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Research Letter

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Improving the diagnosis and management of acute schistosomiasis with antibody, antigen and molecular techniques: lessons from a cluster of six travellers

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Acute schistosomiasis (AS) is a syndrome caused by trematodes of the genus *Schistosoma* and mainly affecting travellers, non-previously exposed to the infection, visiting endemic areas.[1] Although clinical presentation of AS usually consists of mild unspecific symptoms, severe neurological, respiratory and cardiac manifestations can also occur during the acute phase of the infection.[1,2] Besides the potential severity of the disease, diagnosis of AS is still a great challenge. Suspicion is based on clinical presentation, eosinophilia and exposure to contaminated freshwater. Eggs in stools and urine are usually absent at early stages. Thus, microbiological confirmation relies on antibody detection by serological testing, which presents variable sensitivity and specificity depending on the antigen and assay format used.[3] A recently reported presumed hybrid infection between human and non-human *Schistosoma* species, with atypical clinical manifestations and no visible egg production, evidently illustrates the diagnostic challenges faced, including the lack of well-validated and generally available tools to monitor treatment response.[4]

Here, we present a cluster of six travellers with suspected AS. Adult worm antigen-immunofluorescence assay (AWA-IFA, in-house test),[5,6] soluble egg antigen–enzyme-linked immunosorbent assay (SEA-ELISA, in-house test),[5,6] adult worm-derived circulating anodic antigen (CAA, SCAA500, in-house test)[6–8] and Dra1 and Sm1-7 polymerase chain reaction (PCR) were evaluated retrospectively for diagnosis and treatment monitoring.[9,10]

Six 18-year-old Spanish men with no previous medical history experienced symptoms 4–8 weeks after a single swimming event in Chicamba Lake, Mozambique, on 14 July 2019. They presented with dry cough (6/6), fever (5/6), diarrhoea (5/6), headache (4/6), rash (3/6), abdominal pain (2/6), odynophagia (2/6), splenomegaly (1/6) and angioedema (1/6). Eosinophilia (700–8440/mm^3) was detected in all of them 7–10 weeks after water exposure. Given the remarkable respiratory symptoms, a chest CT scan was performed in five patients, showing multiple bilateral pulmonary nodules (≤25 mm) surrounded by ground-glass attenuation (Supplementary Figure S1 available as Supplementary data at *JTM* online). Under the clinical suspicion of AS, five were treated with prednisone (1 mg/kg/day, 6 days) and a single dose of praziquantel (40 mg/kg) at Week 8. Coinciding with steroids withdrawal on Day 6, one patient presented a

Table 1. Evaluation of worm antigen-immunofluorescence assay (AWA-IFA), soluble egg antigen–-enzyme-linked immunosorbent assay (SEA-ELISA), adult worm-derived circulating anodic antigen (serum CAA), Dra1 PCR and Sm1-7 PCR

	Symptoms	Pre-treatment	Post-PZQ (first)	PZQ (second)	1 m post	3 m post	6 m post
Weeks after water exposure	**5**	**7–9**	**13**	**17–18**	**22**	**30–32**	**43–47**
Adult worm AWA-IFA (titre, cut-off: 16)							
Patient 1		1024	512	512		512	128
Patient 2	16	1024		1024		1024	
Patient 3		512	1024	1024	256	512	512
Patient 4		>1024	>1024	>1024	>1024		1024
Patient 5		>1024	1024	512		>1024	1024
Patient 6					256	512	512
SEA-ELISA (titre, cut-off: 32)							
Patient 1		128	512	512		512	128
Patient 2	<32	64		256		256	
Patient 3		64	256	128	128	256	128
Patient 4		>2048	512	512	512		512
Patient 5		64	64	64		128	128
Patient 6					256	256	256
Adult worm-derived circulating anodic antigen (serum CAA) (pg/ml, cut-off: 1 pg/ml)							
Patient 1		30.5	18.9	16.7		0.7	1.3
Patient 2	1.1	108.2		0.5		0.5	
Patient 3		1.3	0.1	0	0	0.1	0
Patient 4		35.6	10.4	18.6	0.1		0.8
Patient 5		6.3	0	0		0	0
Patient 6					0	0	0
Sm1-7 PCR (cycle threshold values)							
Patient 1		31.0	32.8			36.3	
Patient 2		Neg	34.2			37.1	
Patient 3		37.2	34.8			Neg	
Patient 4		32.8	34.3				
Patient 5		33.8	35.5			34.6	
Patient 6						34.5	
Dra1 PCR							
Patient 1		Neg	Neg			Neg	
Patient 2		Neg	Neg			Neg	
Patient 3		Neg	Neg			Neg	
Patient 4		Neg	Neg				
Patient 5		Neg	Neg			Neg	
Patient 6						Neg	

m, months; PZQ, praziquantel.

paradoxical reaction, which consisted of worsening of respiratory symptoms, reappearance of fever, headache, rash, abdominal pain and a remarkable elevation of eosinophil count. For this patient, admission to hospital and prolonged steroids regimen was required. All five patients received a second course of 3 days of praziquantel at 40 mg/kg/day at Week 18–19. The sixth patient, who initially attended another hospital, received only one dose of praziquantel (40 mg/kg) at Week 15. All six cases were followed for 6 months and all of them presented a complete resolution of symptoms and a normalization of eosinophil count (Supplementary Figure S2 available as Supplementary data at *JTM* online).

Regarding routine diagnostic procedures, no *Schistosoma* spp. eggs were found in any of the stool or urine samples, while specific antibodies (Indirect Hemagglutination Assay, Biosynex, Fumouze Diagnostics) were detected in two cases, both of them only after the second dose of praziquantel. This was in contrast to the retrospectively performed AWA-IFA and SEA-ELISA, which demonstrated specific antibodies in all cases, starting at Week 7–9 and remaining positive until Week 43–44. Actually, AWA-IFA was also detected in the only sample obtained 5 weeks after water exposure (Table 1).

Serum CAA was detected (concentration range: 1.3–108.2 pg/ml) in 5/5 patients at Week 7–9 and decreased rapidly following treatment. Only two of the five subjects remained CAA-positive after the first dose of praziquantel (Week 17–18), both showing reduced concentrations (16.7–18.6 pg/ml). Except for one patient, who presented a very low CAA concentration (1.3 pg/ml) 6 months after praziquantel treatment, all patients became and remained CAA-negative during follow-up

(Supplementary Figure S2 available as Supplementary data at *JTM* online).

Serum Sm1-7 PCR showed a positive signal in all patients, revealing an infection with a species of the *Schistosoma mansoni* complex, while the serum Dra1 PCR remained negative at all tested timepoints (Table 1). Since these two tests provided information on the nuclear profile, we also performed a cytochrome oxidase subunit I–PCR to characterize the mitochondrial profile in order to test for the presence of hybrids. This however failed because of the low DNA concentration.[4]

Current diagnostic techniques for AS lack sensitivity and species specificity. At early stages, eggs in stool and urine are commonly absent, and diagnosis relies on clinical suspicion and serology. The use of two different serological tests, such as the indirect hemagglutination and the enzyme immunoassay, has been suggested as a strategy to increase sensitivity.[3] However, about one-third of cases remain undiagnosed at first contact even when serological techniques are combined with microscopy.[3] Also in our cluster, where none of the patients presented eggs in stool or urine, the commercial antibody tests showed a poor performance.

In our cohort, AWA-IFA, SEA-ELISA, serum CAA and Sm1-7 PCR all confirmed the diagnosis of AS at least 7–9 weeks after water exposure, while AWA-IFA and CAA detection even showed a marginally positive result at Week 5. All four tests demonstrated to be accurate tools for diagnosis of AS before 12 weeks, when the worms have fully matured and are most susceptible for treatment with praziquantel.[6–9]

Consistently with previous reports, serum CAA was found to be a sensitive and specific tool not only for early diagnosis but also for monitoring treatment. Given that serological tests and PCR on serum may remain positive for months or even years after treatment, when available, serum CAA should be the method of choice for monitoring treatment of AS in non-endemic settings. Although, more post-treatment studies need to be performed to assure that a serum CAA level below the cut-off value indeed reflects full curation.[6–9]

Serum PCR followed by sequencing allows identification and detection of hybrid infections.[4,5] In our cluster, PCR targeting the nuclear DNA allowed the identification up to the *S. mansoni* complex level.[9,10] However, sequencing of the mitochondrial DNA was unsuccessful because of the low DNA concentration. Therefore, a hybrid infection could not be demonstrated.[10]

In conclusion, AWA-IFA, SEA-ELISA, serum CAA and Sm1-7 PCR proved to be good tools for early detection of AS. Additionally, serum CAA was found to be useful for monitoring treatment and Sm1-7 PCR allowed species identification. The implementation of sensitive diagnostic tools into routine health practice would improve the clinical management of AS.

Supplementary data

Supplementary data are available at *JTM* online.

Authors' contributions

D.C.F., J.M. and L.v.L. designed and co-ordinated the study. D.C.F., L.R., A.A.R., N.R.V., L.B.S., M.B. and C.S. collected the clinical data and study samples. M.V.E., L.J.W., P.T.H., I.M., P.C., N.C.S., M.E.V., M.J.A.M., T.H. and L.v.L. did the laboratory analysis. D.C.F. analysed the data and wrote the article. All authors interpreted the results and critically reviewed the article.

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Conflict of interest

The authors declare no conflict of interests.

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