

Neuroschistosomiasis and the Central Nervous System

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Abstract. Schistosomes are the main cause of the neglected tropical disease schistosomiasis. As one of the most serious clinical consequences, neuroschistosomiasis occurs when the host exhibits an inflammatory reaction to eggs of schistosomes laid in the brain and the spinal cord. Two major kinds of neuroschistosomiasis are cerebral schistosomiasis and spinal schistosomiasis, which are associated with different types of schistosomes. Cerebral schistosomiasis can be acute, which leads to symptoms such as fever, delirium, visual impairment, ataxia, and headache, whereas chronic cerebral schistosomiasis usually causes epilepsy, brain tumor, and stroke. With regard to spinal schistosomiasis, the most common manifestation is acute myelopathy. Three treatments are effective for neuroschistosomiasis nowadays: schistosomicidal drugs, steroids, and surgical intervention. In terms of prevention, no vaccine is currently available, and avoiding contact with fresh water contaminated with schistosomes is the most effective way. Though neuroschistosomiasis has been increasingly reported, it is still under-recognized in many areas. Since early diagnosis and treatment significantly impact the prognosis of neuroschistosomiasis, it is crucial to improve the diagnostic approaches and treatments further to decrease the potential damage to the central nervous system. Also, the necessity of neuroschistosomiasis prevention should be emphasized to directly reduce the burden of this disease.

Keywords: neuroschistosomiasis, cerebral, spinal, schistosomes.

1. Introduction

The parasitic worms of the genus *Schistosoma* are the source of the acute and chronic illness known as schistosomiasis. Once an egg of schistosomes contacts water, it develops into a miracidium, which looks for the intermediate host, freshwater snails. In water, infected snails will release cercariae that penetrate human skin through human-water contact, leading to an infection of schistosomiasis. Schistosome carriers' excreta containing parasite eggs could contaminate water and cause further transmission. As the second devastating parasitic disease, the influence of schistosomiasis is worldwide: about 240 million individuals have been affected. Furthermore, endemic regions are home to nearly 700 million people [1].

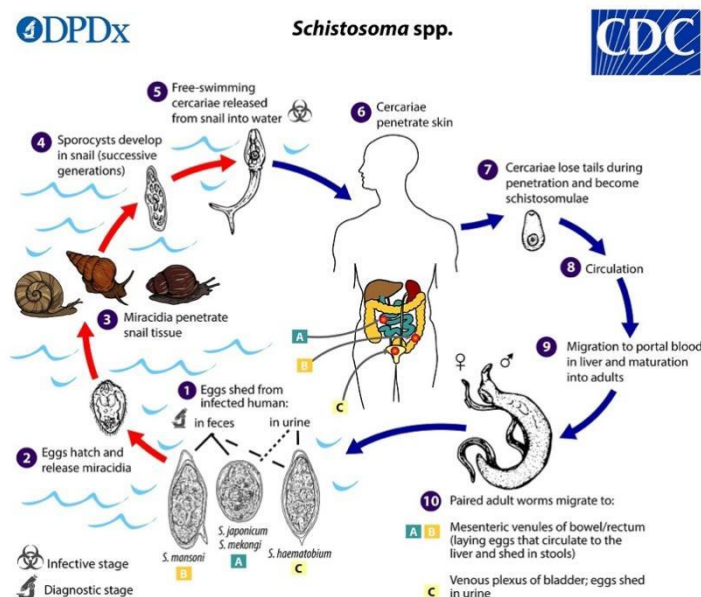


Fig.1 Life Cycle of Schistosomes [2]

Five types of schistosomes could infect humans: *S. haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*, each having a different distribution. *S. haematobium* is transmitted in Africa, the Middle East and Corsica, *S. mansoni* is mainly found in South America, Africa, and Caribbean islands, and *S. japonicum* transmits schistosomiasis in Southeast and East Asia, whereas *S. intercalatum* in Central and West Africa and *S. mekongi* in Laos and Cambodia are distributed in relatively small regions [2]. Among these species, the first three are the main threat. Except for *S. haematobium*, all the other four types of infection would lead to chronic intestinal and liver fibrosis. In contrast, chronic infection of *S. haematobium* would result in urinary tract fibrosis and calcification [3]. Besides human infection, *S. japonicum* and *S. mansoni* are zoonotic parasites. *S. japonicum* is able to infect various types of animals, such as cattle and dogs, while *S. mansoni*, with humans as the primary host, could infect rodents and primates [1].

Neuroschistosomiasis is caused by the infection of *S. haematobium*, *S. mansoni*, and *S. japonicum*, in the human central nervous system (CNS), which has two types of severe manifestations, cerebral and spinal schistosomiasis. While both types of neuroschistosomiasis could lead to severe symptoms, *S. japonicum* results in cerebral damage, whereas *S. haematobium* and *S. mansoni* are often one of the reasons for spinal cord deterioration [4, 5]. Specific symptoms of different patients are determined by how the parasite ova are present in the central nervous system as well as the immune system of the host [6].

Different symptoms can occur during the acute and chronic stages of neuroschistosomiasis. Within the acute phase, travelers to endemic areas and non-immune people are more likely to develop symptoms such as fever and diarrhea [6]. In contrast, residents in the endemic regions usually have chronic complications, and treating chronic neuroschistosomiasis is essential since the infection's intensity and duration determine the disease's severity [6]. Although the hepatointestinal and urinary tract diseases caused by schistosomiasis are more common to know, it is as crucial to study neuroschistosomiasis, which can result in severe clinical manifestations, including disability. Further understanding of neuroschistosomiasis will aid in early diagnosis and medical therapy of the disease, thereby avoiding possible severe symptoms [7]. This review aims to introduce different types of neuroschistosomiasis and how to treat and prevent this neglected tropical disease.

2. Neuroschistosomiasis

2.1. Cerebral Schistosomiasis

Schistosoma japonica is more common to cause cerebral schistosomiasis compared with *S. haematobium* and *S. mansoni*. Schistosomiasis in the cerebral can be acute and symptomatic and has been found in approximately 2-4% of patients [8]. This acute phase is also called Katayama syndrome. Since Acute cerebral schistosomiasis often occurs several weeks after the infection, and due to this delay, it is more likely to be misdiagnosed in non-endemic areas [3]. Patients experience anomalies of the cranial nerve during the acute phase as a result of the development of granulomatous damage and elevated intracranial pressure within the cortex, internal capsule, basal ganglia, and subcortical white matter [7]. In response to egg antigens and adult schistosomes, people will exhibit a humoral-like immune response, which involves the production and deposition of immune complexes [7]. Some distinguishable symptoms are fever, headache, nystagmus, and so on. The main neurological features are diffuse encephalopathy and seizures. A case of a 26-year-old man in July 2000 indicates how the seizure caused by cerebral schistosomiasis is manifested in the form of a burning sensation in fingers, hands, and forearms. Moreover, in this case, other seizure symptoms include clonic movements of the eyelids, mouth, and upper part of the arms, followed by a brief period of confusion [9]. This patient's seizures repeatedly recurred for three months [9].

While some neurological symptoms can last for several weeks or months, some are transient. Headache is usually transient or intermittent. Along with headaches, the mental status of cerebral schistosomiasis patients can be changed as well. Seizures, sensory disturbances (paraesthesia and anesthesia), and weakness of one or more extremities are common in cerebral schistosomiasis patients, whereas it is rare to see cranial nerve palsies or meningeal signs [5, 10]. Furthermore, ataxia and speech disturbances are also transient symptoms of cerebral schistosomiasis [4]. During acute cerebral schistosomiasis, the cerebrospinal fluid (CSF) examination result is usually informative [11]. However, it is possible to have normal or non-specific findings in CSF examination in some cases. Magnetic resonance imaging (MRI) and brain computed tomography (CT) are needed for optimizing the diagnosis. Physicians should pay attention to abnormal signs such as edema and multifocal, tiny, contrast-enhanced damage in the lobes (occipital, parietal, and frontal) detected with the methods mentioned above [4].

In contrast, chronic symptoms of cerebral schistosomiasis, including epilepsy, brain tumor, stroke, and so on, often occur after a patient is infected for several months to years. Since the symptoms of chronic cerebral schistosomiasis are various, and these symptoms are not specific, the diagnosis of chronic cerebral schistosomiasis needs to depend on a combination of the patient's history, imaging results, laboratory discoveries, and pathologic analysis [12]. Without appropriate treatments, chronic cerebral schistosomiasis will begin and progress. This chronic phase of the disease is defined by oviposition, which explains why it is more common to discover chronic complications in endemic areas, where schistosomes deposit eggs in many of the patients' organs, such as the lung, kidney, bowel, and so on [13]. Chronic stage schistosome granulomas are smaller than those that develop following oviposition. [13].

In immune people, cerebral schistosomiasis can be asymptomatic during the chronic phase of schistosome infection. *S. mansoni* eggs are detected in the brains of 25% of hepatosplenic schistosomiasis patients [4]. Among 34 chronic hepatosplenic schistosomiasis patients without overt neurological symptoms, MRI signal abnormalities have been discovered in 59% of them [14]. It is worth mentioning that during the chronic schistosomiasis period, the egg testing result in the stool examination could be negative. Instead, it is vital to use an electroencephalogram that shows clear abnormal signals, including slow waves, paroxysmal rhythm, and seizure discharge, for diagnosis [11].

2.2. Spinal Schistosomiasis

Spinal schistosomiasis is the best-known kind of neuroschistosomiasis. It is more likely to be found in young adults, teenagers, and children that are exposed to contaminated freshwater in endemic regions [5]. Spinal schistosomiasis is mainly attributed to *Schistosoma mansoni* and *S. haematobium*. When the host reacts in an inflammatory manner to the eggs laid in the spinal cord, neurological symptoms occur. Similar to cerebral schistosomiasis, a large number of ova and huge granulomas located in the spinal cord result in the neurological manifestations of spinal schistosomiasis [15]. According to studies, the likelihood of oviposition in the spinal cord is from 0.3% to 13% [7]. Generally, spinal schistosomiasis can be divided into three categories: medullary, myeloradicular, and conus-cauda equina syndrome [5]. For the medullary type with a rapid course, the sensorimotor abnormalities are typically distributed symmetrically; symptoms of the conus-cauda equina syndrome develop more gradually, and the pattern of the sensorimotor anomalies is predominately asymmetric; and compared to the previous two types, the myeloradicular form is the most prevalent with an intermediate level of symptoms [16].

The most common neurological complication of spinal schistosomiasis is acute myelopathy, which is likely to occur symptomatically early after the infection [7]. The portal veins are the places where adult schistosomes live and female schistosomes lay eggs. By way of the Batson venous plexus, the eggs travel to the spinal veins. Through actions that lead to intraabdominal pressure rises, such as defecating and coughing, schistosome ova could enter the veins, which explains why myelopathy happens more frequently in lumbosacral regions [17]. Since sensitized individuals might develop a hypersensitivity reaction to eggs toward exposure to new schistosome antigens, it is possible that myelopathy happens years after the initial infection [13]. Other common manifestations include lower back pain, bladder dysfunction, muscle weakness, and so on [5, 7, 15]. Patients frequently report pain in the lower back and paraesthesia in the lower limbs at the early stage of the onset of spinal schistosomiasis. In many endemic countries, spinal schistosomiasis still plays a significant but underappreciated role in acute myelopathy and requires much more attention.

The diagnosis of spinal schistosomiasis can be classified into definitive and presumptive diagnoses [17]. Only a histopathological examination of biopsy revealing schistosome eggs allows clinicians to definitely diagnose spinal schistosomiasis. However, due to the possibility of further harming the injured nervous tissue, this method should typically be avoided. In contrast, most cases of spinal schistosomiasis are diagnosed using a presumptive diagnosis based on three parameters: clinical manifestations, history or proof of active schistosomiasis, and removal of other causes of interference. The combination of the spinal cord low localization, acute/subacute symptom development, and occurrence of manifestations caused by both medullary and radicular portrays the clinical picture. In terms of history or evidence, physicians usually pay attention to a patient's stool, urine, and blood examinations. To exclude other possible causes, clinicians need to emphasize MRI and CSF examination results for the diagnosis. The final diagnosis of spinal schistosomiasis will depend on a comprehensive analysis of these three factors.

3. Treatment

Regarding neuroschistosomiasis, there is no definitive consensus [7]. Neuroschistosomiasis can currently be treated with schistosomicidal medicines, steroids, and surgery. [5, 7]. Schistosomicidal drugs include praziquantel, oxamniquine, and artemisinin derivatives [13]. Specifically, praziquantel is effective for eliminating any types of adult schistosomes, but not schistosomula or immature migrating larvae. By disrupting the tegument of the parasite, exhausting the glutathione, and interfering with calcium channel activity, praziquantel can cure 70-90% of patients parasitologically [7, 13]. It is important to note that praziquantel can possibly lead to adverse symptoms such as dizziness, lassitude, pain in the lower limbs, and so on, but since these side effects are mild, young children and pregnant women are allowed to use praziquantel as well [5, 15]. While no definitive consensus on the duration of praziquantel usage for neuroschistosomiasis treatment exists, the course

usually ranges from one day to two weeks [13]. For different types of schistosomes, the dose requirements vary: for *S. haematobium* and *S. mansoni*, the dose is usually 40 mg/kg, and the duration is three days, while for *S. japonicum*, the dosage is 60 mg/kg lasting six days [13]. In contrast, neuroschistosomiasis caused by South American *S. mansoni* is the only type that can be treated with oxamniquine, which requires only one dose ranging from 30-50 mg/kg to be effective, and artemether (artemisinin derivative) is the treatment for infection of schistosome aged 7-21 days and is also utilized for chemoprophylaxis [13].

Patients with minor symptoms or no symptoms could use praziquantel alone to treat neuroschistosomiasis, while for patients with moderate or severe symptoms, it is recommended to use corticosteroids as an adjunctive treatment [7]. Steroids should be administered beforehand in order to decrease the severity of the immunological and inflammatory response [13], which can prevent additional tissue damage and decrease schistosome ova deposition [7]. There is currently no definitive consensus or best timing about steroids usage for neuroschistosomiasis treatment. The effects of steroids have not been tested with double-blind randomized studies, but corticosteroids have been discovered to improve acute schistosomal myelitis [7].

Surgical interventions are determined based on different neuroschistosomiasis manifestations. Surgery plays an essential role in the treatment of hydrocephalus and increased intracranial pressure in schistosomiasis that happens in the cerebrum and cerebellum [13]. Ventriculoperitoneal shunt and corticosteroid therapy are used along with surgery for severe symptoms in this case. When clinical treatment does not prevent further acute *S. mansoni* myelitis deterioration, surgical processes, including decompressive laminectomy, mass excision, and root liberation, should be explored [7]. The outcome of surgical treatment is not always favorable. For example, among all the *S. mansoni* myeloradiculopathy patients, only 30% completely recover from the disease. Therefore, after the surgical treatment, rehabilitation, multi-disciplinary care, and support (social, family, and psychological) are vital for further facilitating the therapy [7].

4. Prevention

In general, worldwide health policies should prioritize reducing the prevalence of schistosomiasis. There is currently no vaccine for preventing schistosomiasis. For uninfected individuals, avoiding contact with fresh water that has been polluted with schistosomes is the basic strategy for preventing *Schistosoma* infection, thereby preventing the cercariae from penetrating the skin. Many activities may lead to contact with freshwater, such as swimming, wading, and so on. If there is suspected contact with polluted water, exposed individuals should decrease the risk of infection through vigorous towel drying as soon as possible [2]. However, for people who have an occupation such as fishing and farming that increases the risk of exposure to contaminated water, the World Health Organization recommends preventive chemotherapy that controls the morbidity of schistosomiasis [18]. In using freshwater as the water source for bathing and drinking, especially in endemic areas, it is necessary to boil the water for at least one minute beforehand to eradicate the parasite that might exist [2].

When individuals are infected with schistosomes, the reduction of brain involvement in the disease is largely associated with early diagnosis of the parasitosis and effective treatment. Both praziquantel and oxamniquine can kill adult schistosomes, which prevent further oviposition and ultimate embolization of ova in circulation [4]. By initiating therapy at an early stage, severe symptoms and disability can be effectively avoided. Clinicians should always take schistosomiasis into consideration for people who have a residence or travel history in endemic countries.

5. Conclusion

As a neglected tropical disease, schistosomiasis can lead to serious damage in the central nervous system. Cerebral schistosomiasis can be acute or chronic, leading to different clinical manifestations.

Spinal schistosomiasis is the most well-known type of neuroschistosomiasis, and its severity can range from asymptomatic egg deposition to serious deterioration. Since many of the symptoms are not unique to neuroschistosomiasis, clinicians must comprehensively consider different factors, such as history and imaging data, to achieve an accurate diagnosis. The main treatments for neuroschistosomiasis nowadays are schistosomicidal drugs, steroids, and surgery. Combining these treatments is essential for preventing possible further clinical damage. Prevention of schistosomiasis/neuroschistosomiasis mainly focuses on avoiding contact with contaminated water. Early diagnosis and corresponding action are important for reducing harm to the central nervous system.

Although neuroschistosomiasis is receiving more attention, many questions associated with neuroschistosomiasis still remain unresolved. This disease is misdiagnosed in many endemic areas, which leads to additional harm. The best doses and timing for the three types of treatments are still under-recognized. Future studies should aim to discover methods for distinguishing neuroschistosomiasis more efficiently and accurately. More clinical trials are required to optimize and update the treatments. Also, prevention approaches should be introduced and implemented to decrease the prevalence of schistosome infection, especially in endemic areas.

References

- [1] World Health Organization, Schistosomiasis (Bilharzia). 2022 [cited 2022 August 12]; Available from: https://www.who.int/health-topics/schistosomiasis#tab=tab_1.
- [2] Centers for Disease Control and Prevention, Parasites - Schistosomiasis. 2019 [cited 2022 August 23]; Available from: <https://www.cdc.gov/dpdx/schistosomiasis/index.html>.
- [3] Ross, A.G., et al., Katayama syndrome. *The Lancet infectious diseases*, 2007. 7(3): p. 218-224.
- [4] Pittella, J.E., Neuroschistosomiasis. *Brain Pathology*, 1997. 7(1): p. 649-662.
- [5] Ferrari, T.C.A. and P.R.R. Moreira, Neuroschistosomiasis: clinical symptoms and pathogenesis. *The Lancet Neurology*, 2011. 10(9): p. 853-864.
- [6] Lambertucci, J.R., Acute schistosomiasis mansoni: revisited and reconsidered. *Memórias do Instituto Oswaldo Cruz*, 2010. 105: p. 422-435.
- [7] Carod-Artal, F.J., Neurological complications of Schistosoma infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2008. 102(2): p. 107-116.
- [8] Watt, G., et al., Praziquantel in treatment of cerebral schistosomiasis. *The Lancet*, 1986. 328(8506): p. 529-532.
- [9] Betting, L.E., et al., Seizures and cerebral schistosomiasis. *Archives of neurology*, 2005. 62(6): p. 1008-1010.
- [10] KANE, C.A. and H. MOST, Schistosomiasis of the central nervous system: experiences in World War II and a review of the literature. *Archives of Neurology & Psychiatry*, 1948. 59(2): p. 141-183.
- [11] Hayashi, M., Clinical features of cerebral schistosomiasis, especially in cerebral and hepatosplenomegalic type. *Parasitology international*, 2003. 52(4): p. 375-383.
- [12] Rose, M.F., et al., Atypical presentation of cerebral schistosomiasis four years after exposure to *Schistosoma mansoni*. *Epilepsy & Behavior Case Reports*, 2014. 2: p. 80-85.
- [13] Carod Artal, F.J., Cerebral and Spinal Schistosomiasis. *Current Neurology and Neuroscience Reports*, 2012. 12(6): p. 666-674.
- [14] Manzella, A., et al., Brain magnetic resonance imaging findings in young patients with hepatosplenic schistosomiasis mansoni without overt symptoms. *The American journal of tropical medicine and hygiene*, 2012. 86(6): p. 982.
- [15] Ross, A.G., et al., Neuroschistosomiasis. *Journal of neurology*, 2012. 259(1): p. 22-32.
- [16] Ferrari, T.C., P.R. Moreira, and A.s.S. Cunha, Spinal cord schistosomiasis: a prospective study of 63 cases emphasizing clinical and therapeutic aspects. *Journal of Clinical Neuroscience*, 2004. 11(3): p. 246-253.
- [17] Adeel, A.A., Spinal cord schistosomiasis. *Sudanese Journal of Paediatrics*, 2015. 15(2): p. 23.

[18] World Health Organization, Schistosomiasis: progress report 2001-2011, strategic plan 2012-2020. 2013.