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Ultrasound findings and associated factors to morbidity in *Schistosoma haematobium* infection in a highly endemic setting

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Abstract

OBJECTIVE To evaluate the usefulness of the WHO classification of ultrasound pathological changes and to establish risk factors for morbidity in a highly endemic setting.

METHODS One hundred and fifty-seven ultrasounds were performed on school-aged children previously diagnosed with urinary schistosomiasis in Cubal, Angola. The findings were analysed according to the WHO guidelines. Factors for morbidity were studied.

RESULTS Mean age of the children was 8.7 (SD 3.2) years. Pathological changes were found in 85.3% (84.7% in the bladder, 34.4% the ureter and 6.3% kidney lesions). The global score according to the WHO classification was 5.74. Male gender [OR 2.61 (1.04–6.58); *P* 0.043] and older age [OR 2.96 (1.17–7.46); *P* 0.023] were associated with a higher risk of developing any kind of urinary abnormality. Proteinuria was present in 61.7% of the children. Macroscopic haematuria [OR 2.48 (1.11–5.58); *P* = 0.02)] and a high level of proteinuria > 300 mg/dl [OR 5.70 (2.17–14.94); *P* 300 mg/dl)] were associated with abnormalities of the upper urinary tract and showed good positive and negative predictive values for the detection of pathology in the upper urinary tract (65.5% and 71.1%, respectively).

CONCLUSIONS Severe urinary tract pathology was found in a high percentage of the children in our setting. Microhaematuria and proteinuria were good markers of morbidity, proteinuria being more precise for severe alterations of the upper urinary tract. We suggest initial and evolutive ultrasound in children diagnosed with schistosomiasis, and close monitoring including periodic controls. As schistosomiasis control efforts are currently focused on reducing morbidity, tests that detect the presence or degree of morbidity are essential for targeting treatment and tracking the progress of control campaigns.

keywords schistosomiasis, ultrasound, paediatrics, Angola, urinary schistosomiasis

Introduction

Human schistosomiasis is one of the most prevalent parasitic infections in the world, and after, malaria has the greatest consequences for public health and the economy in endemic countries, mainly in sub-Saharan Africa [1, 2]. More than 200 million people are infected [3, 4], and recently, it has been estimated that haematuria caused by *Schistosoma haematobium* is affecting 70 million people, 18 million of whom have major bladder wall pathology [5]. Other consequences have long been underestimated due to the difficulties of establishing a causal relationship. However, some studies have convincingly shown that schistosomiasis has a direct effect in anaemia, chronic pain, growth stunting and nutritional, and cognitive impairment in endemic areas [5, 6]. The global burden due to schistosomiasis is currently estimated to be 1.7–4.5 million disability-adjusted life years (DALYs) [7].

The 1984 WHO Expert Committee for the Control of Schistosomiasis launched a strategy for morbidity control based on the administration of praziquantel, which is an available, safe and effective drug, and easy to administer

in a single dose [8]. The aim of these programmes was to reduce morbidity. To achieve this objective, it is imperative to characterise pre-treatment baseline morbidity [9].

Ultrasonography is an excellent method to obtain information about internal damage, not only in hospitals but also in communities. It has clear advantages: it is easy to learn and perform, non-invasive, well accepted by patients, cheap and mobile. With ultrasound, we can obtain information about internal damage, and more importantly, about its reversal after treatment, and reappearance after re-infection [10]. Generally, ultrasound interpretation depends on the observer's experience. To facilitate its use for less skilled examiners and to compare findings among different settings, an ultrasound protocol (the Niamey-Belo Horizonte Protocol) was developed by WHO experts in 1997 [11]. This protocol is now accepted worldwide, and it has led to standardisation and reliable comparison between different settings [12, 13].

Both types of schistosomiasis (urinary and intestinal) are endemic in Angola [14, 15]. In the Cubal district in central Angola, a recent survey reported a prevalence of urinary schistosomiasis of 61% for school-aged children; no intestinal schistosomiasis was detected [16]. We aimed to assess the use of ultrasound to detect internal damage of the urinary tract in this same group of children, and whether urine dipstick tests could be useful to predict internal damage in a highly endemic context.

Methods

Study population and data collection

A cross-sectional study was conducted between June and November 2013 in Cubal, the capital of Cubal district, in Benguela province, to estimate urinary schistosomiasis prevalence. Eleven schools in this area were randomly selected, and between August and December 2013, all children under 15 years of age who tested positive for urinary schistosomiasis were invited to undergo an ultrasound exam [16].

Participation in the study was voluntary, and parental consent was obtained. We excluded children whose parents or legal guardians rejected their participation.

Urine samples were collected and tested with a urine dipstick test (Combi-Screen 11SYS) to assess microscopic haematuria and proteinuria. In the case of haematuria, one cross denoted 5–10 erythrocytes per field, two crosses 50 erythrocytes per field, and three crosses 300 erythrocytes per field. For proteinuria, one cross corresponded to 30 mg/dl, two crosses to 100 mg/dl, and three crosses to 300 mg/dl.

Ultrasound examination

Ultrasound assessments were performed 7–14 days after diagnosis of urinary schistosomiasis at Nossa Senhora da Paz Hospital with a portable ultrasonography device (myLab 25 ESAOTE). All the examinations were performed by the same clinician, who had undertaken training and practice focused on ultrasound. A second clinician supervised and compared the results.

The shape of the urinary bladder, bladder wall morphology and the diameters of the ureter and renal pelvis were assessed to determine pathologic changes caused by *Schistosoma haematobium* according to the WHO criteria [11]. Pathologic changes were categorised using the global score as an index of the severity of morbidity and lesions [11]. Pregnancy was recorded if present [9]. The children were asked to drink abundant water before the ultrasound, and the definitive exam was only conducted when the bladder was full. If any renal pelvis dilatation was detected, the ultrasound was repeated after urination to rule out dilatation due to bladder and ureteral repletion.

Patients with at least one point according to the WHO score were considered to have urinary tract abnormalities and patients with at least one point in the upper urinary tract were considered to have upper urinary tract abnormalities for successive analysis.

Statistical analysis

Qualitative variables were presented as absolute numbers and proportions, continuous variables were expressed as means and standard deviations and quantitative variables as medians and p25–p75 quartiles depending on variable normality. Normal distribution was tested with the Shapiro–Wilk test. Differences in normally distributed variables were evaluated using *t*-tests for independent variables and ANOVA. Differences in variables that were not normally distributed were determined with Mann–Whitney and Kruskal–Wallis tests.

We considered sex, age and the presence of haematuria and proteinuria as possible risk factors for urinary abnormalities. The assessment of risk was expressed through odds ratios using chi-squared tests and evaluated for both types of abnormality. Relationships between both types of abnormality and haematuria/proteinuria were also examined through odds ratios using chi-squared tests. Results were considered statistically significant if the two-tailed P value was <0.05. Data collection and calculations were performed using EpiInfoTM version 7 and STATA version 11.

Ethical aspects

The project was approved by the Ethical Review Board of Vall d'Hebron University Hospital, and by regional health and education institutions. Procedures were followed the ethical standards laid down in the Declaration of Helsinki as revised in 2013. We previously conducted informative talks with school principals, teachers, parents and community leaders. Written informed consent was obtained from all parents and legal guardians.

Every pupil diagnosed with schistosomiasis received appropriate treatment (praziquantel 40 mg/kg) on the day of the ultrasound. One of the researchers led treatment at school for children who did not attend hospital on the indicated date and those who refused the ultrasound examination.

Results

Six hundred and twenty-seven children were invited for ultrasound. Of these, 157 of 627 (25%) attended hospital. 86 of 157 (54.8%) were girls, and the mean age was 8.7 (SD 3.2) years. One 15-year-old student was pregnant.

Ultrasound findings

Ultrasound examination showed pathological changes in 134 of 157 (85.4%) children. The bladder was the most common site of alteration and was abnormal in 133 of 157 (84.7%) children. Some type of ureteral dilatation was seen in 54 of 157 (34.4%), and 10 of 157 (6.3%) had kidney pathology. Overall, the mean *S. haematobium* total score was 5.74 according to the WHO guidelines (Table 1). Figures 1-4 present some of the ultrasound findings.

Factors associated with morbidity

Being male [OR 2.61 (1.04–6.58); *P* 0.043] and >10 years old [OR 2.96 (1.17–7.46); *P* 0.023] were associated with a higher risk of developing any kind of urinary abnormalities. Macroscopic haematuria [OR 2.48 (1.11–5.58); $P = 0.02$)] and proteinuria > 300 mg/dl [OR 5.70 (2.17–14.94); $P < 0.01$] were associated with upper tract urinary abnormalities (Table 2). Sensitivity, specificity, positive and negative predictive values of both forms of haematuria and proteinuria, together and separately, are summarised in Table 3.

Discussion

This study revealed an astonishing amount of morbidity in a group of children infected with *Schistosoma*

Table 1 *Schistosoma haematobium* ultrasound findings. WHO scoring

	n	%	Mean score
Urinary bladder			
Shape			
Normal (rectangular) = 0	90	57.3	
Round (distorted) = 1	67	42.6	0.42
Bladder wall			
Wall irregularity (inner surface, thickening < 5 mm)			
No = 0	83	52.8	
Focal = 1	7	4.4	
Multifocal/Diffuse = 2	67	42.6	0.89
Wall thickening (>5 mm < 10 mm)			
No (<5 mm) = 0	86	54.7	
Focal = 1	19	12.1	
Multifocal/Diffuse = 2	52	33.1	1.16
Mass (>10 mm)			
No = 0	106	67.5	
Single = 2	36	22.9	
Multiple = (number) + 2	15	9.5	0.88
Pseudopolyp			
No = 0	151	96.2	
Single = 2	5	3.1	
Multiple = (number) + 2	1	0.6	0.09
Urinary bladder intermediate score	133	84.7	**3.45**
Urethers			
Right urether			
Not visualised = 0	122	77.7	
Dilated; visualised at proximal and/or distal third = 3	10	6.3	
Grossly dilated and/or entirely visualised = 4	25	1.9	0.82
Left urether			
Not visualised = 0	115	73.2	
Dilated; visualised at proximal and/or distal third = 3	17	10.8	
Grossly dilated and/or entirely visualised = 4	25	15.9	0.96
Renal pelvis			
Right pelvis			
Not dilated = 0	151	96.1	
Moderately dilated (parenchyma thickness > 1 cm) = 6	4	2.5	
Marked hydronephrosis (parenchyma < 1 cm) = 8	2	1.3	0.25
Left pelvis			
Not dilated = 0	151	96.1	
Moderately dilated (parenchyma thickness > 1 cm) = 6	5	3.1	
Marked hydronephrosis (parenchyma < 1 cm) = 8	1	0.6	0.24
Upper urinary tract intermediate score	56	35.7	**2.28**
Final *Schistosoma haematobium* score	134	85.4	**5.74**

Bold values refer to urinary bladder intermediate score, upper urinary tract intermediate score and final Schistosoma haematobium score.

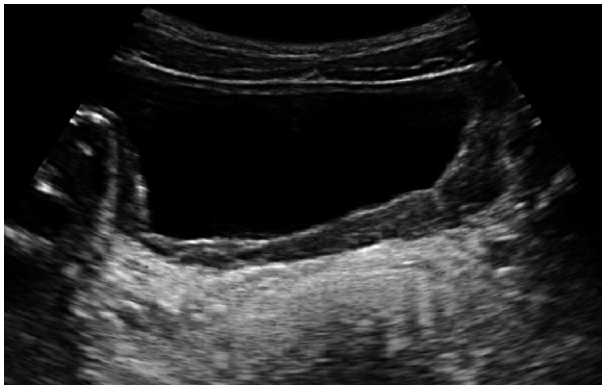

Figure 1 Diffuse wall thickening. The bladder's inner surface has a thickness bigger than 5 mm.

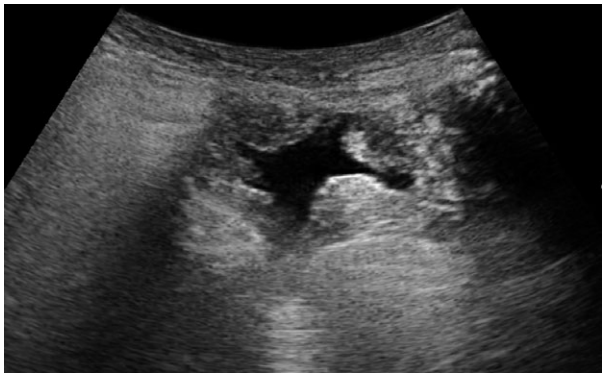

Figure 2 Multiple masses in the vesical wall. Localised thickening of the wall, bigger than 10 mm. There are four separate masses, indicated in the figure.

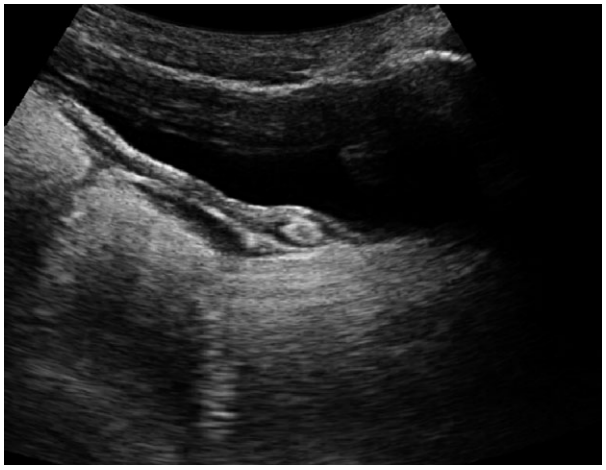

Figure 3 Uretheral inflammation. This image shows dilatation of the Intramural portion of the ureter (final part).

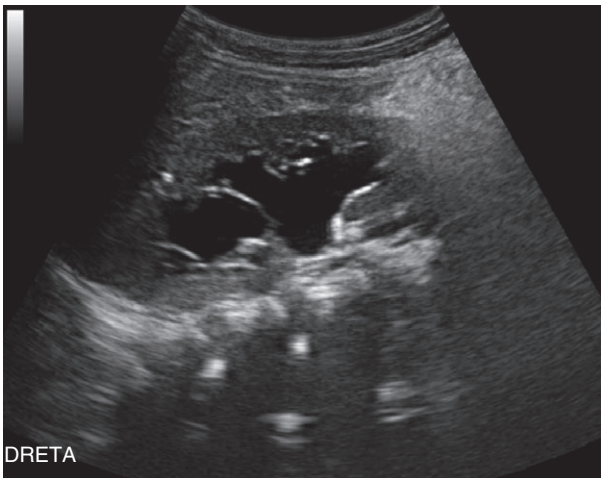

Figure 4 Kidney hidronefrose. Severe dilatation of the renal pelvis with parenchyma compression (parenchyma < 1 cm).

haematobium; only 15% had a normal ultrasound. Moreover, one-third of the children had upper urinary tract pathology, which is a severe manifestation of urinary schistosomiasis. According to the WHO ultrasound scoring, mean lower tract score was 3.45, upper tract score was 2.28 and total score was 5.74. The burden of pathology is much higher in this setting than in most studies performed in high endemic areas [17–20]; only small studies in very hyperendemic areas in sub-Saharan Africa have shown similar results [21, 22]. Overall, this finding is consistent with a previous epidemiological study in the area that revealed a prevalence of urinary schistosomiasis of at least 61% among students, in the absence of public health measures. Only 1.5% of the students had received praziquantel in the previous year [16].

In the lower urinary tract, irregularities of the bladder wall were the most common findings. Others were distorted bladder shape and bladder wall thickening. The frequency of bladder masses bigger than 1 cm was not negligible; pseudopolyps were less frequent. In the upper urinary tract, distal ureter dilatation was the most common distortion, entirely or more frequently in its distal part. This finding is particularly important, due to its situation at the very end of the urine flux. Urine flux obstruction at this point may be critical, becoming the first step for the development of hydronephrosis. Furthermore, its particular shape, resembling an eye, may have educational and informative value. This sign represents a distal ureteritis in the intramural traject of the ureter when scanned in its axial section. Inflammation and oedema in the distal ureter increase its volume, opening the different layers of the bladder wall. These results are

Table 2 Risk factors associated to morbidity

	Total *n* (%) *N*: 157	Urinary abnormalities[1] *N*: 134	OR (CI 95%)	*P*	Lower urinary tract abnormalities[2] (%) *N*: 133	OR (CI 95%)	*P*	Upper urinary tract abnormalities[3] (%) *N*: 56	OR (CI 95%)	*P*
Gender										
Male	86 (54.8)	78 (58.2)	2.61 (1.04-6.58)	**0.04**	78 (58.6)	2.83 (1.14-7.09)	**0.02**	32 (57.1)	1.16 (0.60-2.24)	**0.74**
Age										
≤10	90 (57.3)	82 (61.2)	1	–	82 (61.6)	1	–	29 (51.8)	1	–
>10	67 (42.7)	52 (38.8)	2.96 (1.17-7.46)	**0.02**	51 (38.3)	3.22 (1.28-8.05)	**<0.01**	27 (48.2)	0.70 (0.36-1.36)	**0.32**
Haematuria										
Negative	12 (7.6)	11 (8.2)	1	–	11 (8.3)	1	–	3 (5.3)	1	–
+ (5-10 eryth/field)	30 (19.1)	25 (18.7)	0.45 (0.04-4.36)	**0.48**	25 (18.8)	0.45 (0.04-4.36)	**0.48**	8 (14.2)	1.09 (0.23-5.07)	**0.91**
++ (50 eryth/field)	24 (15.3)	22 (16.4)	1.00 (0.08-12.27)	**1**	22 (16.5)	1.00 (0.08-12.27)	**1**	10 (17.9)	2.14 (0.46-9.97)	**0.33**
+++ (300 eryth/field)	91 (58)	76 (56.7)	0.46 (0.05-3.84)	**0.46**	75 (56.4)	0.42 (0.05-3.54)	**0.42**	35 (62.5)	1.87 (0.47-7.40)	**0.37**
Macroscopic haematuria	30 (19.1)	27 (90.0)	1.68 (0.47-6.08)	**0.42**	26 (86.7)	1.21 (0.38-3.86)	**0.74**	16 (53.3)	2.49 (1.10-5.58)	**0.02**
Proteinuria										
Negative	60 (38.2)	53 (39.5)	1	–	53 (39.8)	1	–	15 (26.8)	1	–
+ (30 mg/dl)	45 (28.7)	37 (27.6)	0.61 (0.21-1.83)	**0.38**	37 (27.8)	0.61 (0.21-1.83)	**0.38**	14 (25)	1.35 (0.57-3.20)	**0.49**
++ (100 mg/dl)	23 (14.6)	17 (12.7)	0.37 (0.11-1.27)	**0.11**	17 (12.8)	0.37 (0.11-1.27)	**0.11**	8 (14.3)	1.60 (0.57-4.52)	**0.37**
+++ (300 mg/dl)	29 (18.9)	27 (20.1)	1.78 (0.35-9.18)	**0.48**	26 (19.5)	1.15 (0.27-4.79)	**0.85**	19 (33.9)	5.70 (2.17-14.94)	**<0.01**

Table 3 Microhaematuria, macrohaematuria and proteinuria sensitivity, specificity, negative and positive predictive values

Pathology	Sensitivity (CI 95%) (%)	Specificity (CI 95%) (%)	Positive predictive value (CI 95%) (%)	Negative predictive value (CI 95%) (%)
Microhaematuria				
Any level	91.8 (85.8-95.8)	4.3 (0.1-21.9)	84.8 (77.9-90.2)	8.3 (0.2-38.5)
Upper urinary tract	94.6 (84.1-98.8)	8.9 (4.2-16.2)	36.5 (28.7-44.9)	75 (42.8-94.5)
Macrohaematuria				
Any level	20.1 (13.7-27.9)	86.9 (66.4-97.2)	90 (73.5-97.9)	15.7 (9.9-23.2)
Upper urinary tract	28.6 (17.3-42.2)	86.1 (77.8-92.2)	53.3 (34.3-71.6)	68.5 (59.7-76.4)
Proteinuria				
Any level	60.4 (51.6-68.8)	30.4 (13.2-52.9)	83.5 (74.6-90.3)	11.7 (4.8-22.6)
Upper urinary tract	73.2 (59.7-84.2)	44.5 (34.6-54.8)	42.3 (32.3-52.7)	75 (62.1-85.3)
Severe proteinuria +++ (300 mg/dl)				
Any level	20.1 (13.7-27.9)	91.3 (85.5-95.1)	93.1 (83.8-97.1)	16.4 (10.2-24.3)
Upper urinary tract	33.9 (23.2-45)	90.1 (73.1-97.9)	65.5 (58.9-76.1)	71.1 (63.2-85.3)
Macroscopic haematuria and/or proteinuria				
Any level	33.3 (23-44.9)	70 (34.7-93.3)	89.7 (72.6-97.8)	11.9 (4.9-22.9)
Upper urinary tract	51.7 (32.5-70.5)	76.3 (63.4-86.4)	51.7 (32.5-70.5)	76.3 (63.4-86.4)

consistent with findings in other studies [21, 23], but occurred a higher proportion in our setting.

Boys had a higher risk of having any lesion in the urinary tract; this difference has been previously shown and is usually attributed to a higher parasite burden due to swimming or working on irrigated agricultural farm lands [16, 24, 25]. Regarding the alterations of the upper urinary tract, no difference by sex was observed.

Older children had a significantly higher risk of lesions in the lower urinary tract; this difference could not be observed on the upper urinary tract abnormalities, possibly due to the fewer cases in this group. This finding seems logical as older children had more prolonged contact with the parasite, and therefore a longer time to develop complications.

Regarding haematuria, we found no significant association between the absence or presence of microhaematuria and the damage at any level of the urinary tract, probably because both haematuria and alterations in the urinary tract are virtually universal in this group of children. Consequently, sensitivity is very high, but specificity is low. Positive predictive value is high in this context for detecting abnormalities at any level, but very low for upper urinary tract pathology. Other studies have shown no association between the presence of haematuria and urinary tract pathology [24, 26].

Interestingly, high proteinuria levels (>300 mg/dl) were significantly associated with the presence of upper urinary tract abnormalities, but not with the presence of bladder abnormalities. This finding seems logical because high proteinuria levels are associated with severe renal damage, and it is particularly important. Persistent proteinuria in childhood may cause a hypercoagulable state, dysregulation of fluid, electrolyte imbalance, susceptibility to infections and a tendency to anaemia and malnutrition [25, 27], contributing to the early consequences of schistosomiasis, such as nutritional and cognitive impairment or stunting. However, some level of proteinuria is virtually universal in children with urinary schistosomiasis, as a consequence of the damage caused by the passage of eggs through the bladder wall. This has been clearly shown in the experimental model in an animal host [28], and it is one of the few causes of proteinuria with a non-renal origin. The detection of proteinuria in urine strips has been used along with microhaematuria as a predictor of the presence or absence of schistosomiasis [29, 30]. Urine reagent strips are cheap and easy-to-perform tests, available in most settings. Taking levels of proteinuria into account would be also useful to stratify the risk of severe disease and early complications [26, 31].

Regarding macroscopic haematuria and proteinuria, the positive predictive value of each one is high for detecting abnormality at any level, but very low for upper tract urinary pathology, and the negative predictive value is high for upper urinary tract pathology and very low for detecting pathology at any level. Combining both parameters, we find a good balance between them. If we take into account only cases with a high level of proteinuria (3 crosses or >300 mg/dl), the positive predictive value for both any abnormality and upper tract pathology increases, maintaining negative predictive value.

Given these results, we think that microhaematuria is a good indicator of general damage, and proteinuria

(mainly severe proteinuria) with or without macrohaematuria is a good indicator of more severe damage in the upper urinary tract.

Therefore, we highly recommend an initial ultrasound for children with urinary schistosomiasis showing any of these alterations. Closer monitoring including periodic controls and assessment of nutritional and growth status is also highly recommended. Repeated ultrasound should be taken into account to evaluate future control programmes, because ultrasound can not only be used to detect the presence or absence of schistosomiasis, but also to measure current pathology in the urinary tract. Thus, the WHO ultrasonography protocol applied to a community is a good morbidity predictor.

Most of these pathological alterations, even those with a worse prognosis, have been shown to be reversible, particularly if treated at a young age [21]. This poses a challenge for public health managers and for clinicians working in this area.

Limitations of the study include the small percentage of eligible children who underwent ultrasound and the lack of information about parasite burden in urine, as urine filtration was not performed due to insufficient laboratory capacity.

Conclusion

This study provides further evidence that severe urinary tract pathology in children with urinary schistosomiasis can be found even early in life and that the prevalence of pathology can be high. In a highly endemic situation, microhaematuria and proteinuria are good markers of morbidity due to schistosomiasis, proteinuria being more precise for severe alterations of the upper urinary tract. As schistosomiasis control efforts are currently focused on reducing morbidity, tests that allow the diagnosis of the presence or degree of morbidity are essential for targeting treatment and tracking the progress of control campaigns.

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