ACUTE NEUROSCISTOSOMIASIS: TWO CASES ASSOCIATED WITH CEREBRAL VASCULITIS

STÉPHANE JAUREGUIBERRY*, SÉVERINE ANSART, LUCIA PEREZ, MARTIN DANIS, FRANÇOIS BRICAIREF, AND ERIC CAUMES

Department of Infectious and Tropical Disease, Hôpital Tenon, Assistance Publique Hopitaux de Paris, Paris, France; Department of Infectious and Tropical Disease and Parasitology-Mycology, Hôpital Pitié-Salpêtrière, Assistance Publique Hopitaux de Paris, Paris, France

Abstract. Encephalitis and focal neurologic deficits can occur during the acute phase of schistosomiasis. We report two cases in which cerebral imaging showed cerebral vasculitis located in arterial junctional territories. These neurologic complications may be caused by eosinophil-mediated toxicity. Immediate treatment should consist of corticosteroids rather than specific antischistosomal drugs, which may aggravate the disorders.

INTRODUCTION

Acute schistosomiasis may be complicated by life-threatening neurologic involvement. This is an uncommon complication, described in 2.3% of 1,200 cases of acute *Schistosoma japonicum* infestation among soldiers during the Leyte campaign in 1944. Its pathophysiology remains unclear. The role of eggs or micro-emboli from the heart (during endomyocardial fibrosis) have been discussed. We report two new cases of brain involvement, complicating the acute invasive phase of schistosomiasis, where the signs point to cerebral vasculitis.

CASE REPORTS

The first patient was a 54-year-old man from Lebanon who had been living in Mali for several years was medically evacuated for confusion. He reported repeated exposure to fresh ground water in the Bamako region. Ten days before evacuation, he developed a high fever (40°C) and received presumptive treatment of malaria with quinine. The fever abated but he complained of disorientation, bewilderment, and irritability, and was diagnosed with a cerebellar syndrome and left hemiparesis. On admission, he was afebrile and had a Glasgow coma score of 9/15, persistent motor paresis, and confusion. There was no neck stiffness, jaundice, skin lesions, or spleen, liver, or node enlargement. His blood eosinophil count was 3,070/mm³ (normal < 500/mm³). The cerebrospinal fluid contained less than 1 cell/mm³, 4.8 mmol/L glucose, and 0.26 g/L protein; no bacteria or viruses were detected. Serologic test results for helminths (fascioliasis, schistosomiasis, filariasis, toxocariasis, trichinellosis, cysticercosis) and protozoa (trypanosomiasis, toxoplasmosis) were negative. Results of stool examination by Ritchie, Kato, and Baërman analysis were negative and the patient still had a lake in the Dogon area of Mali. His eosinophil count was 2,000/mm³, and acute schistosomiasis was suspected. Electrocardiography showed inverted ST waves in leads V3 to V5. The troponin Ic level was normal and cardiac kinetics was regular and homogeneous. Results of echocardiography were normal.

Magnetic resonance imaging (MRI) of the head showed multiple infaracts bilaterally in the cortex and white matter (semioval centrum), suggestive of cerebral vasculitis. Cerebral involvement during the invasive stage of helminthiasis (i.e., trichinellosis, hookworm, strongyloidiasis, ascariasis) was suspected, and albendazole was prescribed (800 mg/day for 5 days) because of its broad spectrum. His neurologic status improved slowly and he was transferred to another unit before being seen again four months later.

Serologic test results for schistosomiasis based on hemagglutination (Cellognost-Schistosomiasis; Chiron-Behring, Marburg, Germany) and indirect immunofluorescence (*Schistosoma mansoni* in-house prepared antigen; Laboratoire de Parasitologie-Mycologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France) were then positive (immunofluorescence 1:320), thus showing seroconversion for schistosomiasis. The other serologic test results for helminths and protozoa were negative and the patient still complained of psychomotor slowing and insomnia. Praziquantel, 40 mg/kg (one dose), was prescribed, but the patient returned to Mali and was lost to follow-up.

The second patient was a 21-year-old French man (tourist) who was hospitalized for persistent myalgias, headache, dry cough, loss of appetite, and fever (38–39°C). One month earlier, he developed a maculopapular rash just after bathing in a lake in the Dogon area of Mali. His eosinophil count was 2,000/mm³, and acute schistosomiasis was suspected. Electrocardiography showed inverted ST waves in lead V4. The troponin level was 13.9 µg/L (normal < 0.2 µg/L). Results of echocardiography were normal. Aspartate and alanine aminotransferase levels were 89 IU/L and 215 IU/L, respectively (normal < 40 IU/L). Multiple stool and urine samples were negative for parasite eggs, larvae, and adult forms. Serodiagnosis of schistosomiasis was positive by indirect immunofluorescence (1:800) (S. mansoni in-house prepared antigen; Laboratoire de Parasitologie-Mycologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France) and by hemagglutination (1:512) (Cellognost Schistosomiasis; Chiron-Behring, Marburg, Germany). Tests for circulating antigen in blood smears were not performed. Treatment with praziquantel (40 mg/kg)
was started. Two days later, he abruptly developed mental confusion, anosognosia, disrupted flow of thought, and splinter hemorrhages under his nails. His temperature was normal. An MRI of the head showed multiple bilateral brain infarcts; they were located in the border zone and were suggestive of cerebral vasculitis (Figure 1). Anticardiolipid antibody titration results were positive (IgM 28 IU, normal < 15 IU). Computed tomography of the heart was normal, with no signs of myocarditis or endomyocardial fibrosis.

Steroid therapy (prednisone, 1 mg/kg) was started, and the symptoms disappeared within 48 hours. Four months later, *S. haematobium* eggs were found by direct microscopic examination of centrifugated urine samples from both the patient and five of his friends who had bathed in the same lake.

**DISCUSSION**

Neurologic complications generally occur in the later stages of schistosomiasis and are caused by a granuloma reaction around eggs or adult forms in the brain. However, neurologic deficits have also been described during the acute phase of schistosomiasis, which is also known as invasive schistosomiasis or Katayama fever. The acute phase occurs 2–6 weeks after bathing in infected waters. It is an uncommon complication: for example, only 2.3% of 1,200 U.S. soldiers with acute schistosomiasis developed neurologic disorders during The Philippines campaign of World War II. In contrast, neuroschistosomiasis can be life-threatening. It has been suggested that these disorders may be caused by cardiogenic cerebral emboli secondary to endomyocardial fibrosis induced by eosinophil toxicity.

We describe here two cases of acute neuroschistosomiasis in which cerebral vasculitis was the most likely cause of the neurologic manifestations. Neurologic complications of acute neuroschistosomiasis potentially include headache, confusion, seizures, loss of consciousness, focal deficiencies, visual impairment, ataxia, urinary incontinence, and motor paralysis. They usually disappear either spontaneously or after steroid therapy. It is interesting that in one of our patients neurologic symptoms occurred early after praziquantel therapy.

The pathophysiology of acute neuroschistosomiasis is unclear. Sarrazin and others incriminated cardiogenic emboli secondary to endomyocardial fibrosis (EMF), but such disease usually occur during prolonged hypereosinophilia. Cerebral MRI showed multiple brain infarcts suggestive of widespread cerebral vasculitis or cerebral embolism in our two patients and also in three previously reported cases. Clinical examination of one of our patients showed splinter hemorrhages, which are another sign of vasculitis, whatever its origin. This sign can be seen during endocarditis and other disorders causing vasculitis.

Other features supporting the responsibility of vasculitis rather than embolism in the onset of neurologic complications are the rapid efficacy of steroid therapy in one of our patients, the onset of cerebral disorders after treatment with praziquantel in the other patient, and the lack of cardiac involvement in both cases. Furthermore, similar clinical and pathophysiological features pointing to microthrombi in cerebral vessels have been described during the course of trichinellosis, another helminthic disease. In addition, in these latter series, there was no parasite larvae in the brain of autopsied patients, and imunoallergic toxicity was the major pathophysiological finding reported to explain these signs.

One striking finding in our two patients, together with the patients with trichinellosis referenced above, was their marked eosinophilia. Recent reports mention the toxicity of eosinophilic granules for endothelial cells. Major basic protein and eosinophilic cationic protein can damage nearby tissues, especially endothelia. Endothelial cells can express adhesion molecules such as platelet activating factor (PAF) and vascular cell adhesion molecule, which attract eosinophils and promote their adherence. Eosinophils also express adhesion molecules such as intercellular adhesion molecule-1 and receptors for PAF, which augment the thrombotic effect.

Major basic protein and peroxide released from eosinophil granules have direct toxicity for endothelial cells and muscle cells of the heart, which potentially results in endomyocardial fibrosis. Signs of cardiac vasculitis and necrosis have been seen at biopsy in patients with EMF. Furthermore, eosinophil-derived neurotoxin is directly toxic for nerve tissue.

Thus, eosinophil-mediated toxicity, leading to vasculitis and small-vessel thrombosis, is the most likely pathophysiological mechanism in acute neuroschistosomiasis. This would explain how acute schistosomiasis with hypereosinophilia can be associated with neurologic deficits in the absence of cardiac involvement. Antibodies to phospholipids and circulating immune complexes could contribute to these complications.

Encephalopathy can occur when circulating eosinophil counts are persistently high, as in idiopathic hypereosinophilia without evidence of EMF. Recent MRI studies of patients with idiopathic hypereosinophilia have shown multiple lesions in the cortical and subcortical regions located in...
arterial junctional territories, a pattern similar to that seen in acute neuroschistosomiasis.\textsuperscript{16} Consequently, acute neuroschistosomiasis should be treated with corticosteroids rather than praziquantel, which can trigger neurologic complications as in our second patient. Furthermore, a clinical deterioration, including neurologic involvement in one patient, has recently been reported in 40\% of 10 patients with acute schistosomiasis treated with praziquantel.\textsuperscript{17} In contrast, corticosteroids can attenuate the neurologic and cardiac toxicity of eosinophils and also the hypersensitivity reaction to parasite toxins.\textsuperscript{6,12} Subsequently, treatment with praziquantel should be postponed until neurologic recovery.

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Authors’ addresses: Stéphane Jauréguiberry, Service des Maladies Infectieuses et Tropicales, Assistance Publique Hôpitaux de Paris, Hôpital Tenon, 4 Rue de la Chine, 75020 Paris, France, Telephone: 33-1-56-01-74-13, E-mail: stephane.jaureguiberry@tnn.aphp.fr. Séverine Ansart, Service de Maladies Infectieuses, Center Hospitalier Universitaire Cavale Blanche, 29609 Brest, France, Telephone: 33-2-98-34-71-91, E-mail: sansart@chu-brest.fr. Lucia Perez, Service de Médecine Polyvalente Unité 53, Center Hospitalier du Mans, 194 Avenue Rubillard, 72000 Le Mans, France, Telephone: 33-2-43-43-25-27, E-mail: lucia.perez@infonia.fr. Martin Danis, François Bricaire and Eric Caumes, Service des Maladies Infectieuses et Tropicales, Assistance Publique Hôpitaux de Paris, Hôpital Pitié Salpêtrière, 47–83 Boulevard de l’Hôpital, 75013 Paris, France, Telephone: 33-1-42-16-01-14, E-mails: martin.danis@psl.aphp.fr, francois.bricaire@psl.aphp.fr, and eric.caumes@psl.aphp.fr.

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