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Original Article

Human urogenital schistosomiasis in West and Sub-Saharan Africa migrants in Sardinia, Italy: A retrospective monocentric study

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Abstract

Introduction: *Schistosoma* (*S.*) *haematobium* is the aetiological agent of urogenital schistosomiasis endemic in Sub-Saharan Africa and the Middle East. Microhaematuria is strongly associated with schistosomiasis diagnosis. Praziquantel (PZQ) is the treatment of choice.

Methodology: We conducted a monocentric survey among African migrants from January 2017 to December 2018. The diagnosis of *S. haematobium* was performed by direct microscopic examination of urine. The treatment was PZQ 40 mg/Kg/die for three days.

Results: We enrolled 91 male patients with a median age of 20.2 years (IQR 18.9-23.4)]. Forty-five (49.5%) described a history of haematuria. Sixteen (17.6%) evidenced the presence of red blood cells (RBCs) during urine microscopy. Eighteen (19.8%) had urogenital schistosomiasis. Their median white blood count (WBC) was 5.15×10^9/L (IQR 4.45-6.08) and it was 6.37×10^9 /L (IQR 5.14-8.27), $p = 0.009$, after 15 days from treatment. Baseline eosinophil count was 0.5×10^9/L (IQR 0.3-0.6) and 0.7×10^9/L (IQR 0.2-1.9; $p = 0.032$). According to the univariate analysis, origin from Mali [odds ratio (OR) 3.6 (CI 1.2-10.9), $p = 0.022$] and microscopic evidence of RBCs [OR of 10.7 (CI 2.5-45.1), $p = 0.001$] were main predictors of urogenital schistosomiasis diagnosis. One (5.6%) treatment failure was registered. Three (16.7%) patients had bladder cancer.

Conclusions: Detection of RBCs was a significant predictor of *S. haematobium* infection and could be used as a screening method in migrants coming from endemic areas. Early urogenital schistosomiasis diagnosis and ultrasound diagnostic tools are crucial for reducing the risk of potential neoplastic evolution.

Key words: Schistosomiasis; neglected diseases; refugees; migrants; praziquantel.

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Introduction

Schistosomiasis is a neglected tropical disease caused by flat trematode [1]. Schistosomiasis in humans is generally caused by six different species: *Schistosoma (S.) haematobium*, *S. mansoni*, *S. japonicum*, *S. guineensis*, *S. intercalatum*, and *S. mekongi* [2].

Schistosomiasis transmission cycle requires an asexual replication in an intermediate host, the freshwater snail (*Biomphalaria* spp. snails for *S. mansoni*, *Bulinus* spp. snails for *S. haematobium* and *Oncomelania* spp. snails for *S. japonicum*) [1,2]. Infection in humans can occur by contact with free-swimming cercariae, which are the infective stage of schistosomes released by the intermediate host [3].

S. haematobium, the aetiological agent of human urogenital schistosomiasis, has been reported in 54 countries and is endemic in Sub-Saharan Africa and the Middle East [3]. Nevertheless, Schistosomiasis is extraordinarily uncommon in Europe. An outbreak occurred in Corsica in 2013, showing the Mediterranean basin could be a potential transmission area [4]. More than 112 million people affected by *S. haematobium* infection are estimated every year, with 436 million people at risk of urogenital infection [5]

The two most common signs of urogenital schistosomiasis are haematuria and dysuria. Moreover, it can be associated with severe urinary tract manifestations, such as bladder and urethral fibrosis and hydronephrosis [6-8].

The chronic inflammation due to *S. haematobium'*s eggs is the principal step toward the squamous cell bladder cancer development [9].

In endemic areas, the presence of turbid urine, microhaematuria, or proteinuria are frequently reported and strongly related to urogenital schistosomiasis. Therefore, different screening programs with strip tests direct detection are conducted among school-age children [10-12]. However, the gold standard for the schistosomiasis diagnosis remains the eggs' detection in urine with microscopy, despite the risk of false-negative samples [13].

Praziquantel (PZQ) is the first-line treatment, with high efficacy in recovery, egg reduction rate, and its relatively low frequency of side effects [14].

The migration's flows from Sub-Saharan Africa and the Middle East can be related to a consequent *S. haematobium* spread in the Mediterranean basin. The potential complications, including death, are emerging problems in terms of control, prevention, and healthcare costs.

As well as the rest of Europe, Italy is not an endemic area for schistosomiasis. Normally, urogenital schistosomiasis is an imported disease.

Our aim is to describe the prevalence, urine characteristics, possible complications, and predictors for the aetiological diagnosis of urogenital schistosomiasis, among migrants from West and Sub-Saharan Africa in our area.

Methodology

We conducted a retrospective, single-center survey among African migrants. Data collection included patients evaluated from January 2017 to December 2018. We included all adult patients (age > 18 years) coming from West and Sub-Saharan Africa. Diagnostic procedures, clinical evaluation, and treatment were performed at the University Hospital of Sassari (Italy).

Data regarding demographics, clinical history (macrohaematuria, abdominal pain, dysuria), and laboratory findings were collected from patients' medical records. Most evaluated comorbidities were human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), conducted with ELISA test.

Laboratory assessments and follow-up

Two urine samples were collected for diagnosis: the first was collected between 10.00 am and 2.00 pm and the second after physical activity (jump the rope, hop on the spot, or go up and down the stairs), to increase the *S. haematobium* eggs excretion.

The macroscopic urine examination was based on the Vogel scale (yellow, red, or brownish). Macroscopic characteristics were classified as clear, opalescent, or turbid. Macrohaematuria was defined as red or brownish urine at the macroscopic evaluation.

Microhaematuria was defined as the presence of three or more erythrocytes per field with a 40× magnification.

For the diagnosis of *S. haematobium* infection, urine was centrifuged at 3000 revolutions per minute (rpm) for ten minutes. *S. haematobium* eggs detection was performed by direct microscopic examination with 4× magnification of the whole urine pellet. The egg vitality was evaluated by 20× and 40× magnification.

All patients with confirmed urinary schistosomiasis underwent baseline blood examinations and abdominal ultrasounds. The follow-up was performed after 15 days after the end of treatment with a blood and urine examination. All patients repeated urine microscopy after treatment.

Hypereosinophilia was considered as eosinophil count over 0.6 cells × 10^9/L.

Statistical analysis

Data have been reported as the median and interquartile range (IQR). Wilcoxon-Mann-Whitney test was applied to compare baseline blood examinations with those repeated 15 days after the treatment. Statistical significance was considered present with a p value (p) ≤ 0.05.

Statistical analysis was carried out with STATA/IC® V16.1, using the univariate logistic regression model to identify five potential associated factors as predictors for the diagnosis of Urogenital Schistosomiasis. We evaluated origin from Mali, history of haematuria, anamnesis positive for abdominal pain or dysuria, macroscopic characteristics (current macrohaematuria or turbid urine), and the presence of RBCs at the microscopy. It was considered a confidence interval (CI) of 95%, and a $p < 0.05$ indicated statistical significance.

Ethical issues

Data were fully anonymized and analyzed retrospectively. For conducting this kind of a study a formal consent from the Ethical Committee, according to the current Italian law from Italian Medicines Agency and Italian Data Protection Authority is required. All patients signed the informed consent at their first evaluation.

Results

Demographics and clinical features

Overall, 91 patients were included in this study. All of them were male, and the median age was 20.2 (IQR

18.9-23.4). Most part of the patients (21.9%) came from Mali, and 87.9% arrived in Italy after being in Libya for a variable length of stay.

Forty-five (49.5%) patients described a macrohaematuria history. Thirty-three (36.5%) were asymptomatic, and 30 (32.9%) had abdominal pain or dysuria at the time of the visit.

At the macroscopic urine evaluation, only 15 (16.5%) were turbid samples, and only in one case (1.1%), macrohaematuria was present. Clinical and urine characteristics have been summarized in Table 1. Microhaematuria was highlighted by microscopy in 16 cases (17.6%). *S. haematobium* vital eggs were identified in 18 (19.8%) patients.

The median age was 19.2 (IQR 18.2-23.5). Seven (38.9%) were from Mali, 4 (22.2%) from Senegal, 4 (22.2%) from the Gambia, and 3 (16.6%) from other West and Sub-Saharan African Countries.

All the patients were treated with PZQ, with a dosage of 40 mg/kg daily for three consecutive days. Five (27.8%) patients had also HBV infection. None were HIV or HCV positive.

Main laboratory alterations and outcomes

Main blood exam alterations have been reported in Table 2. At the baseline blood exams, WBC median was 5.15 × 10^9/L (IQR 4.45-6.08), at the control WBC median was 6.37 × 10^9/L (IQR 5.14-8.27), p = 0.009. The eosinophil median count was 0.5 × 10^9/μL (IQR 0.3-0.6) and 0.7 × 10^9/L (IQR 0.2-1.9) before and after PZQ treatment, respectively (p = 0.032).

Before treatment, only three (16.7%) patients had hypereosinophilia, while after 15 days from the anti-helminthic treatment with PZQ, the increase in eosinophil count was evidenced in seven cases (38.9%).

Three (16.7%) patients were diagnosed with urological lesions that were consequently surgically removed with transurethral resection of the bladder (TURB). In all of them, the histological analysis identified a squamous cell carcinoma of the bladder.

Table 1. Clinical and urine characteristics in 91 patients.

Signs and Symptoms	N (%)
Asymptomatic	33 (36.3)
History of macrohaematuria	45 (49.5)
Abdominal pain	30 (32.9)
Turbid urine	15 (16.5)
Current macrohaematuria	1 (1.1)
Microscopic presence of RBCs	16 (17.6)

RBCs: blood red cells.

They were all young (28, 25, and 18 years old, respectively).

At the end of the follow-up, only one (5.6%) treatment failure was reported.

Laboratory findings of patients included in our study have been summarized in Table 2.

Logistic regression analysis

Five independent variables were analyzed with the logistic regression model in order to evaluate their predictive value for urogenital schistosomiasis diagnosis. Origin from Mali [odds-ratio (OR) 3.6 (CI 1.2-10.9), p = 0.022], history of macrohaematuria [OR of 8.3 (CI 0.5-129.8), p = 0.132], anamnesis for dysuria [OR of 3.7 CI 0.4-31.6), p = 0.233], presence of turbid urine or current macrohaematuria [OR of 0.5 (CI 0.2-1.9), p = 0.324] and microscopic evidence of RBCs [OR of 10.7 (CI 2.5-45.1), p = 0.001]. The results have been shown in Table 3.

Discussion

According to the European Center for Disease Control (ECDC), in a considerable number of European Countries, migrant populations are at increased risk of infectious diseases such as tuberculosis, parasitosis, HIV, and viral hepatitis [15].

Urogenital schistosomiasis is endemic in Sub-Saharan Africa and the Middle East and is becoming a global healthcare problem due to the increasing migration flow [16].

Our study reported 18 cases of urogenital schistosomiasis among 91 immigrants who came from

Table 2. Laboratory findings in 18 positive patients with urogenital schistosomiasis at baseline and after 15 days from the treatment.

	Baseline exams		15 days exams		*p*-value
	Median	IQR	Median	IQR	
WBC (cells × 10^9/L)	5.15	4.45-6.08	6.37	5.14-8.27	0.009
RBC (cells × 10^{12}/L)	5.36	4.76-5.64	5.36	4.85-5.64	0.082
Platelets (× 10^9/L)	225	198-244	209	193-262	0.369
Hb (mmol/L)	9.34	9.12-9.77	9.31	8.94-9.62	0.072
Eosinophil (cells × 10^9/L)	0.5	0.3-0.6	0.7	0.2-1.9	0.032
Creatinine (μmol/L)	75.16	72.50-83.11	81.35	75.16-86.65	0.272
AST (ukat/L)	0.42	0.35-0.50	0.41	0.38-0.54	0.493
ALT (ukat/L)	0.27	0.25-0.44	0.28	0.25-0.4	0.228

IQR: Interquartile range; WBC: white blood cells, RBCs: blood red cells, Hb: hemoglobin, AST: Aspartate transaminase, ALT: Alanine transaminase.

Table 3. Univariate logistic regression analysis.

Variable	Odds ratio	CI	*p*-value
Country of origin	3.6	1.2-10.9	0.022
History of macrohaematuria	8.3	0.5-129.8	0.132
Abdominal pain or dysuria	3.7	0.4-31.6	0.233
Turbid/haematic urine	0.5	0.2-1.9	0.324
RBCs at microscopy	10.7	2.5-45.1	0.001

CI: confidence interval; RBCs: Red Blood Cells.

a high-risk area for *S. haematobium*, such as West and Sub-Saharan Africa. Comparing our results with other national literature, we found a lower prevalence of urogenital schistosomiasis cases [17,19].

According to the WHO's preventive chemotherapy and transmission control (PCT) for schistosomiasis, other countries have a high relative risk of schistosomiasis [20], at the univariable logistic regression model, origin from Mali was a significant predictor for urogenital schistosomiasis, in our study.

Abdominal pain or dysuria and a history of macrohaematuria were reported by most patients. However, none of those symptoms or signs resulted significantly related to *S. haematobium* positivity. At the urine valuation, turbid/haematic urine was observed in a few cases. When considering microscopy, RBCs positivity was evidenced in 16 samples.

When evaluating these markers as predictors for urogenital schistosomiasis diagnosis, a positive relationship between RBCs on microscopy in the urine and *S. haematobium* vital eggs detection was found. This datum is according to available literature [13,22], suggesting the importance of microhaematuria observation as an essential indicator for a possible *S. haematobium* infection among high-risk patients.

Eosinophil count increased after the anti-parasitic treatment. Comparing baseline and 15 days after treatment data, we evidenced a significant increase in both WBC and eosinophils (p = 0.009 and 0.032, respectively). This could be possibly due to parasitic lysis and antigen exposure that can up-regulate cytokine levels and consequently increase the eosinophil number [23].

According to literature data, over twenty million people with chronic schistosomiasis could develop major complications, such as hydronephrosis, kidney failure, and bladder cancer [5]. As consequence, the rapid diagnosis and treatment would represent a long-term benefit for patients.

In Sub-Saharan areas, more than 11,000 deaths per year are caused by *S. haematobium*–related cancer [5]. Among our patients, diagnosed the presence of three cases of bladder cancer occurred, and all of them were at a young age. This result showed how the urinary tract ultrasound examination could be useful as a diagnostic supplement for the early diagnosis of *S. haematobium* to minimize possible complications.

This study presented some limitations. Firstly, the relatively small sample, the retrospectively collecting data, and a male-exclusive cohort are the principal problems. Secondly, the low sensitivity of the diagnosis based exclusively on direct microscopy probably determined an underestimation of the urogenital schistosomiasis cases. To reduce the misdiagnosis risk, new diagnostic tools such as polymerase-chain-reaction (PCR) and antigen-based detection methods of circulating cathodic antigen (CCA) and circulating anodic antigen (CAA) have been developed, and more often applied in clinical practice [13]. Thirdly, our study did not investigate other possible parasitic infections, and another coexisting intestinal schistosomiasis can be found in migrants. These conditions are frequent in African Countries and can modify the clinical and laboratory presentation of the disease.

In conclusion, we evidenced a high proportion of cure rates suggesting that rapid urogenital schistosomiasis detection is fundamental to reducing the risk of potential carcinogenic evolution. RBCs at microscopy were a significant predictor of *S. haematobium* infection and could be used as a screening method in high-risk populations. To further reduce microbiological diagnosis-related limits, innovations such as antigen-based detection or DNA-based tests can improve screening efficiency [13]

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Authors' Contributions

N. Geremia, A. De Vito, V. Fiore and E. Princic drafted the manuscript. Paola Rappelli, Giordano Madeddu and Sergio Babudieri coordinated the investigations and supervised the study. Microbiological investigations were conducted by P. Rapelli and V. Lai. All authors commented and agreed upon the final manuscript.

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