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Paucisymptomatic brainstem lesions revealing CNS schistosomiasis

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Abstract

We describe clinical and magnetic resonance (MR) features in a 69-year-old, Caucasian woman presenting with an unusual meningeal onset of cerebral schistosomiasis. Magnetic resonance work-up demonstrated supra- and infratentorial lesions with prominent brainstem involvement contrasting with the paucisymptomatic clinical presentation. Because of a recent stay in Uganda, including swimming in Lake Victoria, a diagnosis of neuroschistosomiasis was suggested. Serological tests and rectal biopsy confirmed the putative diagnosis. The patient was successfully treated with praziquantel at a dose of 50 mg/kg/day for 15 days. Brain MRI abnormalities improved dramatically within two months.

Key words : Cerebral schistosomiasis ; Schistosomia mansoni ; parasitic cerebral disease.

Introduction

Schistosomiasis, also called bilharzia, is a chronic parasitic infestation caused by trematode blood flukes of the flatworm species *Schistosoma* (Liu, 1993). Schistosomiasis is transmitted to humans by skin contact with infested water. It is estimated that around 200 million people harbour this parasitic infestation. The main forms of human schistosomiasis are caused by four species : i. *Schistosoma mansoni*, which causes intestinal schistosomiasis and is prevalent in 52 countries and territories of Africa, the Caribbean, the Eastern Mediterranean, and South America ; ii and iii. *Schistosoma japonicum and Schistosoma mekongi*, which cause intestinal schistosomiasis and are prevalent in seven African countries and the Pacific region ; iv. *Schistosoma haematobium*, which causes urinary schistosomiasis and affects 54 countries in Africa and the Eastern Mediterranean. All, uncommonly, can infect the central nervous system. When they do so, *S. japonicum* usually affects the brain whereas *S. haematobium* and *S. mansoni* more often involve the spinal cord.

We present a rare case of paucisymptomatic cerebral infestation by *S. mansoni*, predominantly involving the medulla oblongata.

Case report

A 69-year-old, right-handed, Caucasian woman with a long medical history of bronchiectasis due to recurrent episodes of pneumoniae between the ages of 13 and 20, was admitted on April 2004 for mild but unusual headaches and dizziness. The symptoms had started one month prior to admission by a “thunderclap” right-sided headache early in the morning resulting in nausea and vomiting. The patient also complained of chronic bronchorrhoea, and took canrenol 50 mg daily for moderate systemic hypertension. Brain CT scan at this time was unremarkable.

The neurological examination on admission was normal, but the patient complained of slight, persistent instability and mild left sided headache. History taking revealed a 4-year stay in Uganda (from 1997 to 2001) during which the patient recalled an isolated episode of bare-foot walking along the muddy bank of Lake Victoria and a swim in the lake.

Contrast-enhanced brain MR examination was abnormal, showing : i : ill-defined left temporal lesions with focal meningeal thickening and abnormal enhancement, together with ‘oedematous’ changes within the adjacent brain parenchyma of the temporal lobe (Fig. 1C), and ii : abnormal T2/FLAIR hypersignal intensity of the medulla oblongata and multiple parenchymal foci of strong contrast-enhancement ; iii : similar changes within the left middle cerebellar peduncle (Fig. 1A, 1B and 1D). Spinal contrast-enhanced MR was normal (not shown).

The cerebrospinal fluid (CSF) was clear and contained two mononuclear cells/µL. No eosinophils were detected. The protein (44 mg/dL) and the glucose (63 mg/dL) levels were normal but the lactate concentration was slightly increased at 3.8 mM/L (N < 2.4 mM/L). Oligoclonal IgG bands were present in the CSF, with a mixed pattern (pattern III in Andersson *et al.*, 1994) : some bands were also present in the serum but several were CSF specific.

The white blood cell count was slightly increased (11210 cells/ µL), with mild hypereosinophilia

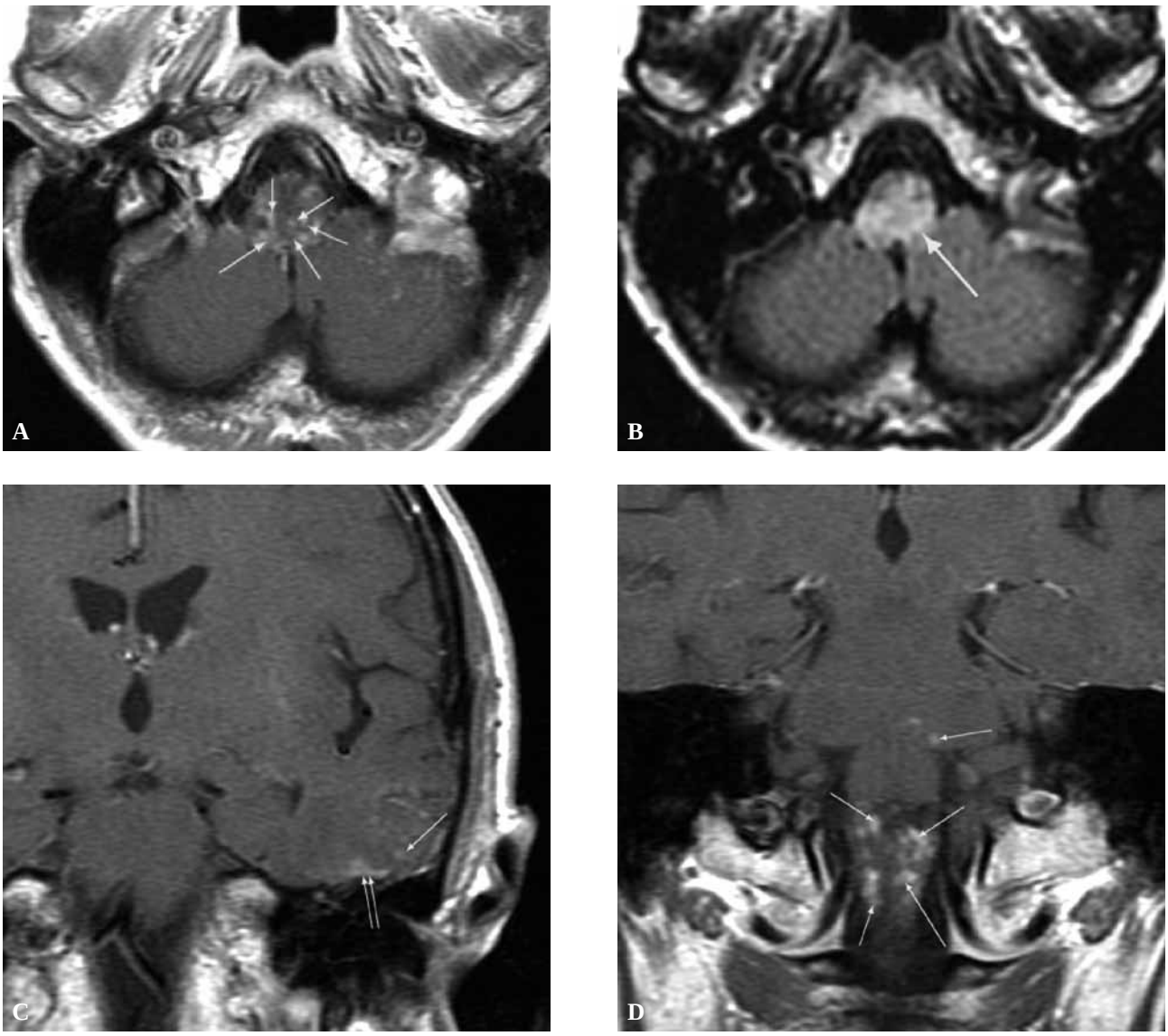

FIG. 1. — Initial magnetic resonance (MR) images at admission. **A** : Contrast-enhanced transverse T1-weighted image at the level of the medulla oblongata showing multiple thin enhanced foci within medullar parenchyma (arrows). Medulla appears slightly swollen ; **B** : FLAIR image at the same slice location as previous image showing abnormal hypersignal intensity within involved parenchyma which reflects oedematous changes (arrow) ; **C** : Coronal post-contrast T1-weighted magnified view showing abnormally enhanced foci within left temporal meninges (paired arrows) and parenchyma (single arrow) ; **D** : Coronal post-contrast T1-weighted view showing the constellation of thin enhanced parenchymal foci within medulla. A few similar foci are seen within the pons (arrows).

at 790/µL (N < 600 /µL). Other blood data were normal : ionogram, hepatic enzymes, coagulation times, haemoglobin, as well as creatinine and blood urea nitrogen.

A Mantoux test was negative.

The following serological tests were also normal or negative : syphilis, borrelia, brucella, legionella, Mycoplasma pneumoniae, toxocara, antinuclear factor and Waaler-Rose.

To exclude systemic sarcoidosis with brain involvement, the patient also underwent a sublingual salivary gland biopsy, which showed no sign of granulomatous disease. A gallium SPECT scan showed bilateral hilar fixation related to the medical history of bronchiectasis with chronic inflammation. Hepatic and cardiac ultrasound scans were normal.

A month after her admission, the results of the serological test for schistosomiasis were available and shown to be positive at 1/320 (Tropical Institute of Antwerp). A rectal biopsy was performed and showed numerous ova of *S. mansoni* with their characteristic lateral spine (Fig. 2).

The patient was treated with praziquantel at a dose of 50 mg/kg/day for 15 days. She also received oral methylprednisolone at an initial dose of 64 mg/day with tapering doses over 15 days. Two months later, the patient was asymptomatic and a follow-up brain MRI showed a complete normalization of the cerebral status (Fig. 3A and 3B).

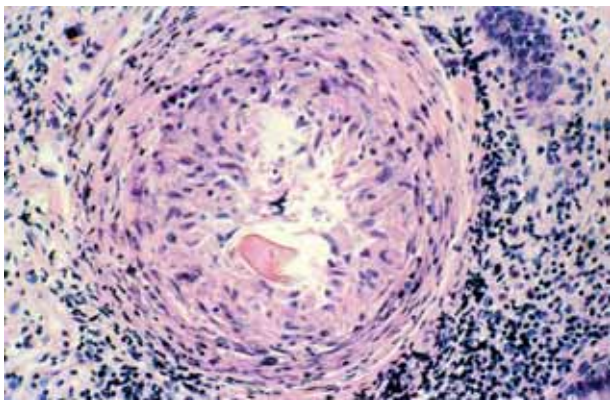

FIG. 2. — *S. mansoni* eggs in the lamina propria of the rectum. Higher magnification (objective × 40) shows a granulomatous inflammatory reaction (Hematoxylin Eosin staining).

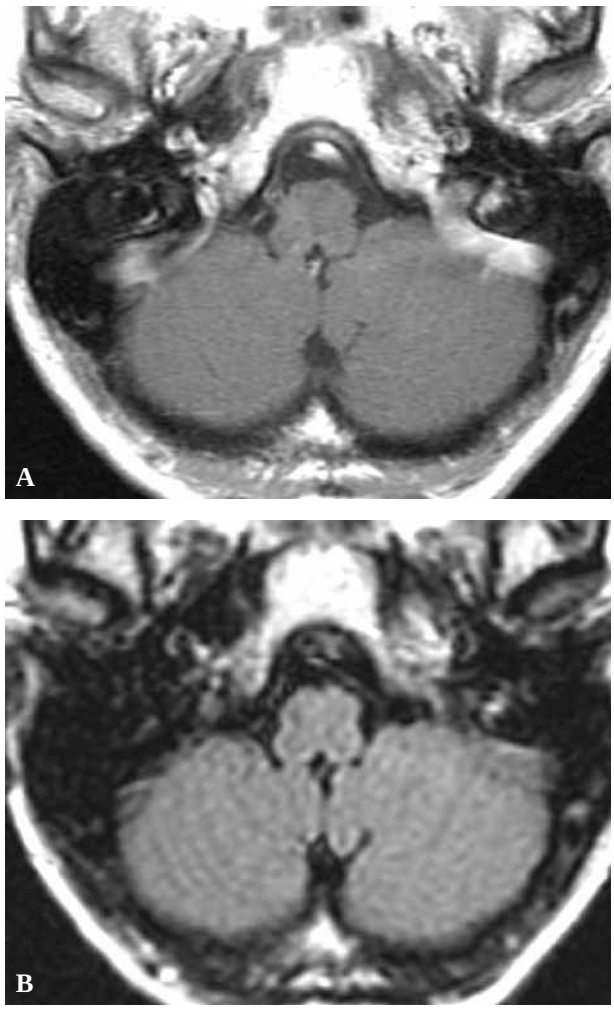

FIG. 3. — Post-treatment MR status at 2 months. **3A & B** : similar slice location and weightings as in Figures 1A and 1B showing complete resolution of the medullar abnormalities ; **3A.** Post-contrast T1-weighted image showing disappearance of any abnormal contrast-enhancement within the parenchyma ; **3B.** FLAIR image showing normalization in size and signal intensity of the medulla oblongata.

Discussion

1. EPIDEMIOLOGY

Schistosomiasis (bilharzia) is a chronic parasitic infestation caused by trematode blood flukes of the species *Schistosoma :* mainly *S. japonicum, S. mansoni and S. haematobium*, the first two causing intestinal and hepatosplenic disease, the latter affecting the urinary tract (Liu, 1993). Though very frequent worldwide, cases of schistosomiasis occurring in Western Europe are imported from endemic areas. Schistosomial infestation is acquired through contact with non-saline water populated by cercariae-infected snails. Cerebral involvement in schistosomiasis is uncommon, particularly in disease caused by *S. mansoni* and *S. haematobium*, due to the shape and size of the ova released by the female schistosomes in the blood flow. Indeed, the ova of *S. mansoni* are larger and it has been suggested that the lateral spine of the ovum impedes its progress along blood vessels. They, therefore, preferentially involve the lower part of the spinal cord. In contrast, the ova of *S. japonicum* are smaller and produced in much greater quantity, which may account for their relatively more frequent deposition in the brain (Scrimgeour and Gajdusek, 1985 ; Liu, 1993). CNS involvement by other species of schistosomes has been reported rarely (Ohmae *et al.*, 2004).

2. NEUROPATHOLOGY

Involvement of the CNS can present at any stage of infestation : in acute schistosomiasis, during evolution of the disease to its chronic form, or concomitantly with the hepatosplenic forms (Pittella, 1991). The acute phase is characterised by a transient clinical syndrome, called the Katayama fever, where neurological symptoms of acute encephalopathy may appear occasionally. This is believed to be an immunological response to the release of eggs or schistosomula, a stage in the evolution of schistosomes (Scrimgeour and Gajdusek, 1985 ; Liu, 1993). In more chronic stages of schistosomiasis, two possible mechanisms of CNS involvement have been proposed :

1/ embolisation of ova from the portal mesenteric system to the CNS via arterial or retrograde venous flow during Valsalva manoeuvres.
2/ In-situ eggs deposition following the abnormal migration of adult flukes, resulting in localized pseudo-tumoral granuloma (Pittella, 1981).

The random distribution of infra- and supratentorial lesions in our case seems to support the first hypothesis of embolisation.

Ova are commonly detected in cerebral tissue of patients with chronic *S. mansoni* and *S. haematobium* infestations ; they are usually asymptomatic. An autopsy-series revealed cerebral involvement in as many as 56% of the autopsied cases with proven

mansoni and/or haematobium schistosomiasis (Gelfand, 1950). A more recent study of 46 autopsy cases of hepatosplenic schistosomiasis in Brazil revealed *S. mansoni* ova in 26% of the brains analysed (Pittella, 1981). Schistosome eggs produce continuous enzymatic and antigenic secretions and induce granulomatous inflammation in infected tissue. The degree of inflammatory response to eggs in the CNS varies with the status of the immune system of the patient. Delayed cell-mediated immunity is an important factor in schistosomiasis (Warren, 1980). However, neurological symptoms can not always be elicited in *S. mansoni* cerebral schistosomiasis because of the random dispersion of eggs and of the slight inflammatory reaction they usually induce (Pompeu and Sampaio de Lacerda, 1979).

Ova can be found almost anywhere in the brain, but mainly in the cerebral and cerebellar hemispheres and leptomeninges. Granulomatous lesions have occasionally been found in the basal ganglia, the choroid plexus, and in the brainstem (Scrimgeour and Gajdusek, 1985 ; Lee, 1995). Large single granulomatous tumoral masses have been described rarely with *S. mansoni*. Pittella *et al.* (1996) reported seven published cases and described four new cases of the tumoral form of cerebral schistosomiasis due to *S. mansoni*. Mass-like lesions can result in life threatening situations (Gjerde *et al.*, 1984) and cases of intraparenchymatous or subarachnoid haemorrhage have been reported (Raso *et al.*, 1964 ; Mattosinho-França *et al.*, 1965 ; Pompeu-Sampaio de Lacerda, 1979).

The MR examination in our patient demonstrated the presence of an ill-defined ambiguous lesion of the left temporal lobe with combined cortico-sub-cortical parenchymal and local meningeal involvement, together with multiple foci of blood-brain barrier breakdown within an oedematous medulla oblongata. The latter were speculated to be responsible for the transient dizziness reported by the patient. Other authors have previously reported ova in the midbrain and in the pons at autopsies of cases with cerebral schistosomiasis (Alemán, 1966 ; Edington *et al.*, 1975 and Gelfand, 1950). To our knowledge, bulbar lesions resulting from *S. mansoni* schistosomiasis have not been described yet in the literature.

3. Diagnosis

Various tests exist to confirm infestation by *S. mansoni*, but the specific diagnosis is often delayed as illustrated in our patient.

Quite often, the combination of thorough questioning about past medical history, stays and trips abroad where the parasites are endemic, with stool, urine, CSF and blood analysis, and contrast-enhanced MR examination may suggest a parasitic infestation, thereby avoiding or postponing the need for brain biopsy. It is important to note that there are no specific clinical findings for cerebral or even spinal cord schistosomiasis.

Blood sampling may reveal eosinophilia but it is quite often absent (Scrimgeour and Gajdusek, 1985 ; Lee *et al.*, 1995). In our case, the absolute number of eosinophils was only slightly increased.

Blankfein and Chirico reported 10 patients with abnormal CSF findings out of 19 cases of acute schistosomiasis. Usually the protein level is under 1g/L (Gjerde *et al.*, 1984) and mononuclear, rarely polymorphonuclear, cells are present (Blankfein and Chirico, 1965). Eosinophils in the CSF are usually absent (Bambirra *et al.*, 1984). Ova have never been found in the CSF, whereas it is frequent to find *S. mansoni* ova in stools ; in cases of *S. mansoni* myelopathy, ova were obtained from faeces in 22% of subjects (Scrimgeour and Gajdusek, 1985). This is explained by the tropism of *S. mansoni* for the rectum (Gutierrez, 1990), eggs breaking out of the vessels into the sub mucosal layer and sometimes escaping in the lumen of the rectum. The detection of *S. mansoni* is based on the typical aspect of its eggs with the classical lateral spine (Fig. 2). It is more common to find classical *S. mansoni* eggs in stool during the acute infestation than in chronic disease. In the latter, a rectal biopsy is preferable (Lee *et al.*, 1993).

Different serological and CSF tests are available including the circumoval precipitin test, haemagglutination immunofluorescence, complement fixation, and ELISA (Enzyme Linked Immunosorbent Assay). The latter is a reliable test to confirm exposure to schistosomiasis.

4. Treatment

Surgical and medical treatments have been proposed, however the optimal method of treatment of cerebral schistosomiasis remains to be determined (Fowler *et al.*, 1999). Oxamniquine, metrifonate, and praziquantel have been used to treat schistosomiasis. These antiparasitic drugs cause death of the adult flukes, thereby interrupting the deposition of ova and thus decreasing the inflammatory response. Their use in non-CNS- *S. mansoni* infestation is well documented. Praziquantel is given as a single oral dose of 40 mg/kg for *S. mansoni* and *S. haematobium* infestations and 60 mg/kg in three doses 4 hours apart for *S. japonicum* infestation. In 1986, Watt *et al.* (1986) treated 9 patients, with seizures caused by cerebral *S. japonicum* infestation, with praziquantel (60 mg/kg) in three divided doses. Eight of them were considered cured after an average of 6 months of radio-clinical follow-up. No adverse reactions were noted, and there was no exacerbation of neurologic signs or symptoms after administration of praziquantel. Therapy-induced reactions to dead worms, as seen in neurocysticercosis, never occur in neuroschistosomiasis and

thus, adjunctive corticotherapy is not mandatory in paucisymptomatic or asymptomatic cerebral schistosomiasis. Although our case seemed minimally symptomatic, we decided to add methylprednisolone to the treatment, to avoid a possible flare-up of the medulla oblongata lesions and a subsequent life-threatening condition. Corticosteroids have been used alone (before a definite diagnosis had been made) or as adjunctive therapy in the treatment of cerebral schistosomiasis, mainly in acute schistosomal encephalopathy and mass lesions resulting in intracranial hypertension. (Kirchhoff and Nash, 1984). Corticosteroids are expected to reduce granulomatous inflammation and oedema avoiding additional tissue damage ; they also seem to impede the deposition of ova, thereby re-enforcing the action of the antiparasitic drugs.

Many questions remain regarding the optimal dose and duration of treatment in the absence of randomised, blinded, and placebo-controlled trials comparing the different treatment options. Although there have been very rare reports of healing of cerebral lesions without any specific therapeutic intervention, the favourable safety profile of praziquantel indicates its use for the treatment of all infested patients (Kirchhoff and Nash, 1984 ; Pollner *et al.*, 1994). Corticosteroids may be helpful in well-selected cases as adjunctive therapy, and should not worsen the infestation, since schistosomes are not opportunistic and are unable to replicate within the human body (Liu, 1993).

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