Schistosomiasis in Belgian Military Personnel Returning From the Democratic Republic of Congo

CPT Annelies Aerssens, MC Belgian Army; Daniel De Vos, PhD*; Jean-Paul Pirnay, PhD*; Cedric Yansouni, MD†; Joannes Clerinx, MD†; Alfons Van Gompel, MD†; SR CPT Patrick Soentjens, MC Belgian Army**

ABSTRACT The detection of schistosomiasis cases among Belgian military personnel returning from a mission in the Democratic Republic of Congo (DRC) prompted a nested case–control study of all military personnel deployed in the DRC between 2005 and 2008 to identify all infections and to start appropriate treatment. Of 197 patients exposed at Lake Tanganyika in the Kalemie area of DRC, 49 (24.9%) were diagnosed with schistosomiasis. Swimming was significantly more frequent than wading in the seropositive group than in the seronegative group (88.9% vs. 73.6%; odds ratio [OR], 2.86; 95% confidence interval [CI], 0.97–9.01). Thirty-one of 49 patients (63.3%) were symptomatic; including skin problems in 34.7%, respiratory symptoms in 12.2%, fever in 14.3%, and 51.0% with gastrointestinal problems. Median eosinophil counts were significantly higher in seropositive patients (375 vs. 138 per μL; Wilcoxon rank sum test [*W*s] = 10,559.00; $p < 0.01$; $r = -0.49$). In total, 20 (40.8%) of the 49 patients were treated for symptomatic infections and the remainder for asymptomatic schistosomiasis. Our study emphasizes the need for active systematic post-tropical screening in military personnel after deployment to *Schistosoma*-endemic regions of the world.

INTRODUCTION

Schistosomiasis is a parasitic disease and a major public health problem affecting more than 200 million individuals annually. The populations at highest risk live in sub-Saharan Africa and South America.[1] In nonendemic countries, the prevalence of imported schistosomiasis is increasing because of increased travel to endemic areas. The Geosentinel Surveillance Network reported 410 cases from 1997 to 2008, of which 83% were acquired in Africa[2] with the risk of infection increasing with travel duration.[3] The TropNetEurop surveillance system reported 88 cases of imported schistosomiasis in Europe during 2007, of which 52 (59.1%) were asymptomatic. More than 10% of these cases developed after various periods of stay in the Democratic Republic of Congo (DRC).[4]

Clusters of schistosomiasis among military personnel returning from endemic tropical areas have been reported throughout the last decades. In 1987, 113 French military personnel developed schistosomiasis during or after deployment in the Central African Republic.[5] In 1995, 26 Brazilian military personnel became ill after deployment in Mozambique[6] and more recently, in 2005 and 2006, 13 French military personnel were infected during operations in Ivory Coast.[7]

There are five principle *Schistosoma* species pathogenic to humans: *S. haematobium*, *S. mansoni*, *S. intercalatum*, *S. japonicum*, and *S. mekongi.* The first two species are responsible for the vast majority of schistosome infections reported in travelers and expatriates. Infection occurs through skin contact with cercaria-contaminated freshwater. Infection with schistosomes may produce three distinct clinical syndromes[8]: cercarial dermatitis or "swimmers itch," acute schistosomiasis or Katayama syndrome, and chronic schistosomiasis. Katayama syndrome usually appears 3 to 8 weeks after infection with a sudden onset of an urticarial rash, low-grade fever, nonproductive cough, and/or abdominal discomfort, and an elevated eosinophil count (>1,000 cells/mm^3), which is said to be universally present.[9] Katayama syndrome is most often observed among nonimmune persons with infections with *S. mansoni* or *S. hematobium*. Because of its asymptomatic or nonspecific presentation, infections are often unsuspected in returning travelers[9] and may evolve into chronic disease.[10] Further, since schistosomiasis may also cause serious pathology, including severe neurological symptoms, exposed but asymptomatic travelers require screening for infection and treatment of schistosomiasis to prevent subsequent disease.[11]

We conducted a nested case–control study of Belgian military personnel returning from missions in the DRC between 2005 and 2008, in which they were exposed to freshwater. The first aim of the study was to identify symptomatic and asymptomatic cases of schistosomiasis to ensure appropriate treatment and to avoid late complications. The second aim was to explore risk factors associated with schistosomiasis.

MATERIALS AND METHODS

Patient Recruitment

From September 2005 to December 2006, a total of 280 Belgian soldiers were deployed in Kalemie, DRC, along the west coast of Lake Tanganyika (5°56′S 29°12′E). Although water from Lake Tanganyika was filtered through a high performance water purifying system that produced safe water

*Military Hospital Queen Astrid, Bruynstraat 1, 1120 Brussels, Belgium.
†Institute of Tropical Medicine, Kronenburgstraat 43/3, 2000 Antwerp, Belgium.

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for daily use, exposure to unfiltered fresh water from the lake was common, during both professional and leisure activities. Despite being briefed on medical risks related to a stay in a tropical area by means of a lecture before departure, a cluster of three patients was identified in December 2006 with symptoms of intestinal schistosomiasis after exposure to freshwater of Lake Tanganyika.[12] Therefore, all military personnel deployed in Kalemie (N = 280) and others, if they had been deployed in other parts of Congo for more than 1 month between 2005 and 2008 (N = 502), were requested to complete a questionnaire, which assessed their exposure to potentially contaminated fresh water during missions in Africa. When exposure was suspected, personnel were seen at the Travel Clinic of the Military Hospital, Brussels, for testing under a human use protocol approved by the Ethical Committee, Brugmann University Hospital, Brussels. During the visit, exposure and symptoms were further explored through a second questionnaire. This procedure was standardized and executed by a team of two medical doctors.

Laboratory Methods

Diagnosis of *Schistosoma* infection was based on two serologic tests: (i) an enzyme-linked immunosorbent assay (ELISA) using a *S. mansoni* egg antigen extract mixed with *S. mansoni* adult worm extract imported from Egypt and (ii) an indirect hemagglutination assay (IHA) titration using an *S. mansoni* adult worm extract (commercial test; Fumouze SA, France) with a cut off dilution of 1:80 (i.e., positive at titer ≥1:160). The combined use of these test results provided a reported detection sensitivity of 100% for *S. mansoni* and *S. haematobium* and 90.0% for Katayama fever, with a specificity of 92.9% in imported schistosomiasis.[13,14]

Additional laboratory tests consisted of a full blood cell count, an eosinophil count, a quantification of serum glutamic pyruvate (SGPT) and serum oxaloacetic transaminase (SGOT), quantification of C-reactive protein (CRP), erythrocyte sedimentation rate, and immunoglobulin E (IgE) response. Finally, one unconcentrated stool sample for each patient was examined (microscopy) for parasite ova. Additional investigations and imaging studies were only performed when indicated. Serologic testing was conducted at the Institute of Tropical Medicine in Antwerp, Belgium; all other tests were performed at the Queen Astrid Military Hospital in Brussels, Belgium.

Case Definition

A positive serologic test (ELISA and/or IHA) more than 3 months after exposure was considered a definitive proof of infection. If the period since last exposure was less than 3 months, testing was repeated at least 3 months after exposure. Patients were followed for at least 1 year after a positive diagnosis. Follow-up visits for symptomatic patients were scheduled at 2 and 6 weeks and after 3, 6, and 12 months. Asymptomatic patients had a follow-up visit at 3 and 12 months, or earlier if they became symptomatic after treatment.

Treatment of Patients

Symptomatic patients were treated for acute schistosomiasis for 3 days with praziquantel (40 mg/kg body weight/day with a maximum of 2,400 mg/d) and corticosteroids (methylprednisolone, 16 mg/d orally), and retreated 1 month later with an additional single dose of praziquantel. Asymptomatic seropositive patients were treated with a single dose of praziquantel (40 mg/kg body weight orally).

Statistics

Data were entered in EpiData software (EpiData version 3.1; January 27, 2008) and analyzed with the statistical package SPSS 15.0 (SPSS, Cary, North Carolina). OR with 95% CI were calculated to compare univariate risk factors between seropositive and seronegative patients. Statistical significance was based on Pearson's χ^2 test whenever appropriate and Fisher's exact test in all other cases. Comparison of continuous measurements was based on the *W*s because of the nonnormal distribution of the data. A two-sided p value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 444/782 (56.8%) soldiers deployed to Congo during the study period completed the questionnaire. A total of 215/280 (76.8%) of the military personnel deployed in Kalemie completed the questionnaire, of which 197 (91.6%) reported exposure to the fresh water from the Lake Tanganyika, a known risk area for schistosomiasis. Forty-nine (24.9%) of the 197 persons reporting exposure to fresh water met our case definition of schistosomiasis. Thirty-three of 49 (67.3%) were seropositive by both ELISA and IHA, whereas 9/49 (18.4%) and 7/49 (14.3%) were seropositive by either ELISA or IHA, respectively. Of the military deployed in other parts of the DRC, only 229 (45.6%) completed the questionnaire with only 43 (18.8%) reporting exposure to fresh water and none of the 43 testing positive for schistosomiasis. Therefore, further analysis was performed only for the Kalemie group (n = 197) (Fig. 1). This focus was further justified by the fact that Lake Tanganyika was identified as a potential source of schistosome infections in the initial cluster of three patients. One patient with a positive serologic test who was born and resided in the DRC until the age of 16 was excluded from the study.

Exposure characteristics, laboratory findings, and clinical symptoms during and/or after deployment in Kalemie were compared between seronegative and seropositive soldiers.

Median duration of stay was 4.0 months for the seropositive group (interquartile range 3.0), compared with 3.0 months for the seronegative group (interquartile range 1.0) (*W*s = 13,319.50; $p < 0.01$; $r = -0.25$). Median age was 38.5 years (interquartile range 9.0) in the seropositive group, compared with 41.0 years of age (interquartile range 10.0) in the seronegative group (*W*s = 4,068.50; $p = 0.03$; $r = -0.16$). The median time from exposure to diagnosis for the seropositive group was 768 days (interquartile range 230).

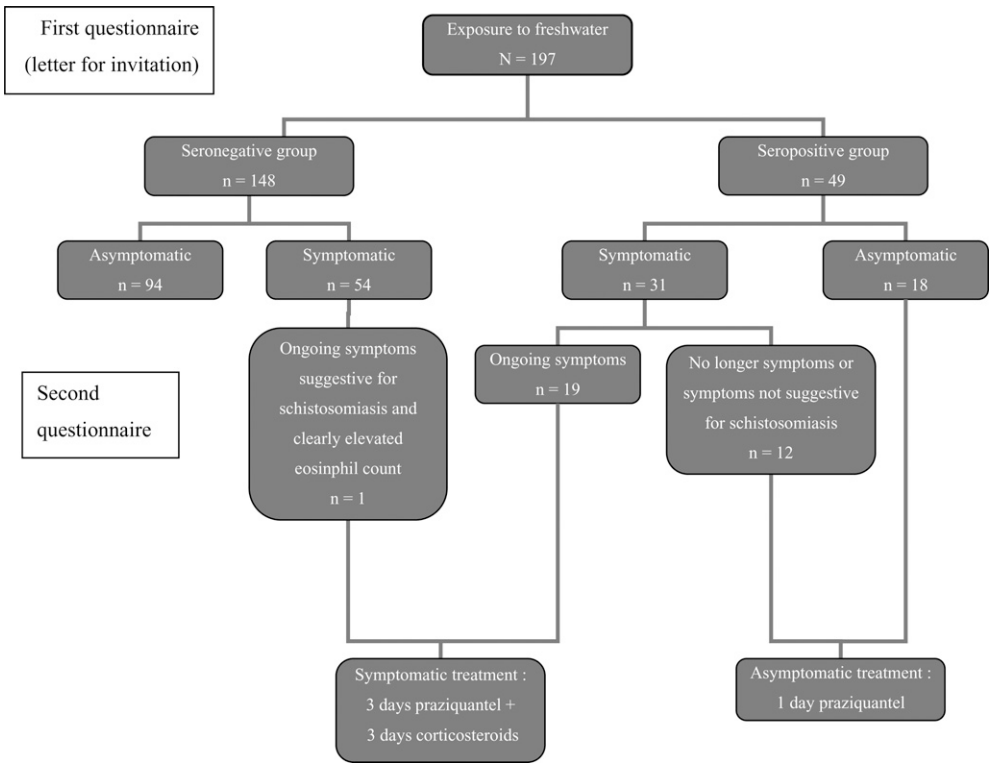

FIGURE 1. Flowchart diagram for enrolled patients.

TABLE I. Characteristics of Exposure

	Seropositive Group		Seronegative Group			
	n = 49	%	*n* = 148	%	OR (95% CI)	*p* Value
Frequency of Exposure						
Frequent	39	81.2	103	72.0		
One or Few Times	9	18.8	40	28.0	1.68 (0.70–4.12)	0.254
Purpose						
Work Related	30	61.2	69	47.9		
Recreational	19	38.8	75	52.1	1.72 (0.84–3.51)	0.107
Access to Water						
Beach	47	95.9	140	94.6	1.34 (0.25–9.51)	0.682
Vegetation	6	12.2	15	10.1	1.24 (0.40–3.69)	0.604
Pontoon	8	16.3	25	16.9	0.96 (0.37–2.46)	1.00
Swimming vs. Wading						
Swimming	40	88.9	95	73.6		
Wading	5	11.1	34	26.4	2.86 (0.97–9.01)	0.038
Previous Exposure						
Yes	11	26.8	26	18.8		
No	30	73.2	112	81.2	1.58 (0.65–3.81)	0.267

Exposure to fresh water habitats ranged from a single exposure to daily contact during deployment in both groups. Swimming was significantly more frequent than wading in the seropositive group than in the seronegative group (88.9% vs. 73.6%; OR, 2.86; 95% CI, 0.97–9.01). There were no significant differences observed between the seropositive and the seronegative group in work-related exposure (61.2% vs. 47.9%; OR, 1.72; 95% CI, 0.84–3.51), in the way freshwater was accessed (e.g., via the beach: 95.9% vs. 94.6%; OR, 1.34; 95% CI, 0.25–9.51), and previous exposure (26.8% vs. 18.8%; OR, 1.58; 95% CI, 0.65–3.81) (Table I). Patients were asked about symptoms associated with schistosomiasis that may have occurred during or after deployment from the time of exposure until the first consultation (Table II). Of the 49 seropositive patients, 63.3% developed symptoms compared with 36.5% in the seronegative group (OR, 3.00; 95% CI,

TABLE II. Clinical Symptoms

	Seropositive Group		Seronegative Group			
	n = 49	%	*n* = 148	%	OR (95% CI)	*p* Value
Skin	17	34.7	20/148	13.5	3.40 (1.50–7.72)	0.001
Generalized Itch	7		7/137			
Itchy Legs	12		14/141			
Rash	6		6/141			
Respiratory	6	12.2	11/148	7.4	1.74 (0.53–5.48)	0.377
Dyspnea	4		6/140			
Cough	3		6/141			
Gastrointestinal	25	51.0	45/148	30.4	2.38 (1.17–4.87)	0.009
Abdominal Pain	11		22/141			
Diarrhea	22		39/142			
Nausea/Vomiting	9		13/141			
Fever	7	14.3	9/148	6.1	2.57 (0.80–8.15)	0.077

TABLE III. Laboratory Findings

	Positive Serology (*n* = 49)		Negative Serology (*n* = 148)			
	Median	Interquartile Range	Median	Interquartile Range		*p* Value
Sedimentation	5.00	4.00	3.00	4.00		0.012
CRP	0.15	0.17	0.10	0.16		0.052
SGOT	23.00	9.00	24.00	8.00		0.874
SGPT	25.00	14.00	26.50	19.00		0.447
IgE (kIU/L)	95.80	594.20	38.40	72.1		<0.01
Eosinophil Count (n/μL)	375.00	405.00	138.00	112		<0.01
Levels of Eosinophil Count (n/μL)	*n*	%	*n*	%	OR (95% CI)	
<600	32	68.1	136	99.3	0.02 (0.00–0.12)	<0.01
600–1000	9	19.1	0	0		
>1000	6	12.8	1	0.7	19.90 (2.26–451.54)	<0.01
Eggs in Feces	3/34					
Biopsy Colonic Mucosa	1/2					

1.46–6.20). Skin problems (generalized itch, itch on the legs, rash, and/or urticaria) (OR, 3.40; 95% CI, 1.50–7.72) and gastrointestinal symptoms (abdominal pain, diarrhea, nausea, or vomiting) (OR, 2.38; 95% CI, 1.17–4.87) were significantly more frequently reported in the seropositive group than in the seronegative group. Respiratory symptoms (dyspnea or cough) and fever were reported more frequently in the seropositive group, but the difference did not reach significance.

A total of 19/49 (38.8%) of the patients were treated for ongoing symptomatic infections, whereas the remaining 30 (61.2%) were treated as asymptomatic cases when symptoms did not occur at time of diagnosis or when symptoms could not be linked to an acute or late schistosome infection (Fig. 1). Symptoms appearing after taking praziquantel were reported by 9/49 (18.4%) of the seropositive patients. Six reported one or more gastrointestinal problems (diarrhea, abdominal discomfort, nausea, and/or vomiting), two reported skin problems (generalized itch and urticaria), and one reported headache. Of the 19 symptomatic patients who received treatment (praziquantel and corticosteroids for 3 days, as described earlier), 16 were retreated at follow-up 1 month later (Fig. 1). The three patients who did not receive a second dose of praziquantel were seen before the implementation of the study protocol. Two seropositive patients in the asymptomatic group demonstrated symptoms compatible with schistosomiasis after receiving a single dose of praziquantel and were subsequently provided treatment with the symptomatic group's regimen.

An overview of the laboratory findings at the time of diagnosis is provided in Table III. The median eosinophil counts were significantly higher among the seropositive group (375 vs. 138 /μL; *W*s = 10,559.00; $p < 0.01$; $r = -0.49$). Of the 19 symptomatic seropositive patients, only nine (47.4%) had an elevated eosinophil count. IgE levels were significantly elevated in the seropositive group compared with the seronegative group (95.80 vs. 38.40 kIU/L; *W*s = 11,111.00; $p < 0.01$; $r = -0.30$). *S. mansoni* eggs were detected in the feces of 3/34 (8.8%) stools examined. Biopsy of colonic mucosa performed in two patients detected *Schistosoma* eggs in one. No significant differences were observed between seropositive and seronegative patients for CRP, sedimentation, and liver function tests (SGOT and SGPT).

DISCUSSION

Belgian military personnel who deployed to tropical regions of the world are at risk for acquiring parasitic infections and associated diseases not endemic to Belgium. The detection of

a first cluster of three patients diagnosed with schistosomiasis implicated Lake Tanganyika, DRC, as the source of infection. This nested case–control study identified a large cluster of schistosome infections and confirmed a strong association between schistosomiasis and military and recreational activities near Lake Tanganyika. Particular exposure characteristics, symptoms, and general laboratory screening tests were nonspecific and did not provide sufficient data for the diagnosis of schistosomiasis among military personnel returning from the tropics. The first cluster of three patients presenting with Katayama syndrome focused attention on the risk of acquiring schistosomiasis in the Kalemie area. Subsequent active case detection in exposed military personnel revealed a sizeable proportion of infected persons, who were asymptomatic or presented with only mild symptoms. These symptoms (i.e., skin problems, fever, gastrointestinal and respiratory symptoms) may have been caused by other environmental factors (i.e., dry and dusty environment or food-borne infections). Because patients were questioned in retrospect, the occurrence of mild symptomatic infections may have been underestimated.

Serology and eosinophil counts are significant markers for the diagnosis of schistosomiasis and are related to disease activity and the stage of infection.[9,10,15,16] However, in this study, the eosinophil counts were not sensitive enough to suspect or to rule out infection in the majority of patients who were asymptomatic or who had only minor symptoms at the time of diagnosis. Variations in disease clinical manifestations and delay between exposure and diagnosis may account for the much higher proportion of patients with high eosinophil counts as reported by Meltzer et al[10] (73%) and Agbessi et al[17] (82%).

Serologic antibody tests are used as the primary tool for diagnosis of schistosome infections among asymptomatic persons. Combining several tests using different *Schistosoma* antigens (adult worm and egg antigens) yielded better results than relying on a single test. The combination of two tests (ELISA and IHA), as proposed by Van Gool et al[14] and used by Bottieau et al,[13] illustrates this point unequivocally by increasing sensitivity to >90%, both in recent and in established infection, while retaining specificity >97%.[14] Our study confirms this substantial gain in sensitivity: 14.3% of the patients with schistosome infections would have been missed using only the ELISA and 18.4% would have been missed using only the IHA. The added value of an ELISA when using an IHA has been disputed,[9] but antigen choice and the disease stage of patient may account for differences in diagnostic yield.

Stool microscopy (without concentration technique) was not sensitive for schistosomiasis, with only 8.8% (3/34) positive for ova. These results are similar to those of Agbessi et al,[17] who stated that eggs in feces are of no use as a diagnostic tool among nonimmune travelers because of the low levels of infection.

It is not surprising that the median time to diagnosis was 768 days. This is a consequence of the absence or the mild nature of disease in the vast majority of infected persons. This study demonstrated that Katayama syndrome was missed in some of the patients because of nonspecific presentation and that many physicians are unfamiliar with the disease.[9,10] Therefore, active systematic serologic screening of exposed asymptomatic persons is the only way to detect unapparent infections and to prevent late-stage disease through early treatment.[9,11]

The most important prevention for infection with schistosomiasis is to avoid exposure to freshwater in tropical areas. Belgian military personnel who deployed in the tropics receive a briefing on the most prevalent medical risks in the tropics and on the importance of preventive measures. Although schistosomiasis is one of the topics of this premission lecture, it is clear that it did not prevent exposure and infection. Reasons for exposure were numerous: collecting water for daily use, diving, instruction on the lake for pioneers and Special Forces, and recreational swimming. It is clear that some of the exposure to fresh water can be avoided, but not all, e.g., collecting lake water for sanitary use. Therefore, other means for prevention should be considered: repellents, mechanical barriers, and/or pre- or postexposure prophylaxis, bearing in mind the climatological conditions. Mechanical barriers described to have a protective effect are vigorous toweling of the exposed skin directly after contact, using insect repellent with N,N-diethyl-m-toluamide (preferably 50%), and putting on tight dry diving suits.[18] Chemoprophylaxis, both with praziquantel and artemisinin derivatives, is promising but not yet been proven to be effective.[19,20] In endemic populations, it has been shown that artemisinin can limit *S. mansoni* infections, but it is not clear to what extent it may be effective to prevent Katayama syndrome in nonimmune persons.[21] More studies are required to identify effective methods for prevention.

In conclusion, our study emphasizes the need for active systematic post-tropical screening in military personnel after deployment to *Schistosoma*-endemic regions of the world. Exploring exposure to parasite-contaminated environments and behavior are important information to augment specific tests to this screening. Registration of accurate risk exposures during and shortly after missions among deployed military personnel should be done. In addition, preventive medicine training and use of protective measures require command emphasis at all levels.

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