

ORGANOMETRIC INVESTIGATIONS OF THE SPLEEN AND LIVER BY ULTRASOUND IN *SCHISTOSOMA MANSONI* ENDEMIC AND NONENDEMIC VILLAGES IN SENEGAL

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Abstract. With the intention of ultrasonographically assessing hepatosplenic morbidity in *Schistosoma mansoni* infection and of validating the grading system applied (Cairo classification), 191 subjects in a schistosomiasis endemic village and 247 controls from a nonendemic village in northern Senegal underwent sonographic examination of the liver and spleen. Measurements of the diameters of the peripheral periportal vein branches, the main portal vein stem, liver size (left lobe and right lobe), and spleen length in the endemic village were compared with those in the nonendemic village to evaluate the much discussed influence of *S. mansoni* infection on those variables. To subtract this presumed influence from reference values for the named variables, they are given as measured in the nonendemic village, stratified by body weight, enabling future investigators on schistosomiasis-induced morbidity to refer to these reference values. The 95th percentile regarding peripheral periportal vein branch diameter in the control groups was exceeded in 24% of the subjects in the endemic group. It was exceeded by 6% for the main portal vein stem diameter, 13% for the left liver lobe, 12% for the right liver lobe, and 14% for the spleen length. According to the Cairo classification, 97% of the endemic population and 81% of the controls had periportal thickening of the liver, mostly grade I. We conclude that 1) hepatic morbidity in the *S. mansoni* endemic area was low, despite strikingly high intensities of infection; 2) the Cairo classification in its present form overestimates periportal thickening, especially in the case of mild morbidity; and 3) body height-dependent reference values, obtained from endemic controls, must be applied for organometric parameters.

Ultrasonography has become a valuable tool in the assessment of hepatosplenic morbidity due to *Schistosoma mansoni* infection, in which periportal thickening in the liver may develop. These liver changes can be detected by ultrasound as thickened hyperechoic streaks accompanying the portal vein branches.

Several classification systems have been developed for the grading of liver changes. In 1990, an expert group was convened under the auspices of the World Health Organization in Cairo and proposed a classification system based on the measurements of the diameters of peripheral portal vein branches, which has been termed the Cairo classification.¹ This classification defines a portal vein branch diameter less than a certain value (cut-off) as normal, greater than this value as pathologic, with additional cut-off values for three increasing grades of severity of lesions. For these cut-off values, age or body height (which naturally influence the normal size of portal vein diameters) of the investigated individuals was not taken into consideration because the majority of the workshop participants were medical doctors practicing with adults, and thus were not very familiar with pediatric practice and the importance of dynamics of children's growth. Since body height-dependent reference values have not been published for an African population, in previous field studies the fixed cut-off values of the Cairo classification have been applied despite their shortcomings.^{2–5} Liver and spleen size measurements of young Zimbabwean schoolchildren whose stools were negative for *S. mansoni* 12 months after treatment with praziquantel have been reported.⁶ These figures could serve as reference values in other endemic settings as well. However, for reasons of compatibility we applied reference values obtained from a con-

trol village. In September and December 1993, we used ultrasonography to study the people in a village heavily infected with *S. mansoni* and a comparable, noninfected village in northern Senegal, serving as a control population. With this study design, we aimed to evaluate the applied grading system by comparing our findings with measurements in the control village. Height-dependent reference values as obtained from the control population are given for liver and spleen size and for the diameters of the portal vein and the intrahepatic, peripheral portal vein branches.

PATIENTS AND METHODS

Study population. Ndombo is a village in northern Senegal, 100 km east of St. Louis. *Schistosoma mansoni* infection was first detected in the area in 1988 and has been spreading rapidly ever since, leading to prevalences of 91% and geometric mean egg loads of 646 eggs per gram (epg) of feces. The 4,000 inhabitants of Ndombo are mostly ethnic Wolof, and the main occupations are agriculture and fishing.^{7,8} One hundred ninety-one randomly chosen inhabitants of Ndombo more than four years of age were investigated in the present study.

The village of Khatete Gaye, which was nonendemic for either *S. mansoni* or *S. haematobium* infection, is situated 30 km south of St. Louis. Most of its 303 inhabitants are ethnic Wolof, and the main occupation is agriculture. All 247 inhabitants more than four years of age who had been living in the village for more than six months were investigated. In both settings, age, sex, weight, and height were recorded for every study participant.

Parasitologic examination. In Ndombo, two stool spec-

imens were collected and processed separately. From each stool sample, two Kato slides (25 mg each) were processed.^{9,10} Egg counts were given as epg, and group mean egg counts were given as geometric mean egg counts (in epg) of those infected. In Khatete Gaye, only one stool sample per person was collected and processed in the same manner as in Ndombo. Urine samples (10 ml each) of all patients, collected between 10:00 AM and 11:00 AM, were microscopically examined for *S. haematobium* infection after filtration with Nytrex[®] filters (Fyltis, Lyon, France).

Ultrasonographic examination. Ultrasound was performed with a SDR 1550 XP machine (Philips, Eindhoven, The Netherlands) with a 3-MHz sector probe for those ≥ 10 years of age and a 5-MHz probe for children < 10 years of age. The study and control groups were examined by the same observer (YY). According to the proposals of the Cairo Working Group,¹ the following measurements were taken: the mean diameter of three peripheral portal vein branches (second intrahepatic branch), the diameter of the portal vein midway between its entrance into the liver and the bifurcation, the liver size at the parasternal and the frontal axillary line, and the spleen length at a longitudinal cut through the region of the splenic hilus. Periportal thickening was graded as follows: diameter of 0– < 3 mm = grade 0; 3–5 mm grade I; > 5 –7 mm grade II; > 7 mm grade III (Cairo classification).¹ According to the Cairo Classification, the portal vein was considered enlarged if it exceeded 12 mm in diameter.¹

Statistical analysis. The SPSS/PC 5 statistical software (SPSS, Inc., Chicago, IL) was used for analysis. Individual egg counts were logarithmically transformed to obtain normal distribution. The Student *t*-test and Chi-square test were applied for comparison of data. For both villages, the relationship of variables to age and body height, and for Ndombo, also to egg excretion, was tested in a multiple regression analysis, with backward elimination of independent variables (elimination criterion $P > 0.05$). The null hypothesis was rejected at an error probability of $< 5\%$ ($P < 0.05$). In addition to the Cairo classification, the measurements of the Ndombo population were also related to the 95th percentiles of the respective variables as measured in the control village. Values exceeding the 95th percentile in the control village were considered pathologic. Group means, standard deviations, and 95th percentiles are presented.

Ethical clearance. Informed consent was obtained from patients or their parents. They had the right to refuse participation without influence on therapy. All patients with *S. mansoni* eggs in their stools were treated with praziquantel, 40 mg/kg of body weight; all patients found infected with intestinal worms were treated with mebendazole, and those with amoeba cysts in their stools received treatment with metronidazole. Pregnant women were asked to refer to the local health center after giving birth to receive treatment. Minor diseases, detected clinically or through ultrasound, were treated according to local standards, and patients with severe diseases were referred to the local health center. The study was approved by the local health authorities, the Ministry of Health of the Republic of Senegal, and the Ethical Committees of the Universities of Bonn and Hannover, Germany. The village inhabitants of Ndombo received extensive health education. Training of local collaborators (medical doctors working at the Richard Toll Centre de Sante Pub-

TABLE 1
Age distribution of the Senegalese study populations in Khatete Gaye (nonendemic) and Ndombo (endemic) and *Schistosoma mansoni* prevalence and intensity of infection in Ndombo*

| | Age (years) | | | | n |
|------------------|-------------|--------------|-------------|--------------|--------------|
| | 4–10 | 11–20 | 21–40 | >40 | |
| Khatete Gaye | 31% (77) | 31% (76) | 21% (51) | 17% (43) | 247 |
| Ndombo | 31% (59) | 27% (53) | 22% (42) | 20% (37) | 191 |
| Prevalence (n) | 97% (57) | 100% (53) | 95% (40) | 100% (37) | 98% (187) |
| GMEC | | | | | |
| log (epg > 0) | 1,215 | 1,880 | 510 | 375 | 901 |

* GMEC = geometric mean egg count (in epg). epg = eggs per gram of stool.

lique) especially in ultrasound reading, was a strong component of the study. The Philips machine was handed over to the local health clinic and is presently in use for routine diagnostic procedures serving the population of Richard Toll and surrounding areas.

RESULTS

The age distributions of the study populations in Ndombo and Khatete Gaye are given in Table 1. There was no significant difference in age or sex distribution between the two study groups (age: $\chi^2 = 0.78$, degrees of freedom [df] = 3, $P = 0.85$; sex: $\chi^2 = 0.6$, df = 1, $P = 0.44$).

Parasitology. In Ndombo, the prevalence of *S. mansoni* infection in the study sample was 98% (n = 187 of 191 with at least one positive stool sample), and the intensity of infection was high, with a geometric mean egg count of 901 epg. The lowest prevalence rate (95%) was found in the 21–40-year-old age group. The intensity of infection was highest in children and adolescents between 11 and 20 years of age with a geometric mean egg count of 1,880 epg, decreasing with age to a mean of 375 epg in those > 40 years old (Table 1). In Khatete Gaye, no infection with *S. mansoni* or *S. haematobium* was detected.

Portal vein branches. According to the Cairo classification, there was no severe case (grade III) of periportal fibrosis in either village. The mean diameters of the portal vein branches in the different age groups are shown in Table 2. The mean diameter in the schistosomiasis endemic village was slightly greater than that in the nonendemic village in all age groups, with differences ranging between 0.17 and 0.71 mm, thus never reaching 1 mm. In the groups 4–10 and 11–20 years of age, however, this difference was statistically significant ($P < 0.0001$, by *t*-test).

Multiple regression analysis showed a strong association between portal vein branch diameters and body height in both villages. The regression equations were for Ndombo: portal vein branch diameter (mm) = $0.022 \times$ body height (cm) + 0.97; for the control village: portal vein branch diameter (mm) = $0.027 \times$ body height (cm) – 0.012. Entering egg load (in epg) into the equation either alone or as an additional independent variable in Ndombo showed that there was no significant relationship between *S. mansoni* infection and size of portal vein branches.

Applying the cut-off values proposed by the Cairo Work-

TABLE 2

Means of outer diameters of portal vein and intrahepatic branches (second branch after the bifurcation of the portal vein) for different age groups in Khatete Gaye (KG, nonendemic) and Ndombo (N, endemic)

| Age (years) | Peripheral portal vein branches in mm (n) | | Portal vein in mm (n) | |
|-------------|---|--------------|-----------------------|--------------|
| | KG | N | KG | N |
| 4-10 | 3.1* (77) | 3.9* (55) | 5.6 (77) | 5.8 (59) |
| 11-20 | 4.1* (76) | 4.7* (53) | 7.1* (76) | 8.1* (53) |
| 21-40 | 4.7 (51) | 4.9 (42) | 9.0 (51) | 9.3 (42) |
| >40 | 4.6 (43) | 4.8 (36) | 9.2 (43) | 8.7 (37) |
| Total | (247) | (186) | (247) | (191) |

* ** The difference between the two villages was significant ($P < 0.001$).

ing Group sensu strictu, 97% of the population of Ndombo and 91% of the population of Khatete Gaye had periportal thickening at levels grade I or II. In Ndombo, there were 18% (34) with grade II; in the control village, the rate was 9% for grade II ($n = 22$, Table 3).

Height-dependent means and 95% percentiles of the portal vein branch diameters and for the liver and spleen sizes in the control village are given in Table 4. Even though group means were not significantly different between the two villages (24%, $n = 46$), those in Ndombo had diameters slightly above the height-dependent 95th percentile of the control population, corresponding closely to the distribution of grade II periportal thickening according to the Cairo classification (Table 5). In Ndombo, periportal thickening as calculated with height-dependent reference values was more frequent in children than in adults (32% versus 15%; $\chi^2 = 6.1$, $df = 1$, $P = 0.01$).

Portal vein. Concerning the diameter of the portal vein midway between its entrance at the porta hepatis and its bifurcation, group means always increased with age, as shown in Table 2. The differences between the two villages were statistically significant only in the group 11-20 years of age (7.1 mm in Khatete Gaye versus 8.1 mm in Ndombo; $P < 0.0001$; Table 2). In subjects > 40 years of age, the mean diameter in the control village exceeded that in the endemic village (9.2 mm versus 8.7 mm; $P > 0.05$). In the other age groups, it was greater in the endemic village, with differences being very small, ranging between 0.1 and 1 mm.

Multiple regression analysis showed a strong association between the diameter of the portal vein and body height in both villages. The regression equations were for Ndombo: portal vein (mm) = $0.051 \times$ body height (cm) + 0.02; for the control village: portal vein (mm) = $0.055 \times$ body height (cm) - 0.68. Entering egg load (in epg) into the equation either alone or as an additional independent variable in Ndombo showed that there was no significant relationship between *S. mansoni* infection and diameter of the portal vein.

Considering an enlarged portal vein diameter to be 12 mm, as suggested by the Cairo Working Group, only one subject in the endemic village of Ndombo and four subjects in the control group (1.6%) had a dilated portal vein. Ap-

TABLE 3

Percentages of normal findings (grade 0, no periportal thickening) and pathologic lesions (grade I and II, periportal thickening) according to the Cairo classification in Khatete Gaye (nonendemic) and Ndombo (endemic)

| | Grade 0 | Grade I | Grade II | Total (n) |
|--------------|---------|---------|----------|-----------|
| Khatete Gaye | 9% | 82% | 9% | 247 |
| Ndombo | 3% | 79% | 18% | 186 |

plying the reference values from Khatete Gaye (Table 4), 6% ($n = 11$) of the Ndombo study patients had an enlarged portal vein, compared with the 5% (5% always exceeding the 95% percentile; $n = 13$) in the control village (Table 5; $P > 0.05$). They were evenly distributed between age groups. Thus, there was no difference between the two villages concerning the portal vein diameter.

Organometry. The length of the left liver lobe was assessed in 246 individuals in Khatete Gaye and in 180 individuals in Ndombo. For the right liver lobe, the number of people investigated were 247 and 191, respectively.

Body height-dependent means and 95th percentiles for liver length in the parasternal and frontal axillary line of the control population are given in Table 4. In the Ndombo study population, 13% ($n = 23$, left lobe) and 12% ($n = 23$, right lobe) exceeded the 95th percentiles of the control village, with the difference between villages being statistically significant (Table 5; $\chi^2 = 7.6$, $df = 1$, $P = 0.006$ for the left lobe; $\chi^2 = 4.8$, $df = 1$, $P = 0.03$ for the right lobe). Table 5 shows the percentage of subjects in Ndombo exceeding the 95th percentile of the values found in the control village (which were used as reference values). This implies that the corresponding figures for the control village would, by definition of a 95th percentile, be 5% for all variables shown. In Ndombo, children were significantly more often affected by left lobe hepatomegaly than adults (18% versus 6%; $\chi^2 = 4.7$, $df = 1$, $P = 0.03$). For right lobe enlargement, there was no difference between children and adults (13% versus 11%; $\chi^2 = 0.3$, $df = 1$, $P = 0.86$). The numbers of uninfected individuals in Ndombo were too low to be tested for significant differences between infected and uninfected within the village. The longitudinal diameter of the spleen (spleen length) was assessed in 185 inhabitants of Ndombo and 244 inhabitants of the control village. In Ndombo, 14% of the subjects had a spleen length exceeding that of the 95th percentile in Khatete Gaye (Table 5; $\chi^2 = 9.8$, $P = 0.002$). The difference between children and adults was not significant (16% versus 12%; $\chi^2 = 0.38$, $P = 0.54$).

DISCUSSION

The time lapse between the infection with *S. mansoni* and the development of periportal (Symmer's) fibrosis in humans is estimated to be at least five years.¹¹ Thus, with the infection in Ndombo having been endemic for about five years at the time of this study, one might expect that hepatic lesions would be just developing. When compared with the 95th percentile in Khatete Gaye (nonendemic), the endemic village showed periportal thickening in only 24% of the population. On the one hand, this can be regarded as an indicator of beginning fibrosis in a quarter of the population of Ndom-

TABLE 4

Reference values of the portal vein, for the second intrahepatic vein branches after the bifurcation of the portal vein in the liver, for the left and right liver lobe, and for the spleen length in individuals living in a *Schistosoma mansoni* nonendemic village in northern Senegal*

| Body height (cm) | | Portal vein branches (mm) | Portal vein (mm) | Left liver lobe (mm) | Right liver lobe (mm) | Spleen length (mm) | n |
|------------------|-----------------|---------------------------|------------------|----------------------|-----------------------|--------------------|----|
| <120 | 95th percentile | 3.6 | 7.8 | 65 | 98 | 82 | 44 |
| | SD | 0.4 | 1.0 | 7 | 8 | 11 | |
| | x | 2.9 | 5.4 | 51 | 82 | 60 | |
| 120-139 | 95th percentile | 4.6 | 7.9 | 69 | 110 | 92 | 42 |
| | SD | 0.6 | 1.1 | 8 | 9 | 12 | |
| | x | 3.4 | 5.9 | 57 | 97 | 68 | |
| 140-159 | 95th percentile | 5.0 | 10.8 | 84 | 140 | 104 | 64 |
| | SD | 0.6 | 1.8 | 9 | 13 | 13 | |
| | x | 4.2 | 7.5 | 66 | 116 | 80 | |
| 160-169 | 95th percentile | 5.6 | 11 | 84 | 141 | 129 | 44 |
| | SD | 0.7 | 1.8 | 9 | 10 | 15 | |
| | x | 4.5 | 8.5 | 68 | 120 | 88 | |
| >169 | 95th percentile | 5.6 | 13 | 83 | 141 | 114 | 53 |
| | SD | 0.6 | 1.7 | 9 | 10 | 13 | |
| | x | 4.9 | 9.2 | 68 | 125 | 92 | |

* Values are as measured in Khatete Gaye. SD = standard deviation; x = arithmetic mean. For this study, only values > the 95th percentile are considered pathologic.

bo. On the other hand, this figure should be interpreted with caution. The differences in the mean diameters of portal vein branches of the people of Ndombo and height-matched controls were only in the range of tenths of millimeters. Considering the resolution capacity of the ultrasound machine used, we conclude that the differences in portal vein diameters between the two villages were minimal.

Altogether, our results confirm those of earlier studies reporting a low rate of hepatic involvement in Ndombo and Richard Toll, a neighboring city of 50,000. In those studies, results were obtained using different classification systems⁵ and clinical methods.⁸ Considering the extremely high intensities of infection in the area, however, the development of more severe hepatic disease in future years is conceivable, but as yet (3/97) has been observed only in a few individual cases (unpublished data).

Several classification systems have been developed to grade periportal thickening. These are mainly qualitative methods as described by Homeida and others¹² or by Doehring-Schwerdtfeger and others,¹³ the latter having been developed for children. The proposals by the Cairo Working Group were set up as an attempt to standardize and quantify ultrasound readings. However, for the cut-offs values proposed, body height dependence of portal vein diameters was not taken into consideration. Adults have larger organs and greater portal vein diameters, which is bound to lead to falsely high percentages of periportal thickening in adults and/or

falsely low percentages in children when fixed cut-off values are used. Our reference values show that even in children with a height < 120 cm, the mean value of 2.9 mm almost reaches the 3-mm cut-off for grade I, and the reference value (mean + 1 SD = 3.3 mm) exceeds the cut-off. Consequently, also in the control village, high percentages of subjects with periportal thickening of grades I and II according to the Cairo classification were detected (82% grade I and 9% grade II).

It is understood that reference values may still vary between different ethnic groups due to different genetic backgrounds as well as different nutritional and other environmental factors with a potential influence on organ sizes. However, we do believe that with the values obtained from a rural African population in a schistosomiasis-free area outside the malaria transmission season, a first step towards the adjustment of existing classification systems has been taken.

The mean length of the left liver lobe was 10-25% smaller than in a group of height-matched *S. mansoni*-negative children in Zimbabwe as reported by de Friis and others, whereas mean values for the right liver lobe corresponded well in the respective height groups.⁶ However, our values were still within the range of the mean + 1 SD of the Zimbabwean population because the SD was up to 25% of the mean. The SD in our study population was smaller, expressing less variation of organ size within height groups, even though the groups had a greater height range (20 cm versus 10 cm in the Zimbabwe group) and groups were slightly greater. Greater values have been published from a German reference population.¹⁴

The frequency of hepatomegaly (13% left lobe and 12% right lobe enlargement) was higher than the 7% detected clinically by Stelma and others during a survey in Ndombo in 1991.⁸ However, ultrasound is known to be a more sensitive method in the detection of organomegaly, so our findings do not necessarily indicate a higher rate of hepatomegaly than in 1991.

The mean values for spleen length reported by Friis and

TABLE 5

Percentages of enlargement of peripheral portal vein branches, portal vein, left liver lobe, right liver lobe, and spleen length (values above the 95th percentile of the control village) in Ndombo (endemic)*

| | Portal vein branches | Portal vein | Left liver lobe | Right liver lobe | Spleen length |
|--------|----------------------|-------------|-----------------|------------------|---------------|
| Ndombo | 24% | 6% | 13% | 12% | 14% |

* Based on reference values from Khatete Gaye. Values are the percentage of cases greater than the 95th percentile of the control village (i.e., corresponding values for Khatete Gaye are 5% for every variable, by definition).

others⁶ are 5–10% smaller than those found in Khatete Gaye, but spleen sizes vary considerably within height groups, which is reflected in the high SD values both in this and in the Zimbabwean group. Spleen lengths of the German population, as mentioned above, have been published by Weitzel and others¹⁵ and are comparable with those reported by Friis and others.⁶ In the German group, SD values were up to 50% of the respective mean values.

The rates of splenomegaly are difficult to judge because the study in Ndombo was undertaken at the end of the rainy season. There was a malaria prevalence of 5% in a different subsample of the same population.⁵ People in Khatete Gaye, where even in the rainy season malaria prevalence is low, were examined during the dry season. The higher percentage of splenomegaly in Ndombo (14% versus 5% in Khatete Gaye) could therefore be related to a higher malaria prevalence.

In summarizing our results, we conclude that ultrasonographic findings characteristic of schistosomiasis induced morbidity were rare in the investigated area, despite strikingly high prevalences and intensities of infection. We showed that in situations like this, with only early stages of hepatic involvement if at all, the Cairo classification overestimates pathologic lesions. The introduction of body height-dependent reference values may possibly improve the accuracy of grading of hepatic involvement, especially in early lesions. We recommend that more studies among normal individuals in an endemic area with different ethnic/genetic backgrounds be undertaken to establish appropriate reference values. We hope that with such reference values as provided here, it will be possible to better describe hepatosplenic morbidity in schistosomiasis in the future.

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