

# First Report of *Schistosoma mekongi* Infection with Brain Involvement

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**We describe, to our knowledge, the first reported case of *Schistosoma mekongi* infection with brain involvement. *S. mekongi* is a distinct species most closely related to *Schistosoma japonicum* that is endemic in a defined area of the Mekong River in Laos and Cambodia and characteristically associated with hepatosplenic disease. The patient had an excellent response to praziquantel therapy but required repeated courses of corticosteroid therapy to suppress recrudescing neurological symptoms.**

**Case report.** A 25-year-old Canadian-born man presented to his local hospital in November 2002 with a 3-week history of headache, nausea, right arm and leg paresthesias, and dysphasia. These symptoms started during a 2-month period in which the patient worked and traveled in Costa Rica and Panama. Previous travel included 2 months in northern Thailand and Laos in 2000. He experienced no illness during his Asian trip other than self-limited diarrhea. His past medical history was unremarkable. The only abnormal findings revealed by physical examination were papilledema and a mild, expressive aphasia. Findings of a complete blood cell count and differential count were normal, with an absolute eosinophil count of  $100 \times 10^9$  cells/L before the initiation of steroid therapy. Glucose and electrolyte levels, urinalysis results, and findings from chest radiography and abdominal ultrasonography were also normal.

CT and MRI of the brain showed 2 contiguous mass lesions (size,  $2 \times 2 \times 2.2$  cm) in the left temporal region, with small areas of hemorrhage and extensive

vasogenic edema, and a much smaller abnormal lesion in the right frontal lobe. A high-grade glioma was suspected, and stereotactic needle biopsy was performed, the results of which showed only "infiltrating plasma cells and lymphocytes, suggestive of encephalitis," as described in the pathology report. During the next month, after each of several attempts to taper and discontinue corticosteroid therapy, the patient required 1 admission to the University of Alberta Hospital (Edmonton, Alberta, Canada) and several admissions to his local hospital, with symptoms of headache, worsening nausea and vomiting, and speech deterioration. On each occasion, he experienced pronounced symptomatic improvement, usually within 24 h after the resumption or increase in dosage of dexamethasone therapy. He was referred back to the neurosurgery service 1 month after his initial presentation, because his condition had not improved. A second MRI showed an increase in the patchy enhancement of the temporal lobe and a marked increase in surrounding edema and swelling (figure 1A and 1B).

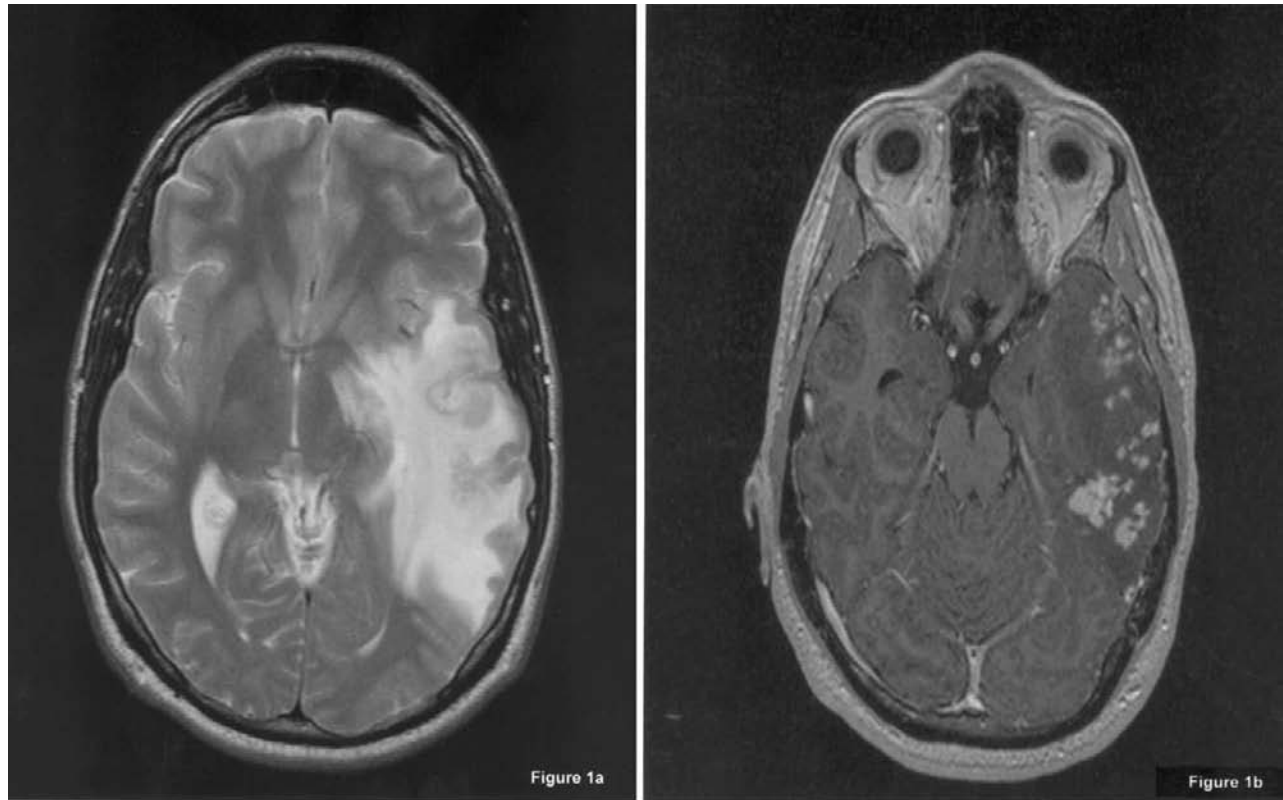
The patient underwent open biopsy of the brain the following day, and examination of a frozen section of the biopsy tissue specimen suggested helminth ova. Pathological examination of the biopsy specimen revealed multiple sclerosing granulomas randomly scattered within the leptomeninges and parenchyma of the brain, with deposits of helminth ova in the center of these granulomas (figure 2). Wet mounts of biopsy

Received 6 June 2003; accepted 18 August 2003; electronically published 8 December 2003.

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**Clinical Infectious Diseases** 2004;38:e1-6

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1058-4838/2004/3801-00E1\$15.00



**Figure 1.** A, Axial T2-weighted MRI of the brain demonstrating extensive abnormal hyperintense signal in the left temporal operculum. B, Contrast-enhanced axial T1-weighted MRI revealing myriad small foci of enhancement throughout the temporal lobe.

specimens showed subspherical eggs with an area of  $54 \times 58 \mu\text{m}$ , which were consistent with *Schistosoma mekongi* (figure 3). A more detailed travel history revealed that the patient had swum in the Mekong River in Laos on 3 or 4 occasions in 2000. Two companions from that trip, both of whom were tested after our patient's diagnosis, were seropositive for schistosomiasis. Our patient's serum was also positive for schistosomiasis (*Schistosoma mansoni* FAST-ELISA, performed at the Centers for Disease Control and Prevention [Atlanta, GA], was positive at 30 activity units, with the positive cutoff being 10 units; the same specimen was also positive for *Schistosoma japonicum* by immunoblot), but examination of a single stool specimen revealed no schistosome ova.

Praziquantel therapy, 60 mg/kg in divided doses, was given, and corticosteroid therapy was continued. The patient was discharged receiving a rapidly tapering dose of corticosteroid therapy but was seen again 2 weeks later with increasing frequency and severity of both headache and nausea. On this occasion, steroid therapy was extended for 6 weeks, at which time the patient was able to tolerate the tapering and discontinuation of therapy without an increase in headache and nausea. A second course of praziquantel, 60 mg/kg, was administered 1 month after the first. Four and one-half months after receiving the first course of praziquantel treatment and 2.5 months after

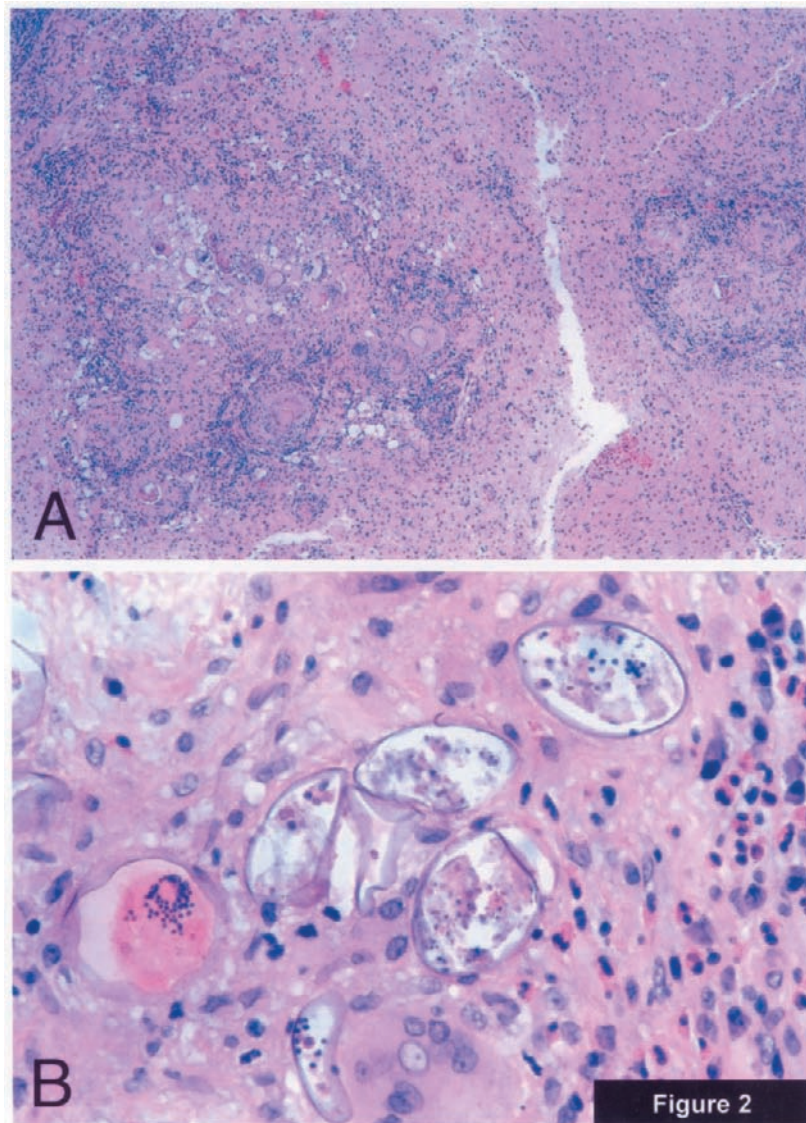
stopping corticosteroid therapy, the patient reported complete resolution of symptoms, findings of a neurologic examination were normal, and an MRI of the brain showed dramatic improvement (figure 4).

## REVIEW AND DISCUSSION

Schistosomiasis, all species of *Schistosoma* included, affects ~200,000,000 people in 77 countries [1]. *S. japonicum* is widely distributed, but is now mainly found in China and The Philippines.

Schistosomiasis was first reported from Cambodia in 1957 [2], but *S. mekongi* was not identified as a separate species until 1978 [3]. *S. mekongi* is most closely related to *S. japonicum* [4] but is differentiated from it by the size of the embryonated ova and by the different species of snail, *Tricula aperta*, that serves as an intermediate host [3]. The distribution of *S. mekongi* is limited to the Mekong River basin in Laos and Cambodia, where some 140,000 people are estimated to be at risk for infection.

The epidemiology and control of this disease were recently reviewed by a team led by Carlo Urbani [5], the physician who died from severe acute respiratory syndrome acquired during the course of his pioneering investigation of that disease. Schis-

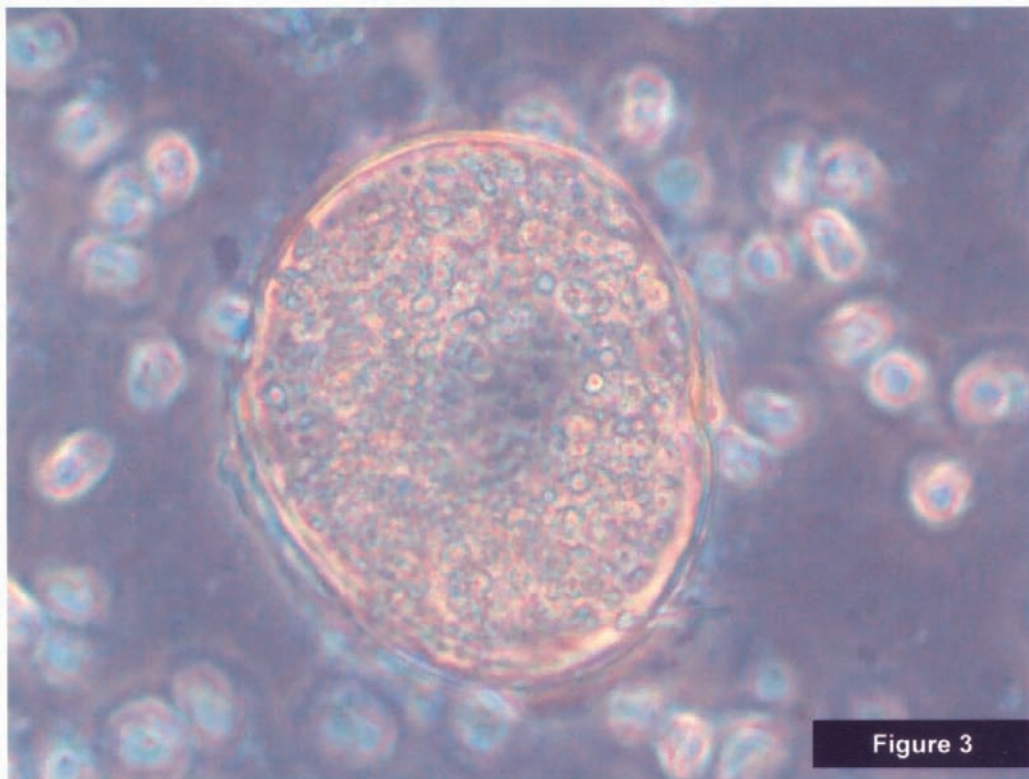


**Figure 2.** Findings from pathological examination of a brain biopsy tissue specimen. *A*, Low-magnification photomicrograph showing nodular granulomas within the parenchyma containing deposits of helminthic ova circumscribed by chronic inflammatory cell infiltrates. (Hematoxylin-eosin stain; original magnification,  $\times 50$ .) *B*, High-magnification photomicrograph demonstrating a cluster of ova in the center of a granuloma. The ova possess a refractile shell but contain disintegrating embryos; one ovum is being phagocytized by a multinucleated foreign body giant cell (*bottom*). *Right*, A mixed inflammatory cell infiltrate of chronic inflammatory cells and eosinophils. (Hematoxylin-eosin stain; original magnification,  $\times 400$ .)

tosomal infection of pigs and dogs has been described, but the epidemiologic importance of these animals has not been established. The prevalence of infection is  $>70\%$  in communities where schistosomiasis is endemic, with a high proportion of infected individuals demonstrating clinical findings attributable to schistosomiasis [6]. Reports of symptomatic disease due to *S. mekongi* describe hepatosplenic disease similar to that seen with *S. japonicum* infection [6]. Control programs based on mass treatment have reduced prevalence in areas in which schistosomiasis is endemic [5].

Spinal cord disease attributable to schistosomiasis has been

documented with *S. mansoni*, *Schistosoma haematobium*, and *S. japonicum* infection [7, 8], although it may be least common in the latter [9]. Brain involvement is uncommonly attributed to infection with *S. mansoni* [7] and, perhaps, even less frequently to *S. haematobium* infection [10]. Gelfand [11] found that ova of *S. haematobium* but not *S. mansoni* were common incidental findings in autopsied brains obtained from infected Zimbabweans. Clinical brain involvement with *S. japonicum* appears to be considerably more common. Among 1049 patients with schistosomiasis admitted to a Shanghai hospital, cerebral involvement was observed in 45 (4.3%) [12]. Neu-



**Figure 3.** Photograph of a wet mount of a brain biopsy tissue specimen showing *Schistosoma mekongi* ovum. (Original magnification,  $\times 400$ .)

rologic symptoms have also been described in patients with acute schistosomal infection [13].

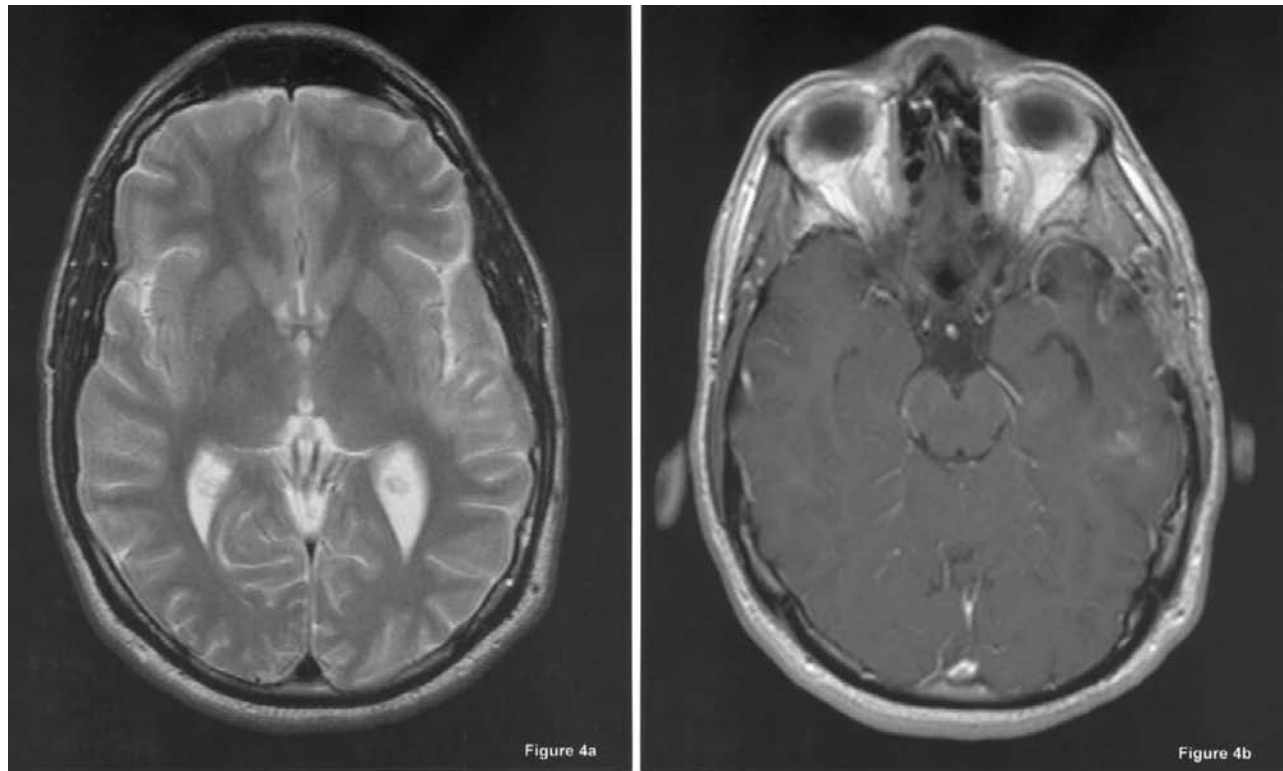
In cases of chronic “tumoral” schistosomal involvement of the brain, the pathophysiologic mechanism is controversial. It has been suggested that embolization of ova may occur from mesenteric or pulmonary sites of adult worm localization, either through vertebral venous plexuses or portosystemic shunts, in patients with advanced hepatosplenic disease [9]. The extraordinary collection of ova in 1 area of the brain in our patient is inconsistent with an anatomically remote source and suggests the ectopic location of a worm pair in the intracranial venous circulation, with local deposition of ova in brain parenchyma. Our patient is extremely unlikely to have had portosystemic shunting because of hepatosplenic disease, in view of his brief exposure to infection, normal ultrasonography findings, and negative findings from a stool examination.

Products actively secreted by schistosome ova provoke a vigorous granulomatous response. This may be particularly prominent in acute infection of a naive host, such as our patient, because down modulation of the response occurs with repeated exposure [14]. With adult worms in their usual anatomical location, this inflammatory process may be important in facilitating passage of ova from mesenteric veins into the intestinal lumen [15]. The inflammatory response is also the main

mechanism of clinical disease in affected patients, whether in the usual sites of involvement—the liver and bowel region—or ectopic sites, as in our patient.

Praziquantel is effective against all species of schistosomes, including *S. mekongi* [16]. Limited available experience suggests that it is also effective against cerebral disease [17]. Praziquantel appears to have been effective in our patient—who has maintained his dramatic improvement at the time of this writing, as demonstrated by clinical and imaging criteria—more than 2 months after stopping corticosteroid therapy. There is evidence from animal models that a prolonged course of praziquantel has an effect on mature schistosome ova, potentially reducing the production of immunogenic secretory products [18]. Richards et al. [18] proposed a 7–10-day course of praziquantel on the basis of their results, but this approach has not been widely adopted in published treatment recommendations.

A single study involving 8 patients, each of whom received a 14-day course of praziquantel for the treatment of cerebral cysticercosis, found a reduction of  $\sim 50\%$  in serum praziquantel levels after the addition of dexamethasone. Both the mechanism and the clinical significance of this interaction are unclear, particularly in the context of single-dose therapy for schistosomiasis [19]. Perhaps of greater concern in treating our patient



**Figure 4.** MRIs of the brain after treatment show almost complete resolution of the abnormal T2 signal (A) and only minor residual enhancement with intravenous gadolinium (B).

was the use of phenytoin, which substantially lowers serum praziquantel levels through hepatic enzyme induction [20]. We administered a second course of praziquantel 1 month after the first in an effort to minimize the risk of treatment failure. Although phenytoin was administered prophylactically by the neurosurgical service throughout the course of our patient's treatment, praziquantel therapy clearly appears to have been effective.

On the basis of the presumed granulomatous mechanism of cerebral involvement and by analogy with other CNS diseases, corticosteroid therapy seems likely to be helpful for reducing the mass effect of tumoral brain schistosomiasis. Corticosteroids can modulate the formation of granulomata [21], but, in certain experimental conditions, they may worsen the outcome of schistosomal infection [21, 22] or the response to treatment [23]. The very limited reported clinical experience appears to support the use of steroid treatment [24]. There have been reports of improvement with administration of corticosteroids only—that is, before the use any specific antiparasitic treatment [25]. Before administration of praziquantel treatment and during the initial weeks after praziquantel treatment was started, our patient had a rapid and striking symptomatic response to corticosteroids on at least 5 separate occasions, with relapse of symptoms when therapy was stopped.

Schistosomiasis was not considered in the differential diagnosis of this patient at presentation to the hospital, perhaps because of a focus on the patient's more recent travel in Central America. Tumor was initially considered the likely diagnosis on the basis of MRI findings. Even if schistosomiasis had been considered earlier in the treatment course, and if specific parasitological and serological studies had been performed, it is unlikely that we would have felt confident in treating him with antischistosomal chemotherapy alone, in the absence of a tissue-based diagnosis. This is because of the serious implications associated with failure to diagnose a neoplasm; because of the substantial likelihood of incidental abnormal results of a stool specimen examination or serological testing, based on his exposure history; and because of the difficulty in assessing a clinical response to praziquantel, because of the major complicating effect of corticosteroid therapy.

We conducted a MEDLINE and Embase search using the subject heading "*Schistosoma mekongi*" and reviewed references from the articles identified for mention of CNS involvement. Similarly, we extensively reviewed the published literature on schistosomiasis of the brain, specifically searching for reference to *S. mekongi* or acquisition of CNS schistosomiasis in Laos or Cambodia. We found no published report of *S. mekongi* infection with brain or spinal cord involvement, nor any reports

of schistosomal brain or spinal cord disease from areas where *S. mekongi* is endemic.

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