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Schistosomiasis in Norwegian students after travel to Africa

ORIGINALARTIKKEL

TRYGVE KRISTIANSEN

E-mail: trygve.kristiansen@helse-bergen.no

Norwegian National Advisory Unit on Tropical Infectious Diseases

Unit for Infectious Diseases

Department of Medicine

Haukeland University Hospital

and

Department of Microbiology

Haukeland University Hospital

He has contributed to the concept and design, to data collection, analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Trygve Kristiansen is a specialist in internal medicine.

The author has completed the ICMJE form and declares no conflicts of interest.

FRANK OLAV PETTERSEN

Regional Advisory Unit for Imported and Tropical Diseases

Department of Infectious Diseases

Oslo University Hospital, Ullevål

He has generated ideas, and has contributed to the concept and design, to data collection, analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Frank Olav Pettersen, PhD, is a senior consultant and specialist in infectious diseases and medical microbiology, and head of unit.

The author has completed the ICMJE form and declares no conflicts of interest.

TORE LIER

Department of Microbiology and Infection Control

University Hospital of North Norway, Tromsø

and

Public Health Agency of Sweden

He has contributed to the concept and design, to data analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Tore Lier, PhD, is a senior consultant and specialist in medical microbiology. He is head of the National Reference Laboratory for the Serological Diagnosis of Parasitic Infections and is in charge of parasitology for the Public Health Agency of Sweden.

The author has completed the ICMJE form and declares no conflicts of interest.

SVEN GUDMUND HINDERAKER

Centre for International Health

University of Bergen

He has generated ideas, and has contributed to the concept and design, to data collection, analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Sven Gudmund Hinderaker, MD PhD, is a professor.

The author has completed the ICMJE form and declares no conflicts of interest.

GOTTFRIED GREVE

Department of Clinical Science
Faculty of Medicine
University of Bergen
and

Department of Heart Disease
Haukeland University Hospital

He has contributed to the concept and design, to data collection, analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Gottfried Greve, MD PhD, is a professor, senior consultant and head of section.

The author has completed the ICMJE form and declares no conflicts of interest.

KRISTINE MØRCH

Norwegian National Advisory Unit on Tropical Infectious Diseases

Unit for Infectious Diseases

Department of Medicine

Haukeland University Hospital

and

Department of Clinical Science

Faculty of Medicine

University of Bergen

She has generated ideas, and has contributed to the concept and design, to data collection, analysis and interpretation, to the literature search, and to the drafting and revision of the manuscript.

Kristine Mørch, PhD, is a senior consultant and specialist in infectious diseases, and an associate professor. She is head of the Norwegian National Advisory Unit on Tropical Infectious Diseases at Haukeland University Hospital.

The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND

Schistosomiasis is a tropical infectious disease in which early diagnosis and treatment can prevent serious illness. This study examined the incidence and diagnosis of schistosomiasis in Norwegian exchange students who had been exposed to freshwater in Africa.

MATERIAL AND METHOD

Students ($n = 318$) from Bergen and Oslo who had travelled to Africa as part of an exchange programme in the period 2003–18, were contacted and included in the study if they had been exposed to freshwater during their stay. A routine workup was performed comprising *Schistosoma* antibody testing, microscopy and/or PCR analysis of urine and faeces, dipstick urinalysis, and blood samples for analysis of eosinophilic granulocytes, creatinine and total IgE. Time, place and type of exposure were recorded in a questionnaire, along with symptoms.

RESULTS

Schistosoma antibodies were detected in 46 (30%) of the 151 students included in the study. None of the seropositive individuals had eggs detected in their urine or faeces, and none had eosinophilia. Two students reported cercarial dermatitis, while one had symptoms consistent with acute schistosomiasis. Rafting was the only form of freshwater exposure reported by 22 (55%) of the 40 seropositive individuals.

INTERPRETATION

A large proportion of the students who had been exposed to freshwater were diagnosed with schistosomiasis. The majority reported no symptoms. Rafting was the most common form of exposure. All were diagnosed by serologic tests, while other routine diagnostic tests for schistosomiasis proved less useful. Serological analysis should be the preferred form of testing for the diagnosis of schistosomiasis in travellers.

Schistosomiasis is a parasitic disease caused by blood flukes of the genus *Schistosoma* (1). The six main species that cause disease in humans are *S. haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum*, *S. guineensis* and *S. mekongi*. Humans become infected through contact with freshwater containing parasites in a motile larval form (cercariae) that can penetrate intact skin. The adult worms colonise veins around the bladder and intestines and produce eggs that are either retained in the tissue or excreted into the surrounding environment. Humans are the definitive host for *S. haematobium* and *S. mansoni*, whereas infections with *S. japonicum*, *S. intercalatum*, *S. guineensis* and *S. mekongi* are zoonoses (2). When eggs present in urine or faeces reach freshwater, the eggs release miracidia that can infect certain species of snails; asexual reproduction within the snails is then followed by the release of infectious cercariae. The adult worms evade the immune response and live for an average of 3–10 years, but worms up to 40 years of age have been described (2). The life cycle of *Schistosoma* is illustrated in Figure 1. Eggs retained within the tissue cause granulomatous inflammation. Chronic inflammation can cause late complications in the form of liver cirrhosis, cor pulmonale and urogenital schistosomiasis.

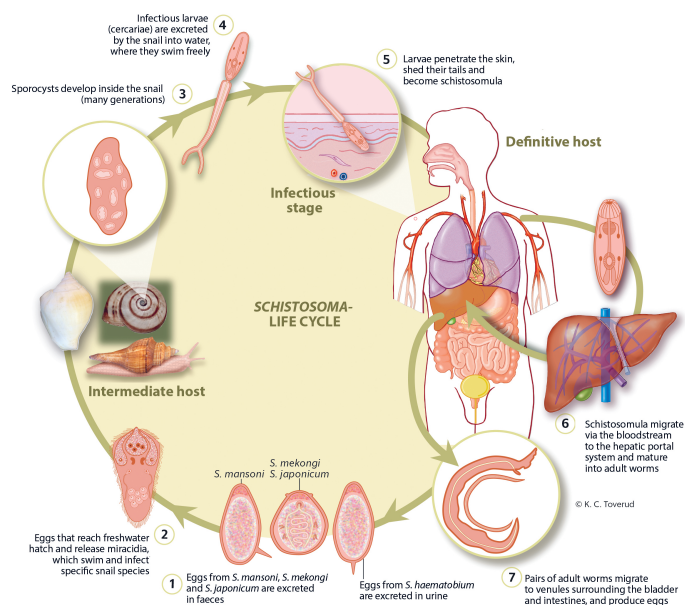


Figure 1 Life cycle of the *Schistosoma* parasite.

A rare but feared complication is neuroschistosomiasis, which is caused by inflammation around ectopic eggs in the central nervous system (2, 3).

In 2017, the WHO estimated that at least 220 million people worldwide were infected with *Schistosoma*, but as a result of ongoing mass treatment, the prevalence is now estimated to be approximately 140 million (1, 4). Over 90 % of infected individuals live in Africa, but the disease also occurs in the Caribbean, South America, the Middle East and Asia. Since 2013, locally transmitted infections have also been reported in Corsica (2, 5). Schistosomiasis is regarded as one of the neglected tropical diseases, and has high morbidity and mortality, especially among the poor in endemic areas where infection pressure is high. The occurrence of the disease in travellers from non-endemic areas is well recognised, but is associated with fewer chronic disease manifestations owing to more limited exposure and a lower worm burden (6, 7). However, neuroschistosomiasis has been described among travellers in several case reports (8–10). Acute schistosomiasis, also known as Katayama fever and Katayama syndrome, has been reported in 7–34 % of European travellers and typically gives rise to symptoms 4–8 weeks after exposure in the form of fever, urticaria and general malaise (6, 11).

Students from Bergen and Oslo have in recent years taken part in regular exchange trips to Africa, mainly to Uganda. At the Norwegian National Advisory Unit on Tropical Infectious Diseases at Haukeland University Hospital and the Regional Advisory Unit for Imported and Tropical Diseases at Oslo University Hospital, we noticed increasing demand among

students for schistosomiasis diagnostic testing.

We also noticed that many of these students tested positive following exposure to freshwater. In 2017, we therefore began an observational study among former exchange students to investigate the type of exposure, the incidence of schistosomiasis and the symptoms and signs, and to compare various diagnostic tests.

Material and method

All medical students who took part in an exchange programme to Africa from the University of Bergen in the period 2003–17 ($n = 299$), as well as a group of students who took part in an exchange programme to Uganda from OsloMet in Oslo in 2018 ($n = 19$), were contacted. If they considered themselves to have been in contact with freshwater during their stay, they were advised to undergo testing for schistosomiasis. Students who stated that they had had contact with freshwater, and who gave their consent, were included in the study. Students were excluded if they had received appropriate treatment for schistosomiasis in the form of praziquantel after exposure.

Routine diagnostic testing was conducted, comprising blood tests for *Schistosoma* antibodies, IgE, eosinophilic granulocytes and creatinine, as well as microscopy and/or PCR analysis of urine and faeces, and dipstick urinalysis for haemoglobin. Depending on their place of residence, participants were tested by their general practitioner, at a local hospital or at study centres in the outpatient clinics of Haukeland University Hospital or Oslo University Hospital. Serological analyses were performed by the Public Health Agency of Sweden or by Leiden University Medical Center in the Netherlands. Both laboratories conduct serological analyses using an immunofluorescence assay (IFA) to detect antibodies against various antigens in adult worms, and an enzyme-linked immunosorbent assay (ELISA) to detect IgG against soluble egg antigen.

Participants were asked to complete a questionnaire containing questions about the type and timing of exposure, as well as symptoms and signs associated with schistosomiasis.

The study was approved by the Regional Committee for Medical and Health Research Ethics (2018/175/REK nord), and all participants provided written consent to participate in the study.

Results

Of 318 persons contacted, 151 (47%) were included in the study. Of the 194 who responded, 28 were excluded because they had not been in contact with freshwater, 14 because they had undergone appropriate self-treatment with praziquantel and one because we did not receive the test results.

In the group from Oslo, 12 out of 18 students were diagnosed with schistosomiasis by the local health service in Uganda about two weeks after their first possible freshwater exposure. These individuals were treated with praziquantel, but because diagnostic testing so soon after exposure is considered unreliable and because the treatment was given before it could be expected to have an effect, the individuals were not excluded. We do not have information about the type of diagnostic testing that was performed on the samples collected in Uganda (urine, faeces and blood).

Serologic tests were performed in all students, but some opted out of the other diagnostic tests. *Schistosoma* antibodies were detected in 46 (30%) of the 151 students included in the study. The results of other routine diagnostic tests in the individuals for whom we received test results are shown in Table 1.

Table 1

Routine tests for schistosomiasis among seropositive and seronegative students ($n = 151$). The table shows the number (%) who tested positive for each test.

Test	Seropositive ($n = 46$)	Seronegative ($n = 105$)
Microscopy, faeces	0/33 (0)	0/35 (0)
PCR, faeces	0/5 (0)	0/4 (0)
Microscopy, urine	0/28 (0)	0/26 (0)
PCR, urine	0/3 (0)	0/2 (0)
Microscopic haematuria	4/23 (17)	2/26 (8)
Elevated total IgE	6/23 (26)	1/25 (4)
Eosinophilia	0/22 (0)	0/37 (0)
Elevated creatinine	0/19 (0)	0/23 (0)

The mean time from exposure to testing was 4 years (range 0–13 years) in the seropositive individuals, and 3 years (range 0–12 years) in the seronegative individuals.

Eggs were not detected in the urine or faeces from any of the seropositive individuals by microscopy. None of the seropositive individuals had eosinophilia or elevated creatinine levels, while 17 % had microscopic haematuria and 26 % had elevated IgE levels.

Two of the seropositive students reported symptoms of cercarial dermatitis ('swimmer's itch') in connection with exposure to freshwater, one reported symptoms consistent with acute schistosomiasis in the weeks following exposure, and two described macroscopic haematuria at a later time point. In addition to haematuria, other signs and symptoms of chronic schistosomiasis can include haematospermia, vaginal bleeding, dysuria, diarrhoea, blood in faeces, and chronic fatigue. However, these signs and symptoms can also have many other causes, and were reported with approximately equal frequency by seropositive and seronegative participants (Table 2).

Table 2

Symptoms and signs among seropositive and seronegative students exposed to freshwater in Africa ($n = 151$). The table shows the number (%) who reported symptoms among those who answered each question.

Symptoms and signs	Seropositive ($n = 46$)	Seronegative ($n = 105$)
Cercarial dermatitis	2/42 (5)	0/77 (0)
Acute schistosomiasis	1/41 (2)	0/77 (0)
Chronic fatigue	2/41 (5)	3/77 (4)
Haematuria	2/42 (5)	0/77 (0)
Dysuria	1/42 (2)	3/76 (4)
Haematospermia	1/16 (6)	1/19 (5)
Vaginal bleeding	1/24 (4)	2/57 (4)
Diarrhoea	4/42 (10)	9/76 (12)
Blood in faeces	2/42 (5)	5/77 (6)

Of the seropositive individuals, 40 reported contact with freshwater in Uganda, two in Tanzania, one in Kenya, one in Burkina Faso, one in Cameroon and one in Laos. Rafting on the Nile was the only reported freshwater exposure for 55 % (22 of 40) of the seropositive students, with *Schistosoma* antibodies detected in 49 % (22 of 45) in this group. Figure 2 shows the various types of freshwater exposure among those who were diagnosed with schistosomiasis.

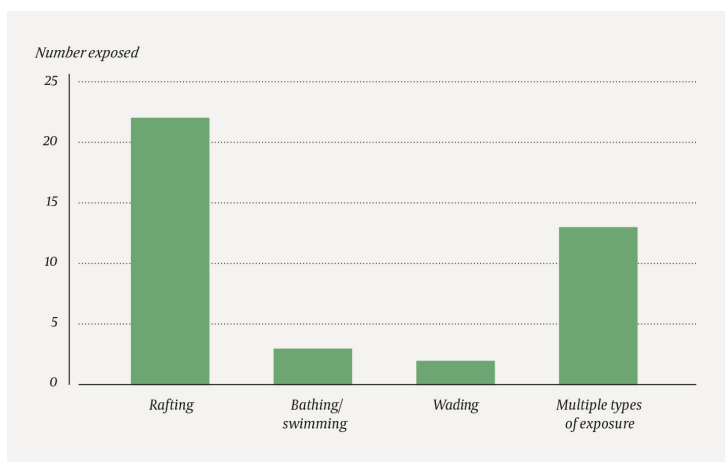


Figure 2 Types of freshwater exposure among students who were seropositive for schistosomiasis. 'Multiple forms of exposure' consists of combinations of the other three exposure types.

Discussion

A strikingly high percentage of individuals in this study tested positive for *Schistosoma* antibodies after brief freshwater exposure in Africa. Travellers often believe that schistosomiasis is only transmitted in stagnant water, and the students were told by locals that rafting did not pose a risk of *Schistosoma* infection. More than half of the students (55 %) in our study stated that their only freshwater contact was through rafting, although we cannot rule out the possibility of infection via domestic water. Cercariae can be infectious for two to three days and can be transmitted via domestic water if untreated surface water is used (2, 12). Another study of 69 people with freshwater contact in the Upper Nile detected schistosomiasis in 17 % of the participants (13).

Only a minority of seropositive individuals reported symptoms in the period after exposure that could potentially be related to chronic schistosomiasis, such as urinary tract, genital and intestinal disorders, or fatigue as a result of chronic inflammation, with the vast majority being asymptomatic (Table 2). Cercarial dermatitis, which can occur after penetration of the skin by cercariae, has been reported in 7–36 % of travellers with schistosomiasis (7, 11). Only 5 % of individuals in the current study were able to recall symptoms of this condition. Only one person who was seropositive reported symptoms consistent with acute schistosomiasis.

Since *Schistosoma* antibodies can be detected in the blood for several years after the infection has resolved or been treated (14), an indeterminate number of students with positive serology might already have cleared the infection spontaneously. As the worms can potentially survive for several decades, however, it is likely that many still had an active infection, and all seropositive students were therefore recommended treatment with praziquantel. The main reason for treating schistosomiasis in travellers is the risk of neuroschistosomiasis. Praziquantel is considered very effective against schistosomiasis, but is unlicensed and expensive in Norway. The recommended dose varies from 40 to 60 mg/kg, split into two doses taken on a single day (2, 7, 15, 16). Praziquantel is effective only against adult worms, and since parasite maturation is assumed to take up to 12 weeks, it is recommended to postpone treatment until at least three months after freshwater exposure, or to repeat the treatment three months after the last exposure if treatment was carried out at an earlier stage. The treatment has few side effects and is considered safe to use during pregnancy.

Tests other than serological assays had little or no diagnostic value in this study. Microscopy for the detection of eggs in urine and faeces is used as a routine diagnostic test for schistosomiasis, but has low sensitivity in travellers because of their brief exposure and hence low worm burden and egg production (6), consistent with our findings in this study.

Serological testing is the most sensitive diagnostic method available to travellers and also

has high specificity (> 95 %). It is therefore suitable for detecting low-grade infection in individuals who have not previously been exposed to or treated for schistosomiasis. The main limitation of the test is its inability to distinguish active versus previous infections. It is also not 100 % sensitive, and some cases of schistosomiasis may be detected by microscopy or PCR despite negative serology (6, 17). Both serological assays and attempts to detect eggs in urine or faeces will give negative results until the parasites are sexually mature and have started egg production. A definitive diagnosis therefore cannot be made until at least 12 weeks after the last exposure. Serological diagnostic testing has previously been performed at laboratories outside Norway and has been very expensive. An affordable *Schistosoma* antibody test is now available at the newly established reference laboratory for parasite serology at the University Hospital of North Norway, Tromsø.

Oslo University Hospital and Haukeland University Hospital now offer real-time PCR analysis for the detection of *Schistosoma* spp. in urine, faeces and serum. PCR testing is more sensitive than microscopy (17–19) and is not dependent on a highly trained microscopist. PCR testing of serum can detect infection as early as a few weeks after exposure, and has high sensitivity provided that repeat sequences in the *Schistosoma* genome are used as the target region (17, 18, 20, 21). PCR can be positive for more than a year after treatment has been completed, owing to the presence of DNA from retained eggs (17).

Another interesting diagnostic method is antigen testing, in which the detection of circulating anodic antigen (CAA) in serum appears particularly promising with respect to diagnosing travellers and assessing treatment responses (19). The test is not yet commercially available, and its practical utility is currently uncertain.

This observational study has a number of limitations that may have affected the results. The fact that many years had passed between exposure and diagnosis in some individuals, might have led to poor recall and thus less accurate descriptions of symptoms. It would have been helpful to have the results of other diagnostic tests, including microscopy and PCR analysis of urine and faeces, for all participants; however, many opted out of these additional tests as serological analysis is easy to perform and is the most sensitive method. We did not collect information about any prior stays in endemic areas by the students, and therefore cannot rule out the possibility that some may have lived in endemic areas and have been exposed to schistosomiasis previously, which could result in a positive serology result. It would also have been useful to obtain data from those students who were not exposed to freshwater, as a negative control, but due to limited resources and the high costs of serological testing this was not possible.

The findings of this study emphasise that contact with freshwater is common among travellers to Africa, and that the incidence of schistosomiasis can be high even among individuals with only brief freshwater exposure. It is likely that the infection is underdiagnosed in Norway since many do not develop symptoms. We generally recommend serological analysis alone when testing for schistosomiasis in asymptomatic travellers with no previous exposure. Serological testing should be supplemented with PCR and/or microscopy for individuals with symptoms and those who have spent longer periods of time in endemic areas. Upon diagnosis of schistosomiasis, a single day of treatment with praziquantel 40–60 mg/kg/day is recommended. Both diagnostic testing and treatment should be performed at least three months after the last possible exposure. Post-treatment confirmation of serological status is not indicated, as antibodies can be detected long after an infection has been cleared. Local purchase and use of praziquantel shortly after exposure is common among travellers, but is not recommended as early treatment is ineffective. Schistosomiasis is a potentially serious disease, and travellers should be warned to avoid skin contact with freshwater in Africa and in endemic areas of Latin America and Asia.

MAIN FINDINGS

Schistosomiasis was detected by serological analysis in 46 of 151 (30 %) students who had been exposed to freshwater in Africa.

Rafting on the Nile was the most common type of freshwater exposure.

Routine diagnostic tests by microscopy and/or PCR analysis of urine and faeces were negative for all seropositive individuals.

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