Circulating Anodic and Cathodic Antigen in Serum and Urine from *Schistosoma haematobium*–Infected Cameroonian Children Receiving Praziquantel: A Longitudinal Study

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A cohort of 148 Cameroonian children infected with *Schistosoma haematobium* was followed before praziquantel therapy and 1, 2, 3, 5, and 12 months thereafter. Egg output, the reagent strip index (RSI, a pathological marker), and circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) in serum and urine were quantified. At enrollment, the median level of egg output was 365/10 mL of urine; 97% of children had a positive RSI; CAA was detected in serum from 76% of children and in urine from 64%; and CCA was detected in serum from 55% of children and in urine from 87%. Two months after chemotherapy, egg output and RSI had decreased significantly; reinfection later developed in parallel with increases in the serum and urine concentrations of CAA and the urine concentrations of CCA. The measurement of CAA and CCA is useful for diagnosis, evaluation of disease severity, and follow-up of chemotherapy in individuals infected with *S. haematobium*.

About 100 million people in Africa and southwestern Asia are infected with *Schistosoma haematobium*. This infection leads to considerable morbidity in a high proportion of cases [1]. Adult worms reside mainly in the venous plexus of the urinary bladder, and the pathological features of the infection are the consequence of egg deposition into and around the urinary tract. The disease presents as hematuria, leukocyturia, proteinuria, bladder dysfunction, and renal consequences of obstructive uropathy [1–4]. The worm burden determines the level of egg output, which in turn determines the severity of urinary tract disease [5, 6]. Thus it is important not only to detect the infection but also to ascertain its intensity by the quantitation of *S. haematobium* eggs in urine [7]. Combined semiquantitative data on hematuria, leukocyturia, and proteinuria provide an objective measure of pathological severity [8].

A new approach to the diagnosis of schistosomal infection and the assessment of its intensity is the quantitation of circulating antigens of adult schistosomal worms in urine and serum from infected individuals [9]. The major circulating antigens are glycoconjugates associated with the gut of the adult worm—namely, circulating anodic antigen (CAA) and circulating cathodic antigen (CCA). Sensitive enzyme immunoassays (EIAs) have been developed for the detection of CAA [10] and CCA [11]. Both antigens are genus-specific and have been detected in serum and urine from patients infected with *Schistosoma mansoni* [10–12], *Schistosoma intercalatum* [13], and *Schistosoma japonicum* [14]. Few investigations of circulating antigens in *S. haematobium*–infected patients have been conducted so far. Feldmeier et al. reported on the presence of CAA and CCA in serum from patients with mixed infections due to *S. mansoni* and *S. haematobium* [15]. The effect of various chemotherapeutic regimens on the serum level of CAA was measured in these patients; in this study the course of antigenemia seemed to be directed primarily by the presence of *S. mansoni* [16]. Most patients infected with *S. haematobium* had detectable CAA in urine, but none had CCA in urine [17]. The determination of urinary levels of CAA was used to assess the response to praziquantel therapy in a few patients with mixed infections due to *S. mansoni* and *S. haematobium* [18]. In a recent study, Barsoum et al. detected no CCA in serum from *S. haematobium*–infected individuals [19].

Levels of circulating antigens in infections due to *S. haematobium* appear to differ from those in other schistosomal infections. We addressed this issue in a longitudinal study in Cameroon, where *S. haematobium* has a highly focal distribution [20]. For our study we selected a village bordering a crater lake in the South West province, where *S. haematobium* is the only prevalent schistosomal species. In a cohort of *S. haematobium*–infected schoolchildren monitored for

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up to 12 months after therapy with praziquantel, we evaluated the relation of egg output to hematuria, leukocyturia, proteinuria, and concentrations of CAA and CCA, and we studied the usefulness of measurements of these antigens in assessing the intensity of infection and reinfection.

Patients and Methods

Location and population. The study took place in the village of Barombi Kotto in the South West province of Cameroon. Children attending the local school were included in the study if they (1) had laboratory-proven *S. haematobium* infection; (2) were 4–13 years old; (3) had no other severe chronic disorders; and (4) had oral informed consent given by their parents and the director of the school.

Clinical and parasitological investigations. Each child's height and weight were recorded at enrollment. Enlargement of the spleen and the liver was sought by physical examination. Thick stool smears were examined for intestinal parasites. Thick blood smears were prepared and stained with Giemsa for the detection of malarial parasites.

Viable eggs of *S. haematobium* in urine were quantified on 3 consecutive days before chemotherapy with praziquantel and then on 1 day at each of 5 intervals (1, 2, 3, 5, and 12 months) after chemotherapy. On each of these days, each child ingested a 400-mL volume of a fizzy drink at 10 A.M. and urinated into a flask 1 hour later. A portion of the urine (10–50 mL) was passed through a polycarbonate filter (Nucleopore, Pleasanton, CA) and stained with trypan blue [21]. Eggs were then counted.

Reagent strips (Boehringer, Mannheim, Germany) were used for the semiquantitative assessment of hematuria, leukocyturia, and proteinuria. Individual scores for each of these three parameters—ranging from 0 to 3—were added for calculation of the combined reagent strip index (RSI); thus the RSI varied from 0 to 9 points [8, 22]. The RSI was determined before therapy and at months 1, 2, 3, 5, and 12.

In addition, a 50-mL volume of urine was collected at each time point and frozen at −70°C for use in EIA. Moreover, a 10-mL volume of blood was taken at enrollment (from 100% of children) and at months 1, 3, 5, and 12 (from 65%–75% of children); serum was separated, frozen, and stored at −70°C until use in the EIA.

Treatment. At enrollment, all children infected with malarial parasites received a single dose of sulfadoxine (25 mg/kg) and pyrimethamine (1.2 mg/kg), and all children infected with intestinal nematodes received pyrantel (12.5 mg/kg). Furthermore, all children received praziquantel (donated by Bayer, Leverkusen, Germany) in two doses of 40 mg/kg—the first given at enrollment and the second administered 10 days later. Reinfected children received this regimen again at the end of the study (month 12).

EIA. Monoclonal antibodies were used in the antigen-capture sandwich EIA for the quantitation of CAA [10] and CCA [11] in human specimens, as described previously [23]. The cutoff levels of the CAA-EIA were 200 and 100 pg/mL for serum and urine, respectively; those of the CCA-EIA were 1,500 and 230 pg/mL for serum and urine, respectively (all at a 98% level of specificity) [23]. Values below the cutoff level were scored as 0 pg/mL or as 100 and 230 pg/mL (for urine CAA and urine CCA, respectively) for presentation of data in the figures.

Statistical analysis. The Wilcoxon test and Spearman rank correlation were used for statistical analysis. The results given are median values and 95% confidence intervals or ranges.

Results

In a first screening, 153 (88%) of 173 schoolchildren examined were found to be infected with *S. haematobium*. Of these children, 148 (77 girls and 71 boys) were included in the study. Their median age was 11 years (range, 4–13 years). On admission, 48 children (32%) had splenomegaly and 41 (28%) had hepatomegaly. Moreover, at this time, 46 (31%) were infected with malarial parasites: 44 with *Plasmodium falciparum* and 2 with *Plasmodium ovale*. Examination of thick stool smears revealed *Ascaris lumbricoides* eggs in 49 patients (33%), *Trichuris trichiura* eggs in 11 patients (7%), and hookworm eggs in 1 patient (1%). No *S. mansoni* or *S. intercalatum* eggs were found.

S. haematobium egg output, RSI, and CAA and CCA in serum and urine were studied before chemotherapy in all 148 children; 130 children could be monitored at month 1 (i.e., 1 month after chemotherapy), 142 at month 2, 143 at month 3, 143 at month 5, and 89 at month 12. At enrollment, the median level of egg output was 365/10 mL of urine (range, 1–6,333/10 mL), and 86% of children had more than 50 eggs/10 mL. At this time, 97% of children had a positive RSI (median, 5 points; range, 0–9 points). Also at enrollment, the median serum concentration was higher for CAA than for CCA; in contrast, the median CCA level was higher than the median CAA level in urine (table 1). Changes in egg output, RSI, and circulating antigen levels after praziquantel therapy are shown in table 1.

The level of egg output and the percentage of children with any egg output fell significantly at month 1 and month 2 ($P < .001$). However, by month 3, egg output was already increasing slightly; it increased significantly at month 5 and month 12 ($P < .001$; figure 1, top left).

The RSI fell significantly at month 1 and month 2 ($P < .001$) (table 1). However, like egg output, it began to increase by month 3 ($P < .05$) and increased significantly at month 5 and month 12 ($P < .001$). Ninety-three percent of children again had a positive RSI 1 year after chemotherapy, although values were significantly lower than before chemotherapy ($P < .01$).

Serum concentrations of CAA fell significantly at month 1

Table 1. Level of egg output, RSI, and concentrations of circulating schistosomal antigens in serum and urine from Cameroonian children infected with *S. haematobium*.

Factor measured	Result at indicated month*					
	0	1	2	3	5	12
Egg output (no./10 mL of urine)	365 (231–508), 100	0.4 (0–0.6), 56	0 (0–0), 19	0 (0–0), 27	1 (0–6), 52	24 (7–49), 83
RSI (score†)	5 (4–6), 97	1 (0–1), 52	0 (0–0), 27	0 (0–0), 37	1 (1–2), 76	4 (4–5), 93
CAA (pg/mL)						
Serum	3,099 (1,671–4,287), 76	282 (0–399), 59	. . .	486 (0–1,029), 60	449 (252–900), 62	3,642 (1,260–5,415), 81
Urine	210 (126–288), 64	0 (0–0), 24	0 (0–0), 13	0 (0–0), 30	0 (0–0), 28	0 (0–0), 19
CCA (pg/mL)						
Serum	1,596 (0–1,842), 55	1,641 (0–2,037), 53	. . .	0 (0–1,908), 47	2,640 (2,007–3,456), 73	3,330 (2,193–4,119), 75
Urine	1,002 (849–1,326), 87	362 (0–468), 57	0 (0–0), 22	0 (0–0), 41	390 (0–483), 59	389 (0–567), 60

* In relation to praziquantel therapy; 0 = at enrollment. Results given are the median (95% confidence interval), percentage of children positive.
† See text.

($P < .001$) but increased again at month 3 ($P < .01$). No significant change was noted at month 5, whereas values at month 12 ($P < .001$) were similar to pretreatment values (figure 1, top right; table 1).

Serum concentrations of CCA did not change significantly at month 1 or month 3 but did increase at month 5 ($P < .001$). In addition, levels were higher at month 12 than before treatment ($P < .001$). At month 12, serum levels of CCA and CAA were similar (table 1).

CAA concentrations in urine fell significantly at month 1 ($P < .001$) and month 2 ($P < .05$) but increased at month 3 ($P < .001$), thereafter remaining stable until month 12. These levels were significantly lower at month 12 than before treatment ($P < .001$; table 1).

CCA concentrations in urine fell at month 1 and month 2 ($P < .001$). They then increased slightly at month 3 and markedly at month 5 ($P < .001$) and remained unchanged at month 12 (figure 1, bottom left; table 1). CCA levels in urine were significantly lower at month 12 than before treatment ($P < .001$).

At the time of enrollment, egg output was correlated with RSI ($\rho = .67$, $P < .001$), urine CAA ($\rho = .50$, $P < .001$), urine CCA ($\rho = .44$, $P < .001$), and serum CAA ($\rho = .40$, $P < .001$) but not with serum CCA ($\rho = .11$, $P = .18$). Egg output was correlated at month 1 with RSI ($\rho = .40$, $P < .001$) and urine CCA ($\rho = .19$, $P < .05$); at month 3 with serum CAA ($\rho = .28$, $P < .01$) and RSI ($\rho = .23$, $P < .01$); at month 5 with serum CAA ($\rho = .52$, $P < .001$), RSI ($\rho = .37$, $P < .001$), urine CAA ($\rho = .29$, $P < .01$), and urine CCA ($\rho = .18$, $P < .05$); and at month 12 with RSI ($\rho = .60$, $P < .001$), serum CAA ($\rho = .57$, $P < .001$), urine CAA ($\rho = .42$, $P < .001$), and urine CCA ($\rho = .22$, $P < .05$).

At enrollment, RSI was correlated with urine CAA ($\rho = .35$, $P < .001$; figure 2), urine CCA ($\rho = .31$, $P < .001$; figure 3), and serum CAA ($\rho = .24$, $P < .01$) but not with serum CCA ($\rho = .04$, $P = .61$). At month 12, RSI was correlated with urine CAA ($\rho = .42$, $P < .001$) and serum CAA ($\rho = .40$, $P < .01$).

Levels of each schistosomal antigen in serum and urine were significantly correlated with each other at enrollment. Although serum concentrations of CCA were not correlated with egg output or RSI, they were correlated with urine levels of CCA ($\rho = .42$, $P < .001$), urine levels of CAA ($\rho = .28$, $P < .01$), and serum levels of CAA ($\rho = .21$, $P < .05$).

Discussion

From previous studies [24–28] it has been concluded that a single dose of praziquantel (40 mg/kg) yields a cure rate of 90% among *S. haematobium*–infected children. In our study, two doses of 40 mg/kg yielded a cure rate of 81% 2 months later. By this time, the severity of pathological findings in the

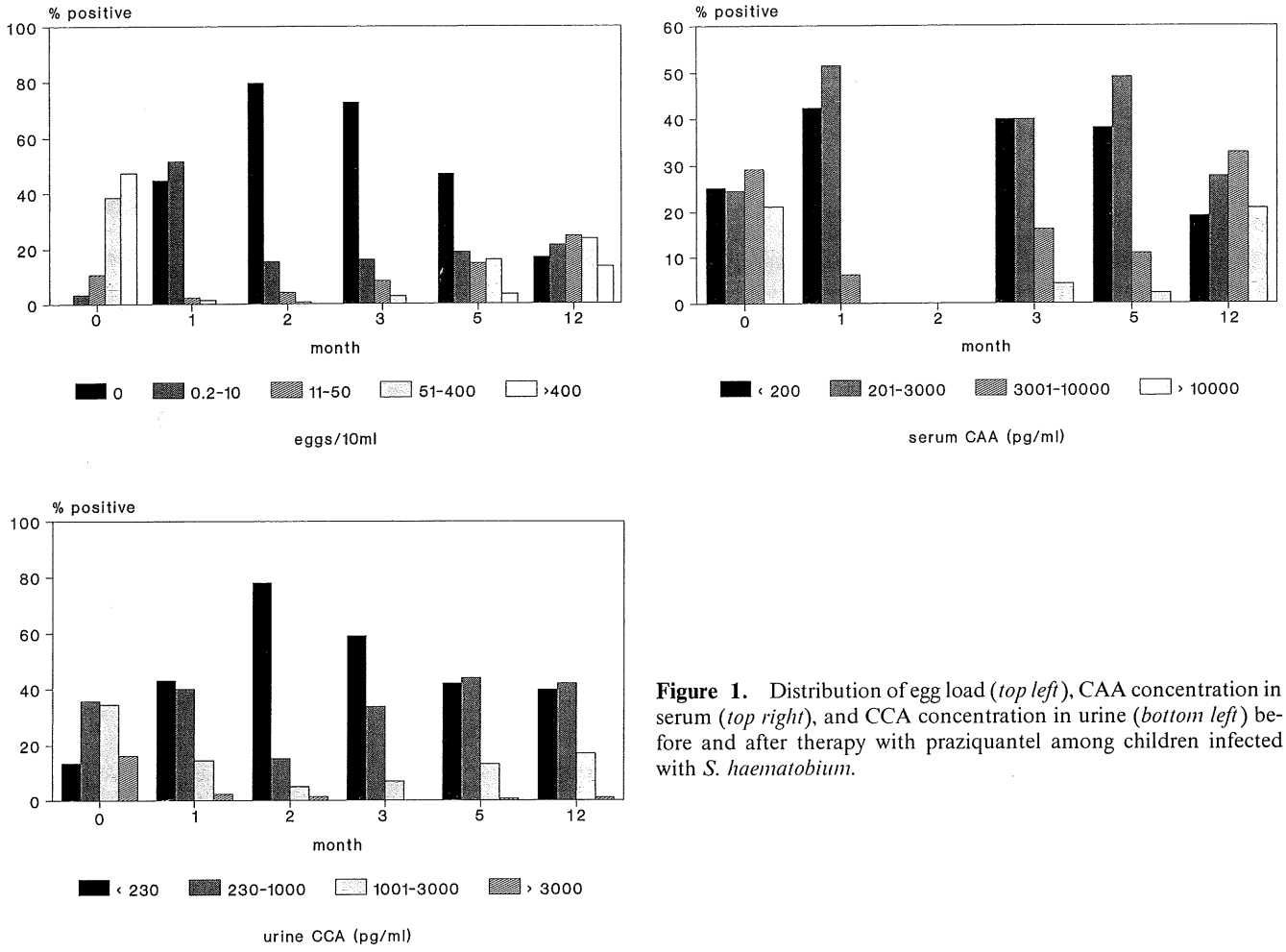

Figure 1. Distribution of egg load (*top left*), CAA concentration in serum (*top right*), and CCA concentration in urine (*bottom left*) before and after therapy with praziquantel among children infected with *S. haematobium*.

lower renal tract was reduced proportionally, as indicated by the RSI; specifically, 73% of children had an RSI score of 0, and the remaining 27% had low scores indicative of mild pathology. In areas with a low rate of transmission of *S. haematobium*, this result could easily be interpreted as reflecting resistance of the parasite to this high dose of praziquantel. However, under the circumstances of the present study, reinfection—even at such an early point—seems more probable.

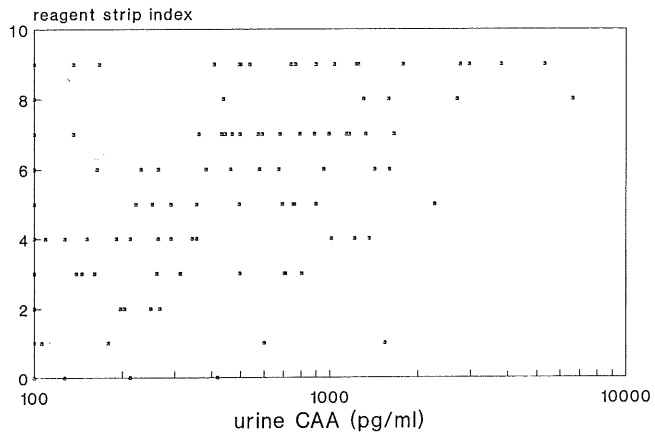

Figure 2. Correlation of reagent strip index (RSI) with CAA concentration in urine ($\rho = .35$, $P < .001$).

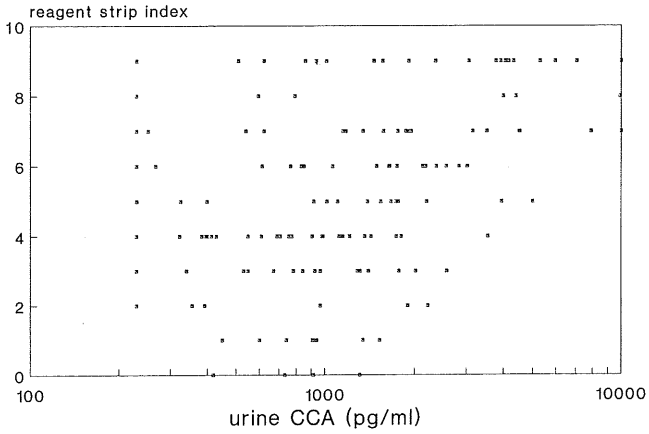

Figure 3. Correlation of RSI with CCA concentration in urine ($\rho = .31$, $P < .001$).

In Barombi Kotto the prevalence of *S. haematobium* infection among children is very high: 88% of 173 pupils examined passed eggs in the urine. During follow-up, reinfection was evidenced by the number of children who were again excreting eggs by 3 months after chemotherapy. Although level and incidence of egg output were still lower than before treatment, the vast majority of children were reinfected by 1 year after chemotherapy.

Ours is the first large-scale trial of urinary schistosomiasis in which levels of worm antigen were measured before chemotherapy and then monitored for 1 year. At enrollment, serum levels of CAA were higher than serum levels of CCA. Moreover, 76% of children had serum CAA concentrations above the cutoff level for the EIA, and the majority had high concentrations. The median CAA concentration in serum was more than 15 times higher than the cutoff. In contrast, the median serum concentration of CCA was barely above the cutoff level. In addition, CCA levels in serum were the only antigen levels that were not correlated with egg output or RSI. Future studies must determine the significance of CCA levels in serum from individuals infected with *S. haematobium*. In the present study, CCA was detected for the first time in the urine of *S. haematobium*–infected patients, and levels of both CCA and CAA in urine were well correlated with egg output and RSI.

In a recent study, Barsoum et al. [19] could not detect CCA in serum from 30 Egyptian patients infected with *S. haematobium*. This discrepancy between their study and ours may be explained by the use of different monoclonal antibodies or a different EIA cutoff value. CCA was clearly demonstrated in urine from infected individuals in the present study. This finding contrasts with our previous results: we found no CCA in urine from 20 *S. haematobium*–infected individuals from Tanzania [17]. However, in that study, we used an indirect hemagglutination assay, and the level of egg output was lower. Because of the lower cutoff point used in our previous study [17], CAA was detected in urine from a higher proportion of patients infected with *S. haematobium* than in the present study (97% vs. 64%).

In a study from Zaire, 80 individuals infected with *S. mansoni* were investigated [23]. CAA was detected in 88% of serum samples and in 62% of urine samples; the corresponding figures for CCA were 79% and 96%, respectively. In the present study we used the same procedure for the pretreatment of samples and the quantitation of antigens as was used in the study in Zaire; thus a direct comparison of antigen concentrations is of interest. The concentrations of CAA in serum from *S. mansoni*–infected individuals were in the same range as those in serum from *S. haematobium*–infected individuals; likewise, CAA concentrations in urine were very similar in the two infections. In contrast, in schistosomiasis mansoni, CCA levels were four times higher in serum and nearly 50 times higher in urine than in schistosomiasis haematobium. It is virtually impossible to compare the intensity of infection with different *Schistosoma* species by quantitation of egg output in stool or urine. For such a comparison, levels of schistosomal antigen may be more appropriate.

In the present study, egg output correlated well with serum levels of CAA and with urine levels of CAA and CCA throughout the follow-up period. Egg output also correlated well with the pathological indicator (RSI) and RSI—like egg output—correlated with levels of CAA in serum and urine. Although 83% of children were reinfected by 1 year after chemotherapy, their median egg output was only 7% of that documented before treatment. It could be supposed that the parasite load was similarly low. Furthermore, the RSI was significantly lower 1 year after than before chemotherapy, although the median RSI was barely reduced—from 5 points to 4 points. In contrast, except for the level of CAA in urine, antigen levels did not change comparably to egg output and RSI by 1 year after chemotherapy. At the latter time, the median CCA level in urine was 39% of the initial value. Median serum concentrations of CAA were similar at enrollment and 12 months after chemotherapy. This result suggests that the actual worm burden was higher at month 12 than was indicated by egg output. Further studies may yield additional evidence for this hypothesis.

The decrease in egg output after chemotherapy and the consequent reinfection of children are closely paralleled by a rapid decrease and a slower increase in RSI. The kinetics of serum concentrations of CAA and urine levels of CAA and CCA also reflects these events. Although the introduction of antigen detection into routine use must await the development of a rapid dipstick method, the quantitative measurement of schistosomal antigens in human specimens clearly can be used to diagnose infection, to measure the severity of pathological manifestations in the lower renal tract, to monitor the impact of chemotherapy in infected individuals, and to investigate ongoing transmission in areas endemic for *S. haematobium*.

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