



Case Report

Cerebral schistosomiasis: Case series from Qatar

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ABSTRACT

Schistosomiasis is the third most widespread devastating parasitic disease worldwide and has a high mortality burden. Neuroschistosomiasis is one of the rare and most severe clinical presentations of the disease. It is caused by granuloma formation around eggs that lodge in the central nervous system, with *Schistosoma japonicum* usually causing most reported cerebral disease. Three unusual presentations of schistosomiasis in Qatar are described herein. The three patients were young males who presented with seizures and tumor-like lesions on brain imaging. The diagnosis was confirmed by biopsy, which showed necrotizing granulomas containing *Schistosoma* eggs. These cases raise awareness of neuroschistosomiasis as a potential cause of tumor-like brain lesions in migrants and returning travelers from endemic areas.

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Introduction

Schistosomiasis is an intravascular disease caused by parasitic trematode worms of the genus *Schistosoma*, known as blood flukes (Colley et al., 2014). It is the third most devastating tropical disease globally, affecting over 240 million individuals worldwide, with a burden of 70 million disability-adjusted life years (Colley et al., 2014; Ross et al., 2017). More than 78 countries are affected, and nearly 800 million people are exposed to the disease (Ross et al., 2017).

The three major *Schistosoma* (*S.*) species known to infect humans are *Schistosoma haematobium* (endemic in Africa and the Eastern Mediterranean), *Schistosoma mansoni* (endemic in Africa, the Middle East, the Caribbean, and South America), and *Schistosoma japonicum* (endemic primarily in China, Japan, and the Philippines) (Ferrari and Moreira, 2011). Two other species, *Schistosoma mekongi* and *Schistosoma intercalatum*, are more geographically restricted to Southeast Asia and Central West Africa, respectively (Gryseels et al., 2006). Adult worms reside for

years in the portal system, mainly in the inferior mesenteric vein of the human body, excreting hundreds to thousands of eggs daily, which may become trapped in nearby tissues inducing a distinct immune-mediated granulomatous response that causes local and systemic pathological effects (Colley et al., 2014).

With the goal of global control and elimination of schistosomiasis, the concept of integrated programs of mass drug administration (MDA) in endemic areas, using a single oral dose of praziquantel 40 mg/kg, has been advocated by the World Health Organization (WHO) (Mutapi et al., 2017). In 2014, such interventions reached 56 million people in 27 low- and middle-income countries of Africa, Asia, and Latin America, and it is approaching the point where most people in endemic areas will receive one or more treatments during their lifetime. However, this strategy is limited by the low coverage rate, low drug compliance rate, and limited funding (Mutapi et al., 2017).

Neuroschistosomiasis is one of the most severe clinical manifestations of the disease. It has been described in soldiers, aid workers, and tourists in areas where schistosomiasis is endemic. Cerebral manifestations are found in approximately 2–4% of infected persons and are usually located in the parietal, temporal, occipital lobes and the cerebellum (Ferrari and Moreira, 2011; Gryseels et al., 2006). Three unusual cases in which schistosomiasis presented as an intracerebral mass lesion are described herein.

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Case reports

Case 1

In December 2016, a 29-year-old Filipino man presented to the emergency department with generalized tonic-clonic seizures. He had been living in Qatar for 4 years and he had last travelled back to the Philippines 1 year previously, where he reported swimming in a lake. His vitals were within normal limits. There was no focal neurological deficit and the rest of the physical examination was unremarkable. His cerebrospinal fluid (CSF) was clear with a white blood cell count of 11×10^6 cells/l; protein and glucose were normal. No parasitic eggs were detected in the stool.

Cerebral magnetic resonance imaging (MRI) revealed left anterior temporal lobe and frontal gyrus areas of high-signal intensity on T2/FLAIR, with a nodular and linear pattern of enhancement in the post-contrast study (Figure 1A, B). A biopsy of the temporal lesion was done. Histopathological examination showed brain parenchyma infiltrated by necrotizing granulomas harboring *Schistosoma* eggs. The eggs had an outer shell and a lateral spine surrounding the developing miracidium, with multiple nuclei. Some of the eggs were calcified (Figure 1C). Serology for *S. mansoni* was positive.

The patient received praziquantel (60 mg/kg per day) for 1 day and prednisolone 30 mg daily for 1 week, which was tapered down by 5 mg weekly. He was discharged after 26 days and showed complete resolution of symptoms at the 3-month follow-up.

Case 2

A previously healthy 26-year-old Filipino male presented to the emergency department in May 2018 due to two episodes of tonic-clonic seizures. He reported a 4-month history of on/off headache. His physical and neurological examinations were normal. Serology for schistosomiasis was positive for *S. mansoni*. No parasitic eggs were detected in the stool.

MRI of the brain showed right parietal and left frontal and parieto-occipital subcortical mass lesions with hyperintensity on T2/FLAIR and hypointensity on T1, with underlying irregular spotty nodular dark signals in the post-contrast study (Figure 1D, E). An underlying significant subcortical white matter branching edema of T2/FLAIR bright signal with mass effect on the left lateral ventricle was seen. A biopsy was performed and a frozen section reported as gliosis. Histopathology showed brain parenchyma with *Schistosoma* eggs surrounded by granulomatous inflammation. A perivascular cuff of lymphocytes was present (Figure 1F).

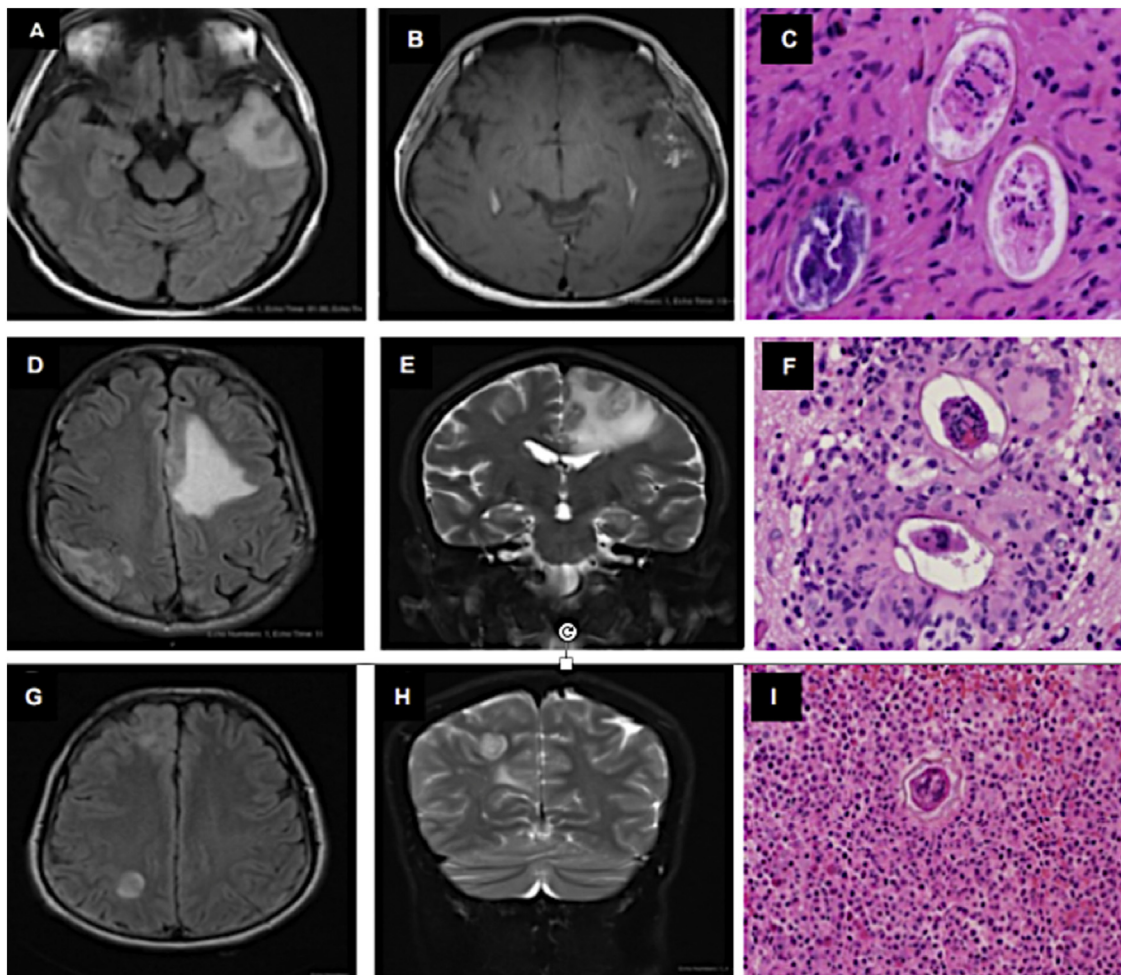


Figure 1. Case 1: (A, B) MRI showing a hyperintense area with irregular borders in the left temporal lobe on T2/FLAIR with a nodular and linear pattern of enhancement in the post-contrast study; (C) pathological examination of the biopsy specimen showing brain parenchyma infiltrated by necrotizing granulomas harboring *Schistosoma* eggs. Case 2: (D, E) MRI showing right parietal and left parieto-occipital subcortical mass lesions with hyperintensity in T2/FLAIR, with underlying irregular spotty nodular dark signals; (F) histopathology showing *Schistosoma* eggs surrounded by granulomatous inflammation. Case 3: (G, H) MRI showing areas of abnormal signal intensity on T2/FLAIR involving the right hemisphere in the region of the frontal, occipital, and parieto-occipital lobes associated with post-contrast enhancement; (I) brain parenchyma with *Schistosoma* egg surrounded by exuberant granulomatous inflammation.

Neuroschistosomiasis was confirmed and the patient was treated with praziquantel (60 mg/kg per day) and prednisolone (50 mg per day) for 2 weeks. He was discharged after 14 days in good general condition. The patient had an excellent response to praziquantel therapy, but required repeated courses of corticosteroid therapy to suppress recrudescence neurological symptoms.

Case 3

A 25-year-old Filipino male presented in September 2010 due to two episodes of tonic-clonic seizures. On examination he was confused, agitated, and disoriented with no focal neurological deficit. CSF examination was normal.

MRI of the brain showed three areas of abnormal signal intensity on T2/FLAIR involving the right cerebral hemisphere in the region of the frontal, occipital, and parieto-occipital lobes, associated with cortical thickening and post-contrast enhancement (Figure 1G, H). An electroencephalogram (EEG) showed evidence of right frontal epileptiform discharge with two episodes of ictal discharge, mainly in the right frontal region, spreading to the left side.

Frameless stereotactic biopsy of the right parietal lobe lesions under neuronavigation was done. Histopathological examination revealed brain parenchyma with *Schistosoma* eggs surrounded by exuberant granulomatous inflammation (Figure 1I). A diagnosis of neuroschistosomiasis was confirmed and the patient was treated with praziquantel (60 mg/kg per day), dexamethasone (12 mg per day), and phenytoin. He was discharged after 14 days in good general condition. Four months after receiving the treatment, the patient reported complete resolution of the symptoms and repeat MRI of the brain showed a dramatic improvement.

Discussion and literature review

Neuroschistosomiasis was first described by Yamagiwa in 1889 (Nascimento-Carvalho and Moreno-Carvalho, 2005). Schistosomiasis is endemic in the Philippines, from where the three reported patients originated (Olveda et al., 2014). It is commonly caused by *S. japonicum* and it is believed that the small size and rounded shape of the eggs enable them to migrate easily to the brain (Nascimento-Carvalho and Moreno-Carvalho, 2005). However it has been reported in the recent literature that *S. mansoni* is a neglected and underestimated cause of neuroschistosomiasis. *S. mansoni* has been reported as the primary cause of spinal cord disease among all species of *Schistosoma* (Vale et al., 2012). Neuroschistosomiasis results when eggs, instead of being eliminated in the feces or urine, spread to the central nervous system (CNS) and generate proteolytic enzymes that cause eosinophilic inflammation and granulomatous reactions, with subsequent replacement by fibrous tissue (Gryseels et al., 2006).

CNS involvement can be in the brain or spinal cord (Vale et al., 2012; Wu et al., 2012). The most common presenting symptoms are headache, cognitive impairment, generalized tonic-clonic seizures, and focal neurological deficits (Jukes et al., 2002; Houdon et al., 2010). Papilledema may be seen as a result of intracranial pressure. Cognitive impairment, poor short-term memory, and slower reaction times have been found among Tanzanian and Egyptian schoolchildren with neuroschistosomiasis (Caumes and Vidailhet, 2010; Jauréguiberry et al., 2007). Furthermore, it has been described in migrants and returning travelers from endemic areas. For instance, two brothers who returned from a trip to Madagascar presented with acute schistosomiasis and exhibited acute disseminated encephalitis (ADEM) (Houdon et al., 2010). The acute neurological presentation, high eosinophilia, multiple brain infarcts, and rapid efficacy of steroid therapy in these cases supported an eosinophil-mediated response to larva migration, leading to vasculitis and small-vessel thrombosis, as the most

likely pathophysiological mechanism in acute neuroschistosomiasis, rather than parasitic embolism (Caumes and Vidailhet, 2010; Jauréguiberry et al., 2007).

MRI is considered the best imaging modality to diagnose neuroschistosomiasis. Typical findings include single or multiple-grouped hyperintense lesions with punctate or nodular post-contrast enhancement giving the characteristic nodular pattern (Wu et al., 2012; Jukes et al., 2002; Houdon et al., 2010; Caumes and Vidailhet, 2010). Other less common patterns have been described, such as the pseudotumoral form or the appearance of intraparenchymatous hematomas or cysts (Preidler et al., 1996). In the three cases reported herein, MRI showed a clustered nodular enhancement pattern, which supports the previous report as a characteristic finding for neuroschistosomiasis. This characteristic pattern may be useful for non-invasive diagnosis and to avoid unnecessary surgery (Betting et al., 2005).

A high index of clinical suspicion is crucial, particularly in patients coming from countries endemic for schistosomiasis (Nascimento-Carvalho and Moreno-Carvalho, 2005). Serology is not recommended due to the high percentage of false-positive results (Llenas-García et al., 2009). For instance, positive serology remains years after infection, and cross-reactions can happen especially with other helminths (Mutapi et al., 2017; Olveda et al., 2014). Histopathology typically demonstrates granuloma formation around eggs embedded in the affected tissue (Colley et al., 2014). We found several eggs on the histopathology slides in all of our cases. The aggressive diagnostic approach (such as a stereotactic biopsy) remains the gold standard to confirm the diagnosis. However, early schistosomiasis still poses a serious diagnostic challenge, with low sensitivity of standard diagnostic methods. The recent literature has shown the superior sensitivity of molecular diagnostic assays with *S. mansoni*-specific real-time PCR and it has been advocated that this assay should be considered as the non-invasive gold standard diagnostic tool for patients with suspected early symptomatic schistosomiasis (Bonnefond et al., 2019; Wichmann et al., 2013).

The treatment of neuroschistosomiasis is challenging and consists mainly of praziquantel plus corticosteroids (Ross et al., 2002). However, in acute neuroschistosomiasis, praziquantel has been found not to be effective and is sometimes associated with severe reactions and even life-threatening clinical deterioration (Caumes and Vidailhet, 2010). Therefore, some authors recommend postponing praziquantel until neurological recovery and the use of corticosteroids as the first-line treatment for acute neuroschistosomiasis; this can attenuate the neurological and cardiac toxicity of eosinophilia and hypersensitivity reaction to parasite toxins (Jauréguiberry et al., 2010). Furthermore, praziquantel needs a good host-specific response against *Schistosoma* to be efficient, which is lacking during the early stage of acute neuroschistosomiasis (Jauréguiberry et al., 2010).

Antiepileptic drugs, preferably levetiracetam, sodium valproate, or carbamazepine for less interaction with praziquantel, are often necessary when the patient presents with seizures (Betting et al., 2005). A study showed that anticonvulsants failed to control the seizures in 250 cases of cerebral schistosomiasis. Complete surgical resection of the epileptogenic zone caused by the scarred schistosomal granuloma resulted in 91.8% of the patients becoming seizure-free (Vale et al., 2012; Lei et al., 2008).

Neuroschistosomiasis was not initially considered in the differential diagnosis of our patients. A tumor was initially considered the likely diagnosis on the basis of MRI findings. Even if schistosomiasis had been considered earlier and if specific parasitological and serological studies had been performed, it is unlikely that we would have felt confident in treating them with anti-schistosomal chemotherapy alone, in the absence of a tissue-based diagnosis. This is due to the serious implications associated

with failure to diagnose a neoplasm and the high likelihood of incidental abnormal results of a stool specimen examination or serological testing based on exposure history.

In conclusion, neuroschistosomiasis persists as a global burden and the diagnosis remains difficult. The clinician should maintain a high level of suspicion when assessing patients presenting with seizures and tumor-like lesions on brain imaging, especially if the patient comes from an endemic area or has visited a rural area in an endemic country. Early and appropriate treatment is of paramount importance to minimize CNS tissue damage and prevent chronic sequelae, which may lead to permanent neurological damage and even death if left untreated. Although not pathognomonic, an MRI finding of a nodular pattern of enhancement should raise suspicion for neuroschistosomiasis.

Disclosures

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Ethical approval

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Conflict of interest

None of the authors has any conflict of interest from publishing this manuscript.

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