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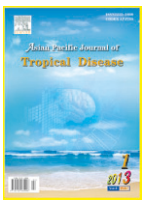

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Schistosomiasis-associated kidney disease: A review

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PEER REVIEW

Peer reviewer

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Comments

In general, this is a good artical in which the authors reviewed the endemic tropical disease, Schistosomiasis, and its related renal involvment features, as well as the risk factors.
(Details on Page 84)

ABSTRACT

Schistosomiasis is a parasitic disease caused by organisms from the genus *Schistosoma*. The disease is endemic in tropical areas, where there are currently millions of people living in areas with transmission risk. Schistosomiasis-associated kidney disease is not frequently described in literature. The disease has a chronic evolution, with variable severity. Glomerulonephritis is described in 10-12% in autopsy studies. Proteinuria is reported in 20% of patients with *S. mansoni* infection. *Schistosomal* glomerulopathy generally occur in young patients, male, with hepato-splenomegaly. The glomerular lesion in schistosomiasis has an immunological nature. Antigens from the parasite seem to be related to glomerulopathy and have been found in the sera of humans and animals infected by the *S. mansoni*. Vesical involvement is common in the infection by *S. haematobium*, a parasitic disease prevalent in African countries. In the *S. haematobium* infection, hematuria and dysuria can be observed due to inflammation and ulceration in the bladder mucosa, generaly occuring 3 to 4 months after primary infection. Specific antiparasitic treatment is indicated to all patients infected by *Schistosoma*. There are 2 drugs available for treatment, praziquantel and oxamniquine. We revise the general aspects of the disease and describe the features of renal involvement in schistosomiasis.

KEYWORDS

Schistosomiasis, *Schistosoma*, Kidney disease, Glomerulonephritis

1. Introduction

Schistosomiasis is a parasitic disease caused by organisms from the genus *Schistosoma*. The species that causes human schistosomiasis are *Schistosoma haematobium, Schistosoma intercalatum, Schistosoma japonicum, Schistosoma mansoni* and *Schistosoma mekongi*[1,2]. The adult worms inhabit the mesenteric vessels of men, the definitive host, and the intermediate forms develop into snails from the genus *Biomphalaria*[3]. The disease is endemic in tropical areas, where there are currently millions of people living in areas with transmission risk[1]. Despite the advances in control and expressive decreases in morbidity and mortality, schistosomiasis continues to spread to new geographic areas, and besides there are reports of resistance to praziquantel, the mainstay of medical treatment1. Schistosomiasis-associated kidney disease is not frequently described in literature. We revise the general aspects of the disease and describe the features of renal involvement in schistosomiasis.

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2. Epidemiology

Schistosomiasis is a tropical disease, reported to occur in more than 70 countries, mainly in Africa, East Mediterranean and South America. From an estimated total of 200 million infected people, 85% of whom live in sub-Saharan Africa, approximately 120 million develop symptoms, 20 million have severe disease and 100000 dies each year[2,3].

In America, the disease is more prevalent in the Caribbean region, Venezuela and Brazil, where the disease is endemic[3,4]. In Brazil, the disease was described in almost all the national territory, but with more prevalence in North states. Its occurrence is directly linked to the presence of the transmitter snails. It is estimated that there are 25 million people in our country in risk of acquiring the disease[4].

The *Schistosoma* species varies according to the geographical area. *S. mansoni* occurs in South America, Caribbean islands, and along with *S. haematobium*, in Africa and the Middle East. *S. haematobium* is also observed in parts of West and Central Africa. *S. japonicum* and *S. mekongi* occur in various Southeast Asian countries, and *S. japonicum* is also found in China and the Philippines. Transmission is focal in endemic countries and most intense in poor rural areas with inadequate sanitation and water supplies. The distribution of schistosomiasis is changing in many areas. The risk for infection is now nonexistent or negligible in previously highly endemic countries, including Japan, Morocco, Tunisia, Iran, Surinam, Venezuela, and the Caribbean countries. Control programs have significantly reduced the incidence of infection and morbidity in Brazil, China, Saudi Arabia, Egypt, and the Philippines[3].

3. Disease cycle

In the disease cycle there are two hosts involved, one definitive and another intermediate.

3.1. Definitive host

Men is the main definitive host and inside the human organism the parasite is in the adult form, sexually reproducing and eliminating eggs of *Schistosoma* in the environment through the feces, which contaminates hydric resources.

3.2. Intermediate host

The biological cycle of *Schistosoma* depends on the presence of intermediate host in the environment. Aquatic gastropoda snails, from the family *Planorbidae* and *Biomphalaria* genus are the organisms that favor asexual reproduction of the helminth. The snails inhabit fresh water colections, usually with slow flow or standing water.

In Brazil, the species *Biomphalaria glabrata, Biomphalaria straminea* and *Biomphalaria* tenagophila are involved in the schistosomiasis dissemination.

3.3. Disease transmission

Humans acquire schistosomiasis through the active skin penetration of the cercariae. After infection, the cercariae evolve to a primary parasitic form called schistosomulae, which initiates the migration process, through blood and lymphatic circulation, until reaches the heart and lungs. The schistosomulae in the blood vessels reaches the liver, where they evolve to adult forms. In the mesenteric portal vessels occurs the sexual reproduction of the parasites, followed by ovoposition. In the aquatic environment, occurs the eggs eclosion and release of active intermediate host-infective forms, called miracidia. Some hours after the penetration of miracidia in the snails, a complex process begins with morphological changes in the parasite which will originate the cercariae. The contact with contamined water by cercariae is the predisposing factor to human infection.

A summary of the schictosomiasis cycle is illustrated in Figure 1.

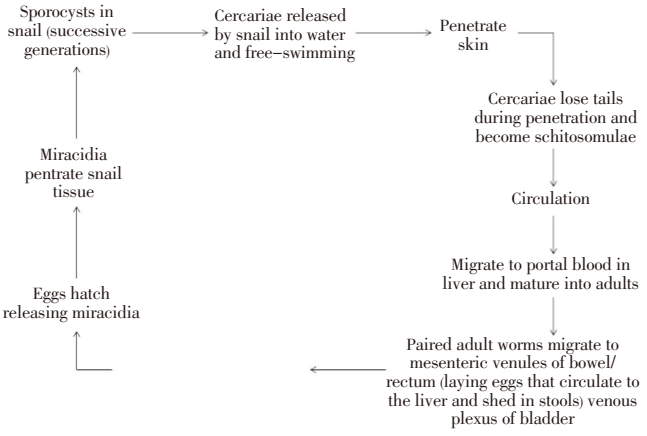

Figure 1. Schistosomiasis life cycle.
Adapted from the Centers for Disease Control and Prevention. Available at http://www.cdc.gov/parasites/schistosomiasis/biology.html.

3.4. Clinical manifestations

Schistosomiasis results from the host's immune response to schistosome eggs and the granulomatous reaction evoked by the antigens they secrete1. The disease has a chronic evolution, with variable severity. The evolution depends on immunological response, the worm development and its ovoposition[4]. The majority of infected persons can remain asymptomatic, depending on the intensity of parasitism. The clinical manifestations correspond to the development stage of the parasite into the host. The infection can be divided in initial and late phase.

The initial phase corresponds to the penetration of cercariae through the skin, with predominance of allergic reactions, including dermatological alterations. In this phase, after approximately 1 week of infection, fever can occur, associated with lymphadenopathy, headache, anorexia, abdominal pain and, less frequently, diarrhea, nausea, vomiting and dry cough[4].

The late phase (chronic form) begins from the 6th month after infection and can last for several years. Signs of disease progression to different organs can occur, including severe complications such as pulmonary hypertension, portal hypertension, ascites and esophageal variceal rupture[4]. There are different forms of chronic schistosomiasis, including the hepato-intestinal, hepatic, hepatosplenic compensated and decompensated. The chronic forms are characterized by granulomatous inflammation and elevated levels of pro-inflammatory cytokines. Eosinophilia is also frequently observed[3]. The natural disease progression is faster in those infected by *S. japonica* than by *S. mansoni*, and occasionally leads to decompensated liver disease[3].

4. Renal involvement

4.1. S. mansoni

The prevalence of renal involvement in schistosomiasis is variable, depending on the study population. Considering all the forms of the disease, the incidence of glomerular involvement is estimated in 5%-6% and increases to 15% in the hepatosplenic form[5]. Glomerulonephritis is described in 10%-12% in autopsy studies[6]. Proteinuria is reported in 20% of patients with *S. mansoni* infection[7].

Schistosomal glomerulopathy generally occur in young patients, male, with hepato-splenomegaly. The majority of patients present the hepatosplenic form of the disease, but renal involvement can also be observed in the hepato-intestinal form[7]. Initially, the glomerulopathy can be asymptomatic or manifest only by hypocomplementemia, but many patients can present nephritic syndrome and non-nephrotic proteinuria (isolated or in association with microscopic hematuria). Renal insufficiency develops in a small part of cases[7]. Subclinical glomerulonephritis is not uncommon in the chronic forms of schistosomiasis, but the true incidence of this complication is not known.

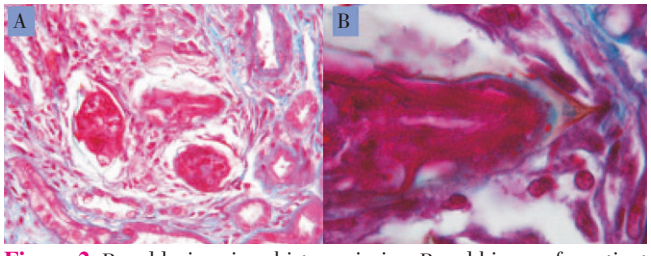

Figure 2. Renal lesions in schistosomiasis – Renal biopsy of a patient with schistosomiasis (S. hematobium) showing (A) Renal granuloma around the eggs of S. hematobium. Masson's trichrome, x400; (B) Apical spine of S. hematobium. Masson'strichrome, x1000. Reprinted from Kidney International, Vol 77 / n 10, Dial & Nöel, Page No. 934, Copyright (2010), with permission from the Nature Publishing Group8.

Renal biopsy evidences immune complex deposition, with *Schistosoma antigens*, in the glomerular basement membrane[3]. The presence of *Schistosoma* eggs, associated with granulomas was also already described8 (Figure 2).

4.2. Glomerular lesion pathogenesis

The pathophysiology of glomerular lesion in schistosomiasis has some common characteristics with the lesion that occur in other parasitic diseases, such as malaria.

The glomerular lesion in schistosomiasis has an immunological nature. Antigens from the parasite seem to be related to glomerulopathy and have been found in the sera of humans and animals infected by the *S. mansoni*[9,10,11].

Antibodies directed against the parasite have also been found in humans and animals with schistosomiasis, which seem to be related to the development of glomerular injury[12]. Among the isolated circulating antigens, those from the digestive tract of the adult parasite are the most involved in the pathogenesis of glomerulopathy[13].

The presence of *schistosomal* antigens in the kidney were found in 43.7% of patients with non-nephrotic proteinuria and in 63.4% of those with nephrotic syndrome and advanced renal insufficiency[14,15].

The presence of *Schistosoma antigens* in glomerular deposits and the detection of circulating immune complexes containing these antigens have been described[16,17]. These findings highlight the hypothesis of immune complex-mediated glomerulonephritis. Hillyer and Lewert[18]described the finding of anti-DNA antibodies in the sera of hamsters infected by *Schistosoma japonicum*, suggesting a role for these antibodies in the context of a polyclonal B-lymphtocites activation[18]. Other studies, however, showed that polyclonal activation of B-cells is not sufficient to induce glomerular injury in animal Schistosomiasis models[19], suggesting that additional mechanisms, such as genetic and environmental factors, plays a role in the development of glomerulonephritis in this disease.

The absence of improvement of glomerular disease with infection treatment in some cases and the lack of correlation between the severity of nephritis and intensity of parasitism favors the hypothesis of participation of auto-immune mechanisms in *schistosomal* nephritis[20]. Furthermore, as the glomerular changes are more prevalent in the hepatosplenic form, the porto-systemic shunt can be involved in the development of glomerular lesions. In experimental studies it has been demonstrated that the portal vein clamping in rats favors immune complex deposits in the kidneys[17]. Despite this, glomerular lesions are not common in patients with cirrhosis, which suggests the participation of auto-immune mechanisms in the *schistosomal* glomerulopathy[21]. The severity of glomerular lesions and proteinuria presents correlation with liver macrophages dysfunction, which can be involved in the decreased immune complex clearance, favoring its deposition in the glomeruli[20].

The pathophysiology of glomerular involvement in schistosomiasis is illustrated in Figure 3.

Table 1
Studies reporting kidney involvement in humans with schistosomiasis.

Author	N	Age (years)	Parasite	Ur (mg/dL)	Cr (mg/dL)	Renal Biopsy	Other findings
Brower *et al.* [28]	329	9 to 16	*S. haematobium*	–	–	–	Hydronephrosis (36%)
Lambertucci *et al.* [23]	1	51	*S. mansoni*	88	2.0	MPGN	Proteinuria (nephrotic)
Rodrigues *et al.* [25]	63	45±11	*S. mansoni*	–	–	Mesangial expansion (63), mesangial proliferation (5), glomerular sclerosis (4)	Proteinuria (12.7%), Hematuria (11.1%)
Dial *et al.* [8]	1	12	*S. haematobium*	–	1.8	MPGN, crescents, interstitial inflammation, granulomas	Proteinuria (nephrotic)
Seck *et al.* [29]	1	10	*S. haematobium*	73	1.8	MPGN, tubulointerstitial fibrosis, granuloma	Proteinuria, Hematuria, Leukocyturia

*Ur – urea, Cr – creatinine, MPGN – membranous glomerulonephritis.

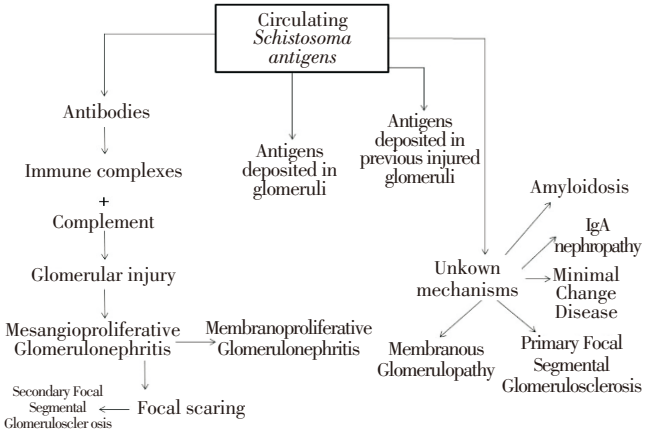

Figure 3. Pathophysiology of glomerular lesion associated with schistosomiasis.
Adapted from Nussenzveig *et al*[27].

In the infection by *S. mansoni*, circulating antigens of the adult parasite and its eggs can be found in different fluids and tissues of the host's body. The kidneys have an important role in these antigens deposits, and there is an important correlation between these circulating antigens and glomerular disease development[5]. *Schistosoma antigens* have been observed in the glomeruli of patients with focal and segmental glomerulosclerosis and mesangial proliferative glomerulonephritis[5].

4.3. Histopathology

In patients with hepatosplenic schistosomiasis, the most frequently found glomerulopathy is mesangial proliferative and membranoproliferative glomerulonephritis[22,23] (Figure 4). The mesangium is the most affected glomerular segment in schistosomiasis. In the electronic microscopy, in the initial phases, there is mesangial expansion associated with mesangial cells hypertrophy and hyperplasia, as well as granular dense deposits, mainly in the subendothelial and mesangial regions[22,24]. In immunofluorescence, IgM, IgG and C3 deposits, with occasional IgA deposits, can be found[5]. Membranous glomerulopathy has not been a frequently found pattern in schistosomiasis. The correlation between this glomerulopathy and the parasitic disease has been questioned by some authors, based on clinical and experimental data[5]. Another possible histological pattern in schistosomiasis is amyloidosis, which can also be found in other chronic parasitic diseases[5].

In a recent study performed in Minas Gerais, Brazil, from 63 patients with schistosomiasis, 8 (12.6%) presented albuminuria higher than 30 mg/d. These 8 patients underwent renal biopsy, which showed mesangial expansion in all cases. In five of them there was mesangial proliferation, and in four there was glomerular basement membrane duplication. Glomerular sclerosis areas were seen in four cases[25].

A classification for *schistosomal* glomerulopathy has been proposed in 5 categories, based on histopathological findings: mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, focal and segmental glomerulosclerosis, exudative glomerulonephritis and amyloidosis[26].

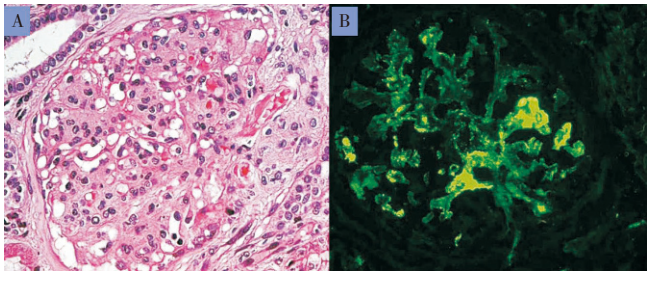

Figure 4. Renal lesions in schistosomiasis – Renal biopsy of a patient with schistosomiasis (*S. mansoni*) showing a type I membranoproliferative glomerulonephritis, with duplication of glomerular basement membrane and cellular proliferation.
(A) and subendothelial deposits of IgG, IgM and C3 identified by direct immunofluorescence (B). Reprinted from Revista da Sociedade Brasileira de Medicina Tropical, Vol 40 / n 4, Lambertucci et al., Pages No. 492–493, Copyright (2007), with permission from the author and the Revista da Sociedade Brasileira de Medicina Tropical[23].

Patients with mesangial proliferative form can be asymptomatic or present minimal urinary changes, such as mild proteinuria and hematuria, or develop nephritic syndrome and develop renal insufficiency[27]. Membranoproliferative glomerulonephritis is associated with hypocomplementemia, with low levels of CH50, C3 and C4, suggesting activation of

the classical complement pathway (Figure 4). An important differential diagnosis in these cases is virus B and C infection, which can cause membranoproliferative glomerulonephritis[27].

Focal and segmental glomerulosclerosis (FSGS) is the third more common glomerulopathy in schistosomiasis, which incidence varies from 11% to 38%[27]. The histopathological findings are similar to that observed in idiopathic FSGS. There are two possible explanations for the occurrence of FSGS in schistosomiasis: primary FSGS, which would occur in the same conditions as observed in HIV, secondary FSGS, whose lesions would be secondary to focal scaring caused by mesangioproliferative glomerulonephritis[27].

Membranous disease, minimal change disease, amyloidosis and IgA nephropathy have been less frequently described in schistosomiasis, and its pathophysiologic mechanisms are still poor understood[27].

4.4. S. hematobium

Vesical involvement in common in the infection by *S. haematobium*, a parasitic disease predominant in African countries[28]. In the *S. haematobium* infection, hematuria and dysuria can be observed due to inflammation and ulceration in the bladder mucosa, generaly occuring 3 to 4 months after primary infection[3]. In endemic areas, many children presents microscopic hematuria, which can became macroscopic with aging. Polyps, hypertrophic nodules and eggs deposition can be observed through cystoscopy. Granulomas, fibrosis and calcifications in the vesical wall can cause vesico-ureteral reflux and obstructive uropathy, leading to hydronephrosis, chronic bacteriuria, vesical cancer and, less frequently, renal insufficiency[3].

5. Evolution and treatment

Some studies show that renal lesions are irreversible because many cases have delayed diagnosis[7]. However, specific antiparasitic treatment can alter the renal disease development or progression when instituted in the initial phases[7]. Patients with proliferative forms do not respond to antiparasitic treatment nor to immunosuppression, suggesting that this type of glomerular involvement has a progressive pattern[7].

Specific antiparasitic treatment is indicated to all patients infected by *Schistosoma*, with specific drugs to achieve infection cure[3]. There are 2 drugs available for treatment, praziquantel and oxamniquine. The praziquantel is available in the dose of 600 mg, being administered in dose of 50 mg/kg for adults and 60 mg/kg for children. Side effects are mild and there is no evidence of severe toxic reactions. Oxamniquine is presented in pills (250 mg) and solution (50 mg/mL). The recommended dose is 15 mg/kg for adults and 20 mg/kg for chidren, in unique dose. Adverse effects include nausea, dizziness and urticariform reaction4. Praziquantel and oxamniquine are drugs available for all infected patients by *Schistosoma* in Brazil without costs to the patients.

6. Control measures

The incidence of schistosomiasis is decreasing in some places due to adequate control measures. The following measures have been adopted in Brazil:

6.1. Intermediate hosts control

The actions directed to intermediate host represent complementary measures to control schistosomiasis and are indicated in situations where the area is still unknown, to investigate and control disease focus and in areas with high prevalence. The following actions can be considered: search in hydric collections to determine its transmission potential; environmental sanitation measures, to difficult the proliferation and development of intermediate hosts, as well as prevent the contamination of water resources by infected men with *S. mansoni* eggs; chemical treatment of water in which snails are present; biological control of snails with competitive species[4].

6.2. Health education

Population`s education regarding the preventive measures is a fundamental part for schistosomiasis control. Health agents and professionals in the primary care can do this, mainly in endemic areas[4].

6.3. Infected individuals` control

Identification of individuals infected by *S. mansoni*, through feces exams each 2 years in endemic areas, is another important measure to control the dissemination of schistosomiasis. Treatment of infected individuals should be done in all the cases to decrease the parasitic load and avoid the development of severe forms[4].

6.4. Environmental sanitation

Adequate sanitation provides conditions to decrease the proliferation and contamination of intermediate hosts, with consequent decreas e in the contact of men with these transmiters (infected snails). The main measures of environmental sanitation to control schistosomiasis includes sanitary landfill, drainage or retification of hydric resources; cleaning and removal of marginal vegetation; adequate water supply for human consumption; sanitation; control of water reservoirs; correction of irrigation systems; and improvement of domiciliary sanitation.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

The authors performed an interesting review regarding schistosomiasis-associated kidney disease. The subject of this paper is of current interest and deserves publication.

Research frontiers

The article highlights important aspects of schistosomal glomerulopathy and brings an update in its prevention and treatment.

Peer review

In general, this is a good artical in which the authors reviewed the endemic tropical disease, Schistosomiasis, and its related renal involvment features, as well as the risk factors. Accept for publication with minor changes.

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