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Case Report

Early complicated schistosomiasis in a returning traveller: Key contribution of new molecular diagnostic methods

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ABSTRACT

Early schistosomiasis poses a serious diagnostic challenge, because current standard diagnostic techniques based on serology and egg microscopy lack sensitivity at the initial presentation. We report spinal cord neuroschistosomiasis in a traveller developing 6 weeks after exposure. The diagnosis was confirmed by *Schistosoma mansoni*-targeted real-time PCR in blood and cerebrospinal fluid, before the results of conventional methods became positive. Molecular assays represent a paradigm shift for the difficult diagnosis of early schistosomiasis and related complications.

Introduction

Neuroschistosomiasis is a rare, life-threatening or incapacitating condition that usually occurs as a long-term complication following the resolution of the acute invasive disease. However, more rarely it may occur early, overlapping or immediately following the acute phase of the disease (Clerinx et al., 2006; Ahmed et al., 2008). Early schistosomiasis poses a serious diagnostic challenge, because current standard diagnostic techniques based on serology and egg microscopy lack sensitivity at the initial presentation. More accurate diagnosis is essential, since the prompt treatment of neuroschistosomiasis with corticosteroids can prevent debilitating outcomes. More reliable tests including molecular methods are needed to improve the diagnosis of early schistosomiasis and to minimize the risk of complications.

The objective of this study was to report the utility of molecular diagnosis in clinical practice for the early detection of schistosomiasis and related complications.

Case report

In April 2012, a 63-year-old French male spent 1 month travelling in the Ivory Coast, where he went swimming in a lake in the Man Region on May 1. After returning to France, he developed a fever on day 25 after this single freshwater exposure, followed by an elevation in eosinophil count on day 29 (0.87×10^9/l). When seen at the outpatient clinic of the University Hospital of Bordeaux on day 36, he presented with febrile eosinophilia. Apart from the elevated temperature of 38.4 °C, the patient was asymptomatic and the clinical examination was normal. His blood eosinophil count was elevated at 1.41×10^9/l (19.1%), while both ELISA (ELISA Bordier) and an indirect haemagglutination inhibition assay (IHI) (Kit H.A.P Fumouze) for Schistosoma antibodies were negative. Stool and urine microscopy was negative for Schistosoma eggs. Figure 1 depicts the clinical course.

Despite the onset of a mild right-sided lower limb paresthesia on day 39, the patient travelled to Cameroon against medical advice. From day 47, saddle hypoesthesia and urinary retention appeared, followed by bilateral lower limb paresthesia and rapidly progressive paraplegia. The patient was repatriated on day 59.

On readmission, he presented flaccid paraplegia with sensory level loss up to L1, anal hypotonia, and absence of deep tendon reflexes in the lower limbs. Cerebrospinal fluid (CSF) analysis showed an elevated protein content (2.90 g/l) and pleocytosis (79 cells/mm^3) with lymphocytic predominance (94%). Spinal cord

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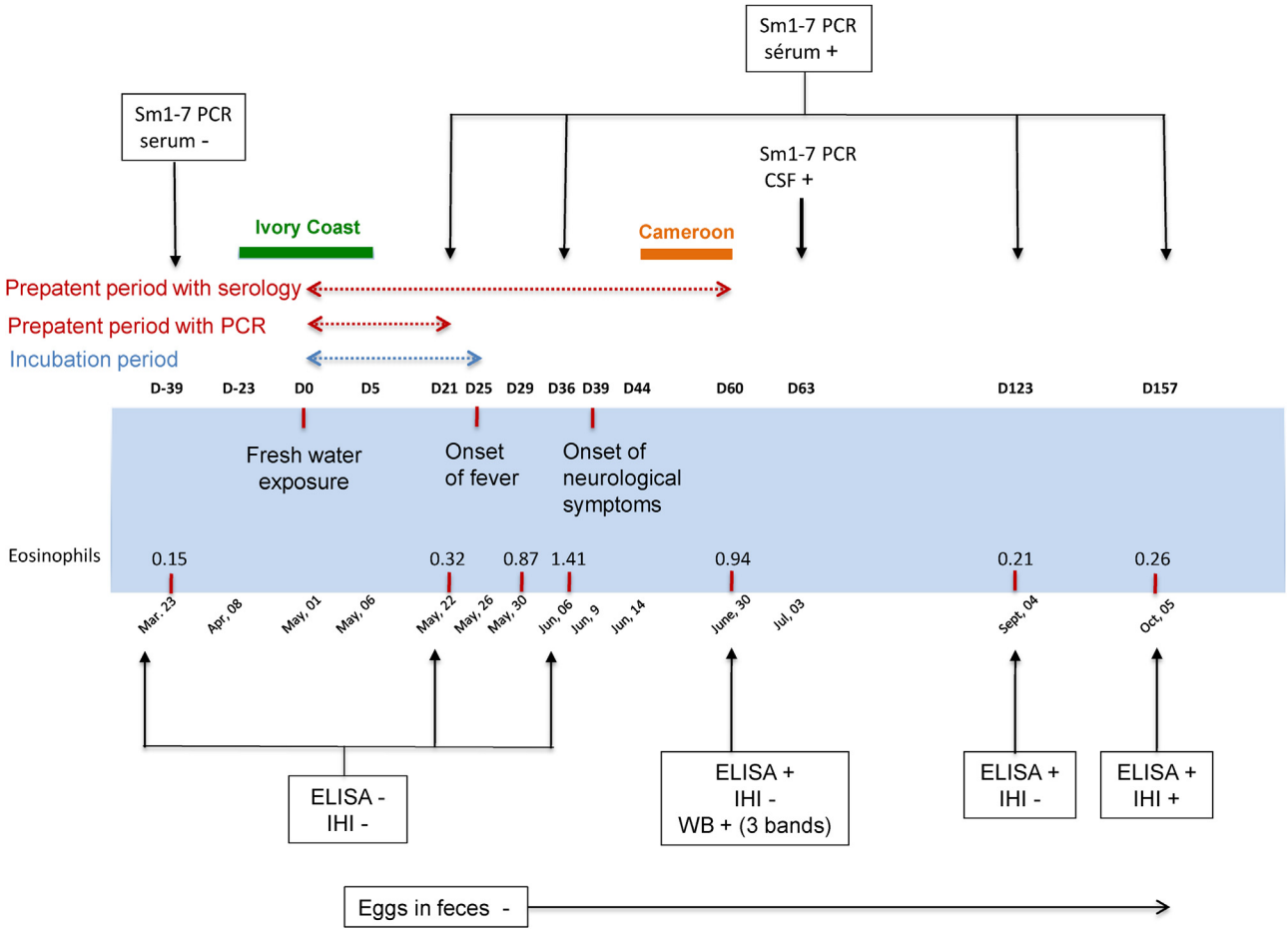

Figure 1. Timelines of symptoms, eosinophilia, serology, and genetic material detection. This timeline highlights the performance of the PCR technique for detecting neuroschistosomiasis associated with an early ectopic lesion. Eosinophils denotes the eosinophil count (number per cubic millimetre); ELISA: enzyme-linked immunosorbent assay; IHI: indirect haemagglutination inhibition assay; PCR: polymerase chain reaction; Sm1-7 PCR targets the Sm1-7 gene of *Schistosoma mansoni* complex species; WB: Western blot IgG (LDBIO Diagnostics).

magnetic resonance imaging (MRI) revealed a hyperintense signal at levels from Th2 to Th8, in T2-weighted sequences, with a heterogeneous diffuse granular enhancement following gadolinium injection, as well as a linear radicular contrast enhancement (Supplementary material, Figure S1). At this stage, the serum schistosome antibody ELISA assay was positive, but the schistosome IHI antibody test remained negative. Again, no Schistosoma eggs were recovered from stool or urine (Supplementary material, Table S1).

The patient was promptly treated with high-dose corticosteroids (methylprednisolone 10 mg/kg, three bolus infusions over 5 days (days 67, 69, and 71), followed by prednisone 2 mg/kg daily for 8 weeks). After 2 weeks of steroids, praziquantel (60 mg/kg in three fractioned doses over 1 day) was given on day 74 to eliminate the matured schistosomes. After a second round of praziquantel and steroids tapered over 4 months, neurological function had not improved despite intense hospital-based rehabilitation. MRI showed a complete resolution of the spinal cord and radicular lesions. When last seen 5 years later, he had suffered from multiple comorbidities due to complete paraplegia sequelae, including several hospitalizations for Fournier's gangrene, necrotic colitis requiring colostomy, and recurrent urinary tract infections due to extended-spectrum beta-lactamase-producing bacterial strains.

Prior to hospitalization, the patient was regularly screened for sexually transmitted infections. Thus, stored serum samples collected prior to as well as during the course of disease were analyzed retrospectively at the Institute of Tropical Medicine, Antwerp, Belgium. Sm1-7 PCR targeting the 121-bp tandem repeat sequence sensitive for *Schistosoma mansoni* complex group described by Wichmann et al. (2009), yielded a consistently positive signal from day 21 onwards. A Dra1-PCR targeting the Dra1 tandem repeat sequence specific for *Schistosoma haematobium* complex group remained negative throughout (Cnops et al., 2013) (Figure 1). This suggests that *S. mansoni* was the infective species involved.

Discussion

=The presence of febrile eosinophilia in non-immune returning travellers with a recent history of freshwater contact should alert physicians to the possibility of a schistosomal infection. Acute symptoms of schistosomiasis typically appear 14 to 60 days after primary infection (Ferrari and Moreira, 2011). As illustrated in this case, the principal challenge is to confirm the diagnosis of acute schistosomiasis at a time when standard diagnostic tests, namely serology and faeces/urine microscopy, are often still negative. In a prospective European-wide multicenter study on 38 patients with acute schistosomiasis, *S. mansoni*-specific real-time PCR in serum was more sensitive (92%) than serology (70%) (Wichmann et al., 2013). A *S. haematobium*-specific real-time PCR in serum has shown promising results for confirming the diagnosis of urogenital

schistosomiasis, but there is a lack of data regarding *S. haematobium* acute schistosomiasis (Cnops et al., 2013).

This patient developed fever and eosinophilia, the hallmark of early invasive infection ('Katayama fever'), soon after exposure, but owing to negative serology, the diagnosis was overlooked at that time; hence a debilitating neurological condition ensued. In contrast, PCR was already positive on day 21 following exposure, even before the onset of fever (day 25) and before the eosinophil count had started to rise (day 29), and well before schistosome serum antibodies could be detected by ELISA and Western blot testing (day 60). This illustrates the excellent diagnostic potential of PCR in the very early stage of infection and its clear superiority over serology and schistosome egg microscopy, both in terms of sensitivity and for early diagnostic confirmation (Wichmann et al., 2009, 2013; Cnops et al., 2012, 2013).

Of note, this patient likely developed spinal cord lesions shortly after schistosome maturation into adult worms and subsequent egg production. Indeed, MRI of the spinal cord showed multiple intramedullary lesions with a granular pattern highly suggestive of an inflammatory granulomatous reaction triggered by eggs embedded in the spinal cord tissue and released by an ectopically migrating pair of adult schistosomes, rather than a vasculitis process. Such a cell-mediated reaction producing peri-ovular granulomas is usually seen during the chronic disease phase. Cases of neuroschistosomiasis appearing during the acute infection stage have been reported only occasionally (Clerinx et al., 2006; Ahmed et al., 2008). The early appearance of spinal cord schistosomiasis offers an argument against deferring anti-schistosomal treatment for too long after primary infection.

Due to the current state of knowledge on schistosomiasis and the emergence of new reliable molecular methods, *S. mansoni*-specific real-time PCR assays should henceforward be considered as the current gold standard for patients with suspected early symptomatic schistosomiasis. In particular, molecular diagnostic methods may considerably reduce the time lapse between infection and diagnostic confirmation, and strengthen post-exposure management of non-symptomatic returning travellers with a recent history of freshwater contact.

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Ethical approval

Approval was not required.

Conflict of interest

All authors report no conflict of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.11.018.

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