalatum* in the West and Central Africa¹³.

The *Schistosoma japonicum*'s life cycle starts when the eggs are eliminated with feces, hatch in the water and release the larvae (miracidia) that are viable for up to seven days until they penetrate the snail *Oncomelania*¹⁴. In the snail there will be two generations of sporocysts and cercariae.

Once released from the snail, the cercariae will swim and penetrate through the skin, shed the tail and become a schistosomulae; they become adult worms and migrate to the mesenteric venules of the small and large intestine¹⁴. Finally, the circle starts again when the eggs move toward the lumen of the intestine and pass with the feces. This life cycle includes snails, domestic and wild animals which makes its control and prevention more complicated; therefore, treating the infection and reducing the *Oncomelania* snail burden is not enough¹⁵.

The physiopathology of chronic schistosomiasis results from the eggs lodging, inducing immune response, granuloma formation, fibrotic changes, damaging the organs and tissues of the human host¹⁶. Adult worms absorb host proteins so if not attacked by the immune system, they can live coated with host antigens for years¹⁷. The shed eggs penetrate the bowel adjacent to mesenteric vessels, whereas unshed eggs go back to portal circulation, lodge and induce granulomatous reaction¹⁶. In the liver the chronic progression causes periportal fibrosis, called

Symmers piperstem fibrosis, if left untreated it will lead to portal hypertension with all the cirrhosis complications¹⁸.

Clinical Manifestations

Clinical manifestations depend on the burden and stage of the disease, the acute phase occurs when cercariae penetrate the skin and produces dermatitis called the swimmer's itch¹⁹; the chronic phase could present months to years after primary exposure, some do not have a clear history of acute phase or just mild and unspecific symptoms¹⁴. After 2-8 weeks of the contact with *S. japonicum*, the migration and maturation of the schistosomulae may produce a systemic inflammatory reaction called Katayama fever, with flu-like symptoms, hepatosplenomegaly, and eosinophilia²⁰.

Schistosoma japonicum causes intestinal manifestations with fatigue, abdominal pain, cramping, anorexia, diarrhea, and dysentery²¹. When there is heavy infestation the symptoms could be severe and may lead to intestinal ulceration, bleeding, anemia, intestinal polyps, dysplasia and even bowel strictures^{14,21,22}.

If *S. japonicum* remains untreated, periportal fibrosis could lead to portal hypertension and gastrointestinal bleeding²³. People with hepatitis B or C and chronic hepatic injury due to schistosomiasis have more risk for a rapid progression to liver disease or development of hepatocellular carcinoma²⁴.

Diagnosis

For decades the gold standard for diagnosis of schistosomiasis infection has been the detection of eggs in fecal smear and the concentration techniques with Kato-Katz thick smear demonstrate the number of eggs excreted daily²⁵. Among people living in endemic areas the approach should be through egg and antigen detection²⁵.

The egg viability test observes hatching miracidia and assesses the treatment effectiveness, so an active infection is when viable eggs are observed whereas no viable eggs and absence of miracidia correlates with past infection or effective treatment¹⁶.

General laboratory examination includes the following and the possible findings are: cell blood count within normal ranges, CBC with anemia or eosinophilia (acute), thrombocytopenia (splenic sequestration), liver function tests could show in the chronic stage a mild elevation of alkaline phosphatase and gamma glutamyl transferase^{26,27}.

For travelers the approach is not the same, serology is the most sensitive test because the parasite burden is low, and it is more useful than egg or antigen detection²⁸. Crude extracts of eggs or adult worms are used as antigen in an ELISA test and antibodies to eggs can be detected from six weeks after exposure²⁹.

Another test is the real-time PCR, in stool samples can be 94% sensitive and 99.9% specific and may offer added value in diagnosing imported schistosomiasis³⁰. The genus-specific PCR can detect all schistosoma species that are infectious to humans and performs very well with feces and urine, but not in serum³¹.

In chronic hepatosplenic schistosomiasis due to *S. japonicum* the ultrasonography can report periportal fibrosis around portal vein like a "bull's eye", hypertrophy of the left hepatic lobe, atrophy of the right lobe, granulomas, splenomegaly and other portal hypertension signs³². Computed tomography and magnetic resonance imaging can demonstrate heterogeneity of hepatic parenchyma, periportal fibrosis, and the presence of venous collateral pathways³³.

Biopsy is an useful diagnostic tool in the setting of intestinal schistosomiasis, it is more sensitive than stool microscopy and it can demonstrate granulomas surrounding eggs even when stool samples are negative³⁴. At an early stage bowel wall biopsy can report mucosal edema, hemorrhage and ulceration, whereas in advanced stage it can detect a thickened bowel wall, polyps, and even strictures³⁴.

Treatment

The treatment for schistosomiasis has important objectives such as reversing acute or early chronic disease and preventing complications. The treatment in the early chronic stage can reverse periportal fibrosis and portal hypertension, but it cannot reverse late stage fibrosis and cirrhotic complications such as esophageal varices³⁵.

Praziquantel is the drug of choice for the treatment of all schistosoma species, it acts against adult schistosoma worms with the purpose to reduce egg production but has poor activity against immature schistosoma larvae³⁶. Therefore, the treatment is mostly effective from four to six weeks after exposure when the schistosoma is a mature worm, corroborated in an animal study that shows no pharmacological effect within 21 first days^{26,37}.

Praziquantel's mechanism of action is on the tegumentary and muscular tissue, causing contractions in the parasite that are followed by its death and also it inhibits the egg production in female parasites^{38,39}. The standard dose is 40mg/kg, but for *S. japonicum* the dose can be 60mg/kg³⁹. A cure rate between 65 to 90% has been described after one regimen⁴⁰. After treatment, follow up in endemic areas should use stool smear after six weeks of treatment; in nonendemic areas since there is no risk for reinfection the control examination can be delayed three to six months²⁹. If there is presence of viable eggs after the treatment, the same dose of initial therapy should be prescribed⁴¹.

Over decades the drug resistance has been a concern; researchers have identified field and experimental isolates that exhibit significantly reduced susceptibility but still the criteria used to classify a resistant strain or evidence of resistance remains controversial^{42,43}.

Schistosoma candidate vaccines are being identified through bioinformatics, OMICs approaches⁴⁴. At least three vaccines (Sm14, Sm-TSP-2 and SM-p80 antigens) in the near future will go through human clinical trials⁴⁵, still an efficacious vaccine has not yet been realized.

Prevention

Strategies to control schistosomiasis in endemic areas include water sanitation, minimizing contact with fresh water, community health-education, eradication of snail species, domestic animals care and treatment, proper work equipment to people at risk of exposition¹¹. Mass treatment has demonstrated to reduce the prevalence and morbidity of schistosomiasis by keeping the parasite load low and by increasing resistance to reinfection⁴⁶.

With the fast economy and technology development in China, the surveillance systems for prevention and control have improved and a great progress has been made in the last six decades⁴⁷. Several interventions to reduce transmission from domestic animals, snails to humans have been adopted as national strategies in China^{11,47}.

Conclusion

Schistosomiasis is one of the neglected tropical diseases currently affecting mostly the poor population and causing thousands of deaths annually worldwide. *Schistosoma japonicum* is found in China, Indonesia, Philippines, and its clinical manifestations depend on the acute or chronic phase, but if left untreated irreversible complications occur. The prognosis for the intestinal cure is optimistic after the administration of praziquantel.

Despite the regional governments and the World Health Organization efforts to maintain surveillance and treatment policies, more attention and support should be paid to this endemic disease, ensuring that the affected population not only receives suitable treatment but also the education and preventive measures that will not expose them to suffer this parasitic disease. More support should be done to prevent resistance to praziquantel and develop a secure vaccine accessible to everyone.

We encourage the education to endemic areas' population to seek medical advice when gastrointestinal manifestations occur, to medical physicians to consider intestinal schistosomiasis as a differential diagnose when referring gastrointestinal symptoms.

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