Atypical presentation of cerebral schistosomiasis four years after exposure to Schistosoma mansoni

Citation
Rose, Matthew F., Eli E. Zimmerman, Liangge Hsu, Alexandra J. Golby, Emam Saleh, Rebecca D. Folkerth, Sandro S. Santagata, Danny A. Milner, and Shakti H. Ramkissoon. 2014. “Atypical presentation of cerebral schistosomiasis four years after exposure to Schistosoma mansoni.” Epilepsy & Behavior Case Reports 2 (1): 80-85. doi:10.1016/j.ebcr.2014.01.006. http://dx.doi.org/10.1016/j.ebcr.2014.01.006.

Published Version
doi:10.1016/j.ebcr.2014.01.006

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:14065337

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Case Report

Atypical presentation of cerebral schistosomiasis four years after exposure to Schistosoma mansoni

Matthew F. Rose a,⁎,1, Eli E. Zimmerman b,1, Liangge Hsu c, Alexandra J. Golby c,d, Emam Saleh d, Rebecca D. Folketh a, Sandro S. Santagata a, Danny A. Milner Jr. a, Shakti H. Ramkissoon a

⁎ Corresponding author at: Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, USA

1 These authors contributed equally to this work.

1. Introduction

Schistosomiasis has affected humans for thousands of years and is now the second most socioeconomically devastating parasitic disease worldwide, affecting over 240 million people in 77 countries on 5 continents and killing 300,000 people annually in sub-Saharan Africa alone. Neuroschistosomiasis is caused by granuloma formation around eggs that lodge in the CNS, with Schistosoma mansoni and Schistosoma haematobium usually affecting the spinal cord and Schistosoma japonicum causing most reported cerebral disease. We report a case of a previously healthy 25-year-old woman native to the United States who presented with a single generalized tonic–clonic seizure without other neurologic symptoms four years after spending a semester in Ghana where she went swimming once in a river. Brain MRI showed areas of signal abnormality and mottled nodular linear enhancement in the left temporal and right posterior temporal/parietal lobes and right cerebellum without mass effect. A biopsy of the left temporal lesion showed prominent granulomas with dense mixed inflammatory infiltrates composed of eosinophils, plasma cells, and lymphocytes surrounding refractile egg shells containing characteristic embryonal cells and von Lichtenberg’s envelope and displaying the pathognomonic spine shape of S. mansoni. Serum ELISA and antibody immunoblots confirmed exposure to S. mansoni. In summary, we describe the atypical combination of cerebral schistosomiasis due to S. mansoni, after a prolonged interval of four years, from a single known exposure.

© 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).
Hence, the tissue preferences of specific *Schistosoma* species lead in turn to some correlations between specific species and the incidence of particular organ injury. For instance, the pathology of *S. mansoni* and *S. japonicum* includes hepatic perisinusoidal egg granulomas/Symmers' pipe stem periportal fibrosis, portal hypertension, as well as Katayama fever. In contrast, the pathology of *S. haematobium* revolves around the urinary tract with frequent hematuria, bladder/lower ureter scarring, and calcification with resulting renal parenchymal damage and kidney failure as well as an association with squamous cell carcinoma of the bladder [3,5,8]. All three *Schistosoma* species can also affect the central nervous system as neuroschistosomiasis [4,9].

Neuroschistosomiasis results when eggs, instead of being eliminated in feces or urine, spread to the central nervous system and induce the formation of granulomas. Involvement of the brain (cerebral/encephalic schistosomiasis or cerebral granulomatous disease) often leads to seizures, whereas involvement of the spinal cord (spinal cord schistosomiasis or schistosomal myeloradiculopathy) can cause cord compression resulting in paralysis. Similar to the organ distribution described above, different *Schistosoma* species have prevalence for affecting either the brain or spinal cord. *Schistosoma japonicum* primarily involves the brain, while *S. mansoni* and *S. haematobium* primarily affect the spinal cord. However, occasional cases of cerebral schistosomiasis due to *S. mansoni* continue to be reported, and it is possible that its frequency of cerebral involvement may be underestimated [10–13]. In areas where *S. haematobium* is endemic, spinal schistosomiasis is the leading cause of spinal cord damage. Involvement of the CNS is thought to be most frequently due to embolization of eggs, but some cases of adult schistosomes traveling to the CNS vasculature have been reported. Symptoms can present soon after infection in the case of acute schistosomal encephalopathy, but delayed reactions for months and sometimes for years have been reported in cerebral schistosomiasis [3,4,9].

2. Case presentation

The patient is a previously healthy 25-year-old female native of Massachusetts, U.S., who presented to the Brigham and Women's Hospital emergency department after the first seizure in her life. She had been feeling fatigued on the train that morning, and her symptoms worsened over the day. A coworker had her sit down, at which point she had difficulty answering questions. She then fell off a chair and had a witnessed generalized tonic–clonic seizure, which lasted for 3 min (without incontinence), followed by 30 min of more pronounced fatigue and confusion. In the emergency department, she was fully alert and oriented, followed all commands without difficulty, and had fluent speech. Concentration, attention, and memory were intact, as was her ability to read, name, and analyze a picture. The remainder of her neurologic exam was normal. A CT scan at that time also showed no abnormalities.

Her past medical history is notable only for headaches and eczema. Her headaches, which began in childhood, are infrequent and occur only once or twice per year. They are usually preceded by a scintillating scotoma and often resolve without medications. She also had a tick bite prior to her current course, though she had no subsequent rash and had a negative Lyme titer. In her family, she has a maternal uncle with epilepsy (unknown type), a maternal aunt with migraines, and a mother with cardiac arrhythmias. She is a vegetarian and does not smoke, drink, or use illicit drugs. She is HIV-negative. She has traveled to England twice and lived in Ghana for one semester of college, four years prior to the onset of symptoms. During that trip, she lived mainly in the university town of Legon, 12 km northeast of the capital city of Accra, and she reported swimming once during the trip in a freshwater river that runs parallel to the ocean, east of the capital city. She did not recall swimming in any lakes. She recalled no particular symptoms during her stay, apart from one episode of dysuria that lasted less than a day. In the last 4 years, she has been perfectly well until this episode.
She was subsequently followed in the clinic at weekly intervals and experienced an episode of altered consciousness (possibly a partial seizure) prior to the 4th visit. Peripheral blood showed no abnormal findings: WBC: 9.3, HGB: 12.9, HCT: 39.8, PLT: 226 (POLY: 58, BAND: 0, LYMPH: 31, MONO: 7, EOS: 2, and BASO: 0). Likewise, serum chemistries were within normal ranges: glucose: 91, BUN: 6, creatinine: 0.64, sodium: 140, potassium: 3.8, chloride: 100, total CO2: 26, alkaline phosphatase: 54, ALT: 11, AST: 17, total bilirubin: 0.2, total protein: 7.5, albumin: 4.6, calcium: 9.4, and magnesium: 1.9.

A lumbar puncture was performed, and CSF showed no abnormal findings: glucose: 55, protein: 19, WBC: 2 (91% lymphocytes), and RBC: 0. Likewise, rheumatologic labs were within normal ranges: CRP: 0.6, MPO: 0, PR3: 4, and ANA and ANCA: negative. She was started on the antiepileptic drug levetiracetam to prevent further seizures.

Electroencephalography (EEG) showed good organization at rest, but occasional abnormal left temporal theta slowing was noted, maximal at T3. There were no definite epileptiform abnormalities (Fig. 2). These findings are suggestive of mild left temporal dysfunction.

Brain MRI imaging showed areas of abnormal T2 and FLAIR signal at the medial and lateral aspects of the anterior left temporal and right posterior temporal parietal lobes (with the left more affected than the right), as well as a similar small area of abnormality of the right cerebellum (Figs. 3A–C). After contrast administration, all these areas showed mottled nodular linear enhancement without significant mass effect (Figs. 3D–F). No associated diffusion abnormality or mineralization or hemorrhage was seen. Likewise, there was no asymmetric hippocampal volume loss or gray matter heterotopia, and ventricles were normal in size. Possible etiologies of these imaging findings could include a spectrum of vasculitides, lymphomatoid granulomatosis, infection, and, less likely, granulomatous disease or tumor.

Additional functional MRI (fMRI) brain mapping was performed for presurgical planning and showed findings consistent with left-sided language lateralization but also showed the functional language regions to be apart from the areas of left temporal lobe signal abnormality. An image-guided left temporal craniotomy for open biopsy of the area of signal abnormality was performed. Upon inspection, the surface of the brain was abnormal with some speckled appearance and some increased vascularity. A 0.5-cm biopsy was taken from the anterior/inferior left temporal lobe and appeared grossly abnormal with areas of possible necrosis. In addition, tissue was sent for microbiologic cultures.

Initial intraoperative consultation with frozen section/smear evaluation showed collections of histiocytes concerning for granulomas, vascular involvement, and necrosis suspicious for an infectious process (Figs. 4A–B). Subsequent evaluation of paraffin-embedded permanent sections showed brain tissue with extensive granuloma formation and dense mixed inflammatory infiltrates comprised of eosinophils, plasma cells, histiocytes, and lymphocytes (Figs. 5A–B). Review of multiple tissue sections revealed refractile shell fragments at the center of each granuloma with occasional intact shells showing the pathognomonic acentric spine shape of S. mansoni (Fig. 6A) [14].

Serum ELISA and antibody immunoblots performed at the Center for Disease Control and Prevention (CDC) confirmed exposure to S. mansoni and showed lack of exposure to S. haematobium, the other most prevalent schistosome species in Ghana. The S. mansoni AB FAST-ELISA produced a score of 100 (positive score considered >10; 99% sensitivity for S. mansoni; 90% sensitivity for S. haematobium; 95% specificity for schistosomal infection). The S. mansoni AB immunoblot was positive, while the S. haematobium AB immunoblot was negative. Hence, the patient was diagnosed with cerebral schistosomiasis (neuroschistosomiasis) due to S. mansoni. Stool and urine were repeatedly negative for ova.

The patient was started on dexamethasone to control inflammation and received praziquantel (2 doses) immediately after the histologic diagnosis in order to kill any remaining adult schistosomes. The steroids were tapered over one month, at which point she received another course of praziquantel (2 doses). She was maintained on levetiracetam for seizures. She has had no additional symptoms in the subsequent

---

**Fig. 2.** Electroencephalography shows left temporal dysfunction. This electroencephalogram (EEG), performed with anterior temporal and standard 10–20 electrodes during the waking, drowsy, and sleeping states, is abnormal because of occasional left temporal theta slowing. These findings are suggestive of mild left temporal dysfunction. There are no definite epileptiform abnormalities.
twelve months. Subsequent serum analysis showed no eosinophilia, and stools continue to be negative for ova.

3. Discussion

Cerebral (encephalic) schistosomiasis was first described by Yamagiwa, a student of Rudolf Virchow, in 1889 [15]. It is most often associated with S. japonicum infection in East Asia, where that species is most prevalent, and has only occasionally been reported to be caused by S. mansoni or S. haematobium. In contrast, both S. mansoni and S. haematobium, but not S. japonicum, are endemic to Ghana, the likely source of infection for the current case [3]. Hence, this presentation of cerebral schistosomiasis due to S. mansoni four years after a single known exposure is an atypical presentation.

Cerebral schistosomiasis can present with variable clinical and imaging characteristics that can overlap with that of epilepsy, brain tumors, vasculitis, stroke, granulomatous disease, and other disorders [4]. Patients can present with a combination of partial or generalized tonic–clonic seizures, increased intracranial pressure, focal neurological deficits, and headache [16]. Electroencephalogram can help localize the disease in some cases but can also be normal in some patients [4,17].

The lesions of neuroschistosomiasis can occur in both the cerebral hemispheres and cerebellum/brain stem. On postcontrast MRI, the lesions can appear as a large mass comprising multiple intensely enhancing nodules or as a central linear enhancement surrounded by multiple enhancing punctate nodules sometimes appearing “arborized.” Occasionally, they have also been reported to appear as nonenhancing irregular “finger-like” areas of abnormal signal consistent with increased edema.

![Fig. 3. Lesions in the temporal/parietal cortex and cerebellum show nodular enhancement and edema. Axial T2 (A) and FLAIR (B, C) MRI images show increased signal at the right cerebellum (A, arrows) and right parietal (B, arrows) and left temporal (C, arrows) lobes consistent with edema. Axial post-gadolinium contrast images show corresponding clusters of small (1–3 mm) enhancing nodules at the right cerebellum (D, arrows) and right parietal (E, arrows) and left temporal (F, arrows) lobes. These findings likely represent granulomatous tissue surrounding the eggs. The differential diagnosis based on these radiologic findings would include a spectrum of vasculitides, lymphomatoid granulomatosis, infection, and, less likely, granulomatous disease or tumor.](image1)

![Fig. 4. Tissue smear and frozen section reveal extensive inflammatory infiltrates and necrosis in the temporal cortex. (A) Smear preparation of left temporal cortex biopsy showing vessels with perivascular inflammation (black arrows) and areas of necrosis. (B) Frozen section of left temporal cortex biopsy showing prominent collections of mononuclear cells (macrophage/histiocyte clusters) and scattered eosinophils concerning for granulomas (yellow arrows). Pathologic differential of this appearance includes infection (TB vs. schistosomiasis), vasculitis, and lymphomatoid granulomatosis.](image2)
edema [18–20]. However, the imaging characteristics of cerebral schistosomiasis due to *S. mansoni*, as in the current case, are not well described because of its comparable rarity. In the current case as well as in three other reported cases of cerebral schistosomiasis due to *S. mansoni*, the imaging does appear to show a similar pattern of enhancing punctate nodules clustered irregularly around some linear enhancement, with surrounding edema. Thus, this imaging pattern may be generally applicable to cerebral schistosomiasis due to both *S. mansoni* and *S. japonicum* [10,11].

Direct pathologic evaluation of the involved tissue, as in the current case, is still the gold standard for diagnosis. Observation of the spine placement on the egg shell (lateral for *S. mansoni*, midline for *S. haematobium*, and absent for *S. japonicum*) is pathognomonic for each species. However, a combination of the serum indirect hemagglutination (IHA) test and enzyme-linked immunosorbent assay (ELISA) shows high sensitivity and specificity for *S. mansoni*, and both are often used in addition to histologic evaluation to confirm the species diagnosis, especially if intact eggs are not identified on histologic sections [16,21]. Other tests such as evaluation of stool and urine for ova can be very useful if positive but are often negative. Overall, as in our case, a combination of these diagnostic approaches is required [4].

Schistosomiasis pathology is driven by host inflammatory response to the eggs and hence correlates with where the eggs are deposited. *Schistosoma mansoni* and *S. japonicum* can cause Katayama fever, hepatic perisinusoidal egg granulomas, and perportal fibrosis and portal hypertension, whereas *S. haematobium* is more frequently associated with hematuria and bladder wall scarring [3,5]. Moreover, specific schistosome species are associated with the development of specific cancers, such as the correlation between *S. haematobium* infection and the development of squamous cell carcinoma of the bladder. In areas where *S. haematobium* is endemic, squamous cell carcinoma of the bladder is the leading form of cancer in the population. Other studies have likewise suggested links between *S. japonicum* and hepatocellular carcinoma and between *S. mansoni* and colorectal adenocarcinoma, although more evidence is needed [8].

Treatment of schistosomiasis consists of antischistosomal therapy (i.e., praziquantel) plus corticosteroids to control the inflammation [22]. Some cases involving the posterior fossa with resulting mass effect may also require treatment with surgical resection [20]. While the current patient showed involvement of both the cerebral cortex and cerebellum, there was no significant mass effect, and the patient was treated successfully with medical therapy after the diagnostic biopsy. Anticonvulsants are frequently needed for a period of time, but studies suggest that long-term antiepileptic therapy is not required in most cases of cerebral schistosomiasis [17]. Unfortunately, neuroschistosomiasis can sometimes result in significant postexposure chronic sequelae including medically refractory epilepsy that may require surgical treatment in the case of cerebral schistosomiasis and paralysis in the case of spinal cord schistosomiasis [4,23]. The worst outcomes have been seen in spinal cord schistosomiasis where some studies have reported that only 15% of treated patients experience a complete recovery, while other studies have shown that early aggressive treatment can lead to full recovery in up to 65% of patients [4,24].

Fig. 5. Extensive granulomas are present in the temporal cortex. (A) A paraffin section of the formalin-fixed temporal lobe biopsy shows reactive brain tissue extensively involved by prominent granuloma formation and reactive gliosis. (B) A magnified view of one granuloma pictured in the yellow box in (A) shows dense mixed inflammatory infiltrates comprised of eosinophils, plasma cells, and lymphocytes.

Fig. 6. An infectious etiology: *Schistosoma mansoni*. (A) Magnification of the center of one of the granulomas reveals an egg with a refractile shell showing the pathognomonic acentric spine shape of *Schistosoma mansoni*. Reynolds’ layer (R) has filled the spine but is not well defined with regard to the remaining egg shell. A single layer of squamous cells (von Lichtenberg’s envelope) (L) is seen at the apex of the egg and is closely adherent to Reynolds’ layer. The envelope surrounds the developing miracidium (M) with multiple nuclei [14]. Neutrophils and histiocytes adjacent to the egg highlight the smaller size of the schistosome nuclei in comparison to those in human cells. (The image is taken at 40× without a condenser in order to increase refraction and highlight the contour of the egg shell. Bar = 10 μm.)
Of note, other schistosome species are found indigenously in the U.S., but die after penetrating human skin, giving rise to a similar initial allergic condition called “swimmer’s itch”, or cercarial dermatitis, but not progressing to the other manifestations of the disease. The primary hosts for these other species are instead water fowl (**Austrobilharzia variegandis**, **Microbilharzia sp.**, **Trichobilharzia ocellata**, **Trichobilharzia ph ysella**, **Trichobilharzia stagnicola**) and rodents (**Schistosomatium douthiti**) [25]. Because the specific snail species required as intermediate hosts for **S. japonicum**, **S. mansoni**, and **S. haematobium** are not present in the United States, the transmission of these organisms in the United States waterways is currently unlikely [25].

4. Conclusions

In summary, we describe the atypical combination of cerebral schistosomiasis due to **S. mansoni**, after a prolonged four-year interval, from apparently a single exposure. The imaging characteristics of irregular nodular enhancement seen in this case mirror those reported in the much more frequent cerebral schistosomiasis due to **S. japonicum** and support previous suggestions that these imaging findings are applicable to cerebral schistosomiasis caused by both species. The clinical manifestations of cerebral schistosomiasis are variable and can overlap with that of epilepsy, brain tumors, vasculitis, and stroke. Hence, a combination of history, imaging data, laboratory findings, and pathologic analysis is critical for diagnosis.

Disclosures

All authors report no disclosures.

Acknowledgments

We thank the Longwood Neuropathology Training Program of Brigham and Women’s Hospital, Boston Children’s Hospital, Beth Israel Deaconess Medical Center, and Harvard Medical School. We also thank Marian Slaney and Sebastian Valentim of the Brigham and Women’s Hospital clinical neuropathology laboratory for their technical expertise in histological preparation.

References

[1] Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis* 2006;6(7):411–25.

[2] Contis G, David AR. The epidemiology of Bilharzia in ancient Egypt: 5000 years of schistosomiasis. *Parasitol Today* 1996;12(7):253–5.

[3] Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. *Lancet* 2006;368(9541):1106–18.

[4] Ferrari TCA, Moreira PRR. Neuroschistosomiasis: clinical symptoms and pathogenesis. *Lancet Neurol* 2011;10(9):853–64.

[5] Kradin RL. Diagnostic pathology of infectious disease. Philadelphia, PA: Saunders Elsevier; 2010.

[6] Kamar V, Abbas AK, Nelson F, Aster JC, Robbins and Cotran pathologic basis of disease. Eighth ed. Philadelphia, PA: Saunders Elsevier; 2010.

[7] Da Silva AJ, Moser M. Illustration of the life cycle of the parasites responsible for causing schistosomiasis [Internet]. Public Health Image Library, Centers for Disease Control and Prevention; 2002 [Available from: http://phil.cdc.gov/phil/details.asp?pid=3417].

[8] Palumbo E. Association between schistosomiasis and cancer: a review. * Infect Dis Clin Pract 2007;15(3):145–8.

[9] Carod-Artal FJ. Cerebral and spinal schistosomiasis. *Curr Neurol Neurosci Rep* 2012;12(6):666–74.

[10] Ropper AH, Stemmer-Rachminov A. Case 21-2001. A 31-year-old man with an apparent seizure and a mass in the right parietal lobe. *N Engl J Med* 2001;345(2):126–31.

[11] Sanelli PC, Lev MH, Gonzalez RG, Schaefer PW. Unique linear and nodular MR enhancement pattern in schistosomiasis of the central nervous system: report of three patients. *AJR Am J Roentgenol* 2001;177(6):1471–4.

[12] Pitéla AJE. Neuroschistosomiasis. *Brain Pathol Zurich Switz* 1997;7(1):649–62.

[13] Scirringreur EM, Gadgisek DC. Involvement of the central nervous system in *Schistosoma mansoni* and *S. haematobium* infection. A review. *Brain J Neurol* 1985;108(Pt 4):1023–38.

[14] Neill PJ, Smith JH, Doughtry BL, Kemp M. The ultrastructure of the *Schistosoma mansoni* egg. *Am J Trop Med Hyg* 1988;39(1):52–63.

[15] Yamagiwa K. Beitrag zur aetologie der jackstochen epilepsy. *Virchows Arch Pathol Anat* 1889;119:449–60.

[16] Wu L, Wu M, Tian D, Chen S, Liu B, Chen Q, et al. Clinical and imaging characteristics of cerebral schistosomiasis. *Cell Biochem Biophys* 2012;62(2):289–95.

[17] Betting LE, Pirani Jr C, de Souza Queiroz L, Damasceno BP, Cendes F. Seizures and cerebral schistosomiasis. *Arch Neurol* 2005;62(6):1008–10.

[18] Liu H-Q, Feng X-Y, Yao Z-W, Sun H-P. Characteristic magnetic resonance enhancement pattern in cerebral schistosomiasis. *Chin Med Sci J Chung-Kuo Hsiueh Ko Hsueh Tsa Chih Chin Acad Med Sci* 2006;21(4):223–7.

[19] Liu H, Lim CCT, Feng X, Yao Z, Chen Y, Sun H, et al. MRI in cerebral schistosomiasis: characteristic nodular enhancement in 33 patients. *Am J Roentgenol* 2008;191(2):582–8.

[20] Shi K, Zhang S, Han L, Lei T. Surgical treatment of cerebellar schistosomiasis. *Neurosurgery* 2009;64(5):941–3 [discussion 943–944].

[21] Van Gool T, Vetter H, Vervoort T, Doenhoff MJ, Wetsteyn J, Overbosch D. Serodiagnosis of imported schistosomiasis by a combination of a commercial indirect hemagglutination test with *Schistosoma mansoni* adult worm antigens and an enzyme-linked immunosorbent assay with *S. mansoni* egg antigens. *J Clin Microbiol* 2002;40(9):3452–7.

[22] Ross AGP, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, et al. *Schistosomiasis*. *N Engl J Med* 2002;346(16):1212–20.

[23] Carod-Artal FJ. Neurological complications of *Schistosoma* infection. *Trans R Soc Trop Med Hyg* 2008;102(2):107–16.

[24] Freitas ARR, Oliveira ACP, Silva LJ. *Schistosomal myeloradiculopathy in a low-prevalence area: 27 cases (14 autochthonous) in Campinas, São Paulo, Brazil*. *Mem Inst Oswaldo Cruz* 2010;105(4):398–408.

[25] Brant JV, Loker ES. Schistosomes in the southwest United States and their potential for causing cercarial dermatitis or “swimmer’s itch.” *J Helminthol 2009;83(2):191–8.*