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Schistosoma mansoni infection in a recently exposed community in Senegal: lack of correlation between liver morphology in ultrasound and connective tissue metabolites in serum

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Summary Four hundred and seventy villagers of Ndombo, a village with recently established intensive transmission of *Schistosoma mansoni* in the Senegal River Basin, were enrolled in a study with the intention to assess hepatosplenic morbidity. All patients were examined parasitologically and by ultrasound. Hepatic fibrosis serum markers were determined in 153 adult patients (aminoterminal propeptide of procollagen type III, hyaluronan and laminin). By ultrasound, about 60% of the patients showed early stages of hepatic involvement, 3% of the patients unequivocally showed severe hepatosplenic pathology (grade 3 according to the Managil classification), whereas in another study performed in the same village 3 years earlier, no patients with severe hepatosplenic pathology had been found. No correlation between the aminoterminal propeptide of procollagen type III, hyaluronan or laminin and the ultrasound findings could be established. These hepatic fibrosis serum markers do not seem to be a sensitive method to detect early hepatic fibrosis in schistosomiasis.

keywords schistosomiasis, Senegal, ultrasound, hepatic fibrosis, procollagen type III, hyaluronan, laminin

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Introduction

Infection with *Schistosoma mansoni* may give rise to intestinal and/or hepatosplenic disease (Chen & Mott 1988). The disease is mostly due to eggs deposited in host tissues by adult female worms which induce inflammatory and fibrotic lesions in host organs. The main lesion in hepatosplenic schistosomiasis is fibrosis in the portal tracts of the liver. Microscopic examination typically reveals eggs with surrounding granulomatous reactions with a mixed leukocytic infiltrate. In advanced disease, the pathognomonic finding of 'pipe-stem fibrosis' is seen. In hepatic involvement without decompensated portal hypertension the diagnosis cannot be confirmed clinically. Hepatomegaly is not a reliable indicator for hepatosplenic schistosomiasis because other diseases have to be excluded and because neither in autopsy (Cheever 1968) nor in ultrasound studies (Homeida *et al.* 1988b) could hepatomegaly be proven to be related to the presence of periportal fibrosis. Even in advanced cases, liver enzymes are only modestly elevated and markers for synthesis in the liver (such as albumin, cholinesterase) only slightly affected.

Ultrasonography can demonstrate hepatic fibrosis. The characteristic finding is periportal fibrosis, additional signs are hypertrophy of the left lobe with atrophy of the right lobe and thickening of the gall bladder wall (Arafa *et al.* 1983; Doehring-Schwerdtfeger & Kardorff 1995). A dilated portal vein, portal-systemic collaterals and splenomegaly can be well visualized in patients with advanced disease (Hill *et al.* 1985; Richter *et al.* 1992a, 1992b). The diameter of the portal vein correlates with the portal pressure (Abdel-Latif *et al.* 1981) and the risk for gastrointestinal haemorrhage (Richter *et al.* 1992b). Ultrasonography, however, is of questionable efficacy to detect early fibrosis. Several classification systems for

fibrosis in schistosomiasis have been proposed. These use mainly qualitative criteria like those described by Homeida *et al.* (1988b), applied in several epidemiological studies (Abdel-Wahab *et al.* 1989, 1992; Davidson *et al.* 1991; Domingues *et al.* 1993; Nko'o-Amvene *et al.* 1993; Houston *et al.* 1993; Tanabe *et al.* 1997). Another classification system ('Managil classification'), developed for use in the field, was initially evaluated in children (Doehring-Schwerdtfeger *et al.* 1989), later in adults (Richter *et al.* 1992b). Another staging system for *Schistosoma mansoni* infection was proposed by a WHO working group ('Cairo classification') (Jenkins & Hatz 1992). This system is based on measurements of the diameters of peripheral portal branches, without clearly defining where to measure the peripheral portal branches and without taking into consideration age or height of the patients. As could be expected, interobserver variation for the distinction of low level periportal fibrosis seems to be rather high (Doehring-Schwerdtfeger *et al.* 1992; Kardorff *et al.* 1996) and suggestions for a modification of the Cairo classification were made (Nooman *et al.* 1995; Boisier *et al.* 1995; Lanuit *et al.* 1996; Kardorff *et al.* 1997; Yazdanpanah *et al.* 1997; Gerspacher-Lara *et al.* 1997).

Several tests to measure circulating collagens, procollagen peptides, extracellular matrix glycoproteins and their fragments in human serum have been developed (Tanikawa 1994). Serum levels of these parameters are thought to be good markers of the ongoing fibrogenesis, fibrolysis or both in the liver. Factors influencing the blood level of these parameters are the liver volume, the activity of fibrogenesis, the amount of accumulated fibrous tissue, the degree of the sinusoidal capillarization, und the rate of sinusoidal clearance.

The objective of our study was to compare ultrasound in the detection of early hepatic fibrosis in schistosomiasis with different serum markers for hepatic fibrosis.

Patients and methods

Study population

A focus with intense transmission of *Schistosoma mansoni* has recently been established in the Senegal River Basin. This epidemic outbreak is probably related to man-made ecological changes in the area. Several epidemiological, immunological and clinical studies have monitored this outbreak of schistosomiasis (Talla *et al.* 1990; Rouquet *et al.* 1993; Gryseels *et al.* 1994; Guisse *et al.* 1997; Stelma *et al.* 1993, 1994, 1995, 1997; Kongs *et al.* 1994, 1996). Our study was conducted in July 1996 in Ndombo, a village located 4 km from Richard-Toll. Most of the inhabitants are ethnic Wolofs. A previous ultrasonographical study had been performed in Ndombo in September-October 1993 (Kardorff *et al.* 1996; Yazdanpanah *et al.* 1997).

Permission to conduct the study was obtained from national health authorities. Informed consent was obtained from village leaders and participating villagers.

Parasitological examination

Egg counts for all individuals were obtained by the standardized Katz-Kato technique. Two stool specimens were collected and per stool sample, two Kato slides of 25 mg each examined.

Ultrasonography

For the ultrasound examinations we used portable ultrasonic equipment (Echo View SDU 350, Shimadzu, Japan) with a convex 3.75 MHz transducer and a microconvex 3.5 Mhz transducer. The examination followed a standardized protocol according to the classification proposed by Richter *et al.* (1992b) and the Cairo classification (Jenkins & Hatz 1992). Inner-to-inner and outer-to-outer measurements of the second peripheral branch after ramification of the portal vein in the left and right liver lobes were made. Measurements were taken at three different branches and their mean calculated. The portal vein inner-to-inner diameter was determined at the liver hilus. Normal values for spleen size in children were defined according to Rosenberg *et al.* (1991). In adults splenomegaly was diagnosed when the longest diameter exceeded 13 cm. Ultrasound examinations were simultaneously performed by two observers.

Serum markers of fibrosis

Hepatic fibrosis markers were determined only in adults because no normal ranges were available for children. Markers were determined from all adults; however, of those 93 patients without fibrosis according to both Cairo and Managil classification (Table 3), only 50 patients were taken at random. Of the 82 patients with fibrosis grade I according to Cairo and grade 2 according to Managil (Table 3), 50 patients were taken at random also.

P-III-NP was determined in serum by a radioimmunoassay (Behring-Hoechst, Frankfurt, Germany) as described previously (Gressner *et al.* 1988a). Hyaluronan was measured by a previously described radiometric assay (Pharmacia, Uppsala, Sweden) (Engström-Laurent *et al.* 1985). Laminin was measured in serum by a competitive radioimmunoassay (Behring-Hoechst, Frankfurt, Germany) with antibodies directed against antigenic determinants of the pepsin-resistant fragment P1 of laminin. The concentration of laminin is expressed in arbitrary U/ml because an international standard of laminin is not available; 1 U/l is defined as the mean quantity of laminin in a group of

apparently healthy Caucasians, and corresponds to about 0.23 μg (Gressner *et al.* 1988b). The cut-off levels used to discriminate normal from elevated levels were 817 U/l for P-III-NP, 100 μg/l for hyaluronan and 1900 U/l for laminin.

To exclude other diseases, serum specimens were tested for anti-HBc, HBsAg and HCV using kits purchased from Abbott laboratories.

Egg-positive patients (*S. mansoni*) were treated after examination with praziquantel, under direct supervision. Patients with intestinal nematodes were treated with mebendazole.

Statistical analysis:

Statistical differences between means were calculated with Student's *t*-test. Correlation between ultrasound findings in different classificaton systems was done by χ^2-test, in the other cases correlation is expressed by the Kendall rank correlation coefficient.

Results

A total of 470 villagers from Ndombo were enrolled into the study (216 males, 254 females, adults > 18 years: 240). The prevalence of *S. mansoni* in stool samples was 81.5%, the geometric mean of egg output in positives was 246 epg (eggs per gram). Most patients had been treated with praziquantel before; however, compliance during earlier treatments was not known and anamnestic data given by the patients themselves were contradictory. Patients therefore were not classified into an untreated and a previously treated group.

Ultrasonographical data on liver and spleen size as well as portal vein diameters are summarized in Table 1. 75% of the population had a left lobe measuring more than 70 mm (enlarged according to Cairo classification). The inner-to-inner diameter of the portal vein was above 12 mm (enlarged according to Cairo classification) in 4/461 (0.9%) of the population. According to the Cairo classification 57% of the patients had low-level fibrosis (grade I); only 3 patients were diagnosed with hepatic fibrosis grade II (Table 2). According to the Managil classification, 61% of patients had low-levels hepatic fibrosis (PPF 1 and PPF 2) and 12 patients (5 children, 7 adults) had periportal fibrosis grade 3 (PPF 3) with hyperechoic streak-like bands extending to the periphery of the liver (Table 2). According to the two observers, hepatic fibrosis could be diagnosed unequivocally only in these 12 patients. Signs of decompensated portal hypertension were not found. χ^2-test for homogeneity in contingency tables showed a highly significant deviation from random expectation ($c^2 = 1 \times 10^{-5}$) (Table 3).

Serum levels of the amino-terminal propeptide of procollagen type III (P-III-NP) were elevated in 19/153

Table 1 Results of ultrasonographic organometry

	Children		
	4–10 years (n = 128)	11–17 years (n = 102)	Adults (n = 240)
Size of left liver lobe (mm)	72 ± 11	81 ± 10	83 ± 13
Length of spleen (mm)	79 ± 18	97 ± 17	94 ± 20
Splenomegaly	14%	25%	11%
Portal vein diameter:			
inner-to-inner (mm)	6.2 ± 1.6	7.4 ± 1.6	8.2 ± 2.2
outer-to-outer (mm)	10.6 ± 2.4	11.7 ± 2.3	13.0 ± 2.6

Figures represent mean ± SD.

Table 2 Periportal fibrosis in 240 adults and 230 children (< 18 years) in Ndombo according to Cairo and Managil classification

	Children (< 18y)	Adults
Cairo classification		
Grade 0	33%	51%
Grade I	67%	48%
Grade II	—	1.3%
Grade III	—	—
Managil classificiation		
PPF 0	28%	45%
PPF 1	8%	11%
PPF 2	62%	41%
PPF 3	2%	3%

Table 3 Correlation between Cairo- and Managil classification (number of patients)

	Managil classification				
Cairo classification	PPF0	PPF1	PPF2	PPF3	Totals
All patients					
Grade 0	146	13	26	1	186
Grade I	20	28	208	9	265
Grade II	0	1	0	2	3
Totals:	166	42	234	12	454
Adults only					
Grade 0	93	10	13	1	117
Grade I	11	14	82	4	111
Grade II	0	1	0	2	3
Totals:	104	25	95	7	231

(12.4%) patients; hyaluronan was elevated in 41/152 (26.8%) cases. However, we found no correlation between elevated serum markers and ultrasound results. Even in the 7 adult patients with periportal fibrosis grade 3 according to the Managil classification, serum fibrosis markers were not significantly elevated (P-III-NP: 787 ± 462 U/l, hyaluronan 87 ± 61 μg/l). Taking organometric indices possibly indicating schistosomal liver disease, no correlation with fibrosis markers could be detected (Kendall rank correlation coefficient for P-III-NP *vs.* size of left liver lobe: $\tau = -0.02$, P-III-NP *vs.* spleen size: $\tau = 0.11$, P-III-NP *vs.* external portal vein diameter: $\tau = 0.011$). There was neither a correlation between P-III-NP and hyaluronan nor between egg counts and markers (data not shown). Laminin was within the normal range in all patients (Fig. 1).

Adult patients were also examined for hepatitis serum antibodies. The prevalence of anti-HBc was 89%, the prevalence of HBsAg was 12%, the prevalence of antihepatitis C antibodies was 2%. The prevalence of sonographically detected fibrosis was similar in patients with and without hepatitis markers (fibrosis grade PPF 3 in HBsAg-positive patients: 0%, in HBsAg-negative patients: 7%; in HCV-positive patients: 0%, in HCV-negative patients: 5%). All seven patients with fibrosis grade PPF3 were HBsAg- and HCV-negative. Serum fibrosis markers also were identical in patients with and without hepatitis antibodies (Table 4).

Discussion

Three percent of the patients in our study showed unequivocal signs of hepatic fibrosis in ultrasound examination. A previous study conducted about 3 years earlier in the same village had found no severe hepatosplenic pathology at all and only mild to moderate periportal thickening (Kardorff *et al.* 1996; Yazdanpanah *et al.* 1997), which indicates that a proportion of patients developed severe hepatosplenic pathology in the three year-period between the two studies. The prevalence of HBsAg, antiHBc- and HCV-serum antibodies was similar in patients with and without fibrosis as detected by ultrasound, indicating that chronic hepatitis is not responsible for fibrosis in this population. Alcohol does not play any role in this population as a cause of chronic liver disease. In summary, we concluded that periportal fibrosis in Ndombo is mainly due to schistosomiasis.

Two publications on the 1993 findings in Ndombo (Kardorff *et al.* 1996; Yazdanpanah *et al.* 1997) give no data on ultrasound findings according to the Managil classification, although both studies were performed by the authors of this classification system. Cairo classification data can be drawn from a table in Kardorff *et al.* (1996) which shows the interobserver variance in measurements. According to this table, in 190 persons one observer saw no grade 0 case at all, while another found 8. Yazdanpanah *et al.* (1997) report 6 cases without fibrosis in 186 persons. If these persons were selected randomly, it would be in contrast to our finding of 42% persons without periportal fibrosis according to the Cairo classification (Table 2). This difference is probably due to the facts that a different ultrasound machine was used and that the cursor markers for electronic measurements vary between scanners. It has to be noted that generally roughly 50% of grade 0 according to Cairo classification is found in community-based surveys, whether in regions endemic for *S. mansoni* (Boisier *et al.* 1995; El-Hawey *et al.* 1995) or not (Nooman *et al.* 1995).

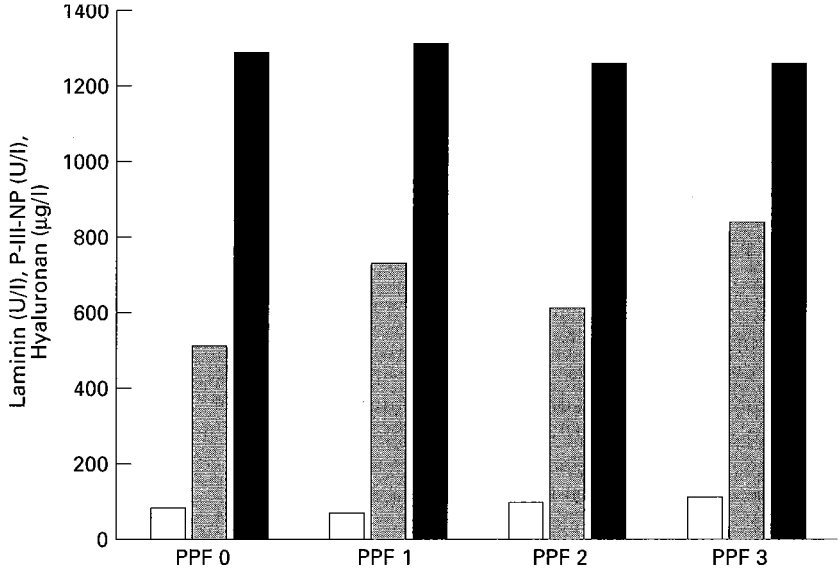

Figure 1 Hepatic fibrosis serum markers in patients with different degrees of periportal fibrosis (PPF 0 to PPF 3) according to Managil classification. □ Hyaluronan (μg/l); ▒ P-III-NP (U/l); ■ laminin (U/l).

Table 4 Hepatic fibrosis serum markers in 137 patients with and without hepatitis serum antibodies

	anti HBc		HBsAg		Hep C	
	positive (n = 143)	negative (n = 18)	positive (n = 16)	negative (n = 115)	positive (n = 3)	negative (n = 134)
P-III-NP (U/l)	613 ± 295	555 ± 281	670 ± 157	630 ± 346	521 ± 300	599 ± 286
Hyaluronan (μg/l)	77 ± 56	73 ± 69	90 ± 59	73 ± 56	53 ± 24	78 ± 57
Laminin (kU/l)	1.292 ± 0.194	1.221 ± 0.137	1.285 ± 0.191	1.286 ± 0.191	1.133 ± 0.058	1.288 ± 0.191

Figures represent mean ± SD.

A significant correlation between the degree of fibrosis according to the Cairo classification and the Managil classification was found, but cases of moderate and severe fibrosis (grade PPF2 and PPF3 according to Managil) were mostly only grade I according to Cairo classification (Table 3). These discrepancies seem to be due to the fact that the classification into grade 0, grade I and grade II in the Cairo system is arbitrary. Neither is classification into PPF 1 and PPF 2 in the Managil system strictly defined, which probably is why we found more PPF 2 than PPF 1 cases. Similarly, a study from Zimbabwe failed to demonstrate a correlation between the Cairo and the Managil classification: of 10 children with PPF 1 according to Managil, 8 had grade 0 according to Cairo classification (Friis *et al.* 1996). In summary, which method is satisfactory to quantify early periportal fibrosis in schistosomiasis cannot be determined. Moreover, low levels of fibrosis were also detected in populations without schistosomiasis mansoni (Kardoff *et al.* 1994; Serieye *et al.* 1996; Yazdanpanah *et al.* 1997). The level of periportal fibrosis in normal subjects without schistosomiasis among the Wolof in this region is not known, which makes it impossible to give exact data on the prevalence of early schistosomiasis-related periportal thickening for Ndombo.

The only methods available so far for the validation of ultrasound are histopathological examinations at autopsy or microscopy of ultrasound-guided liver biopsies. Biopsies obtained by blind liver punction (Cerri *et al.* 1984; Homeida *et al.* 1988a) are not sensitive enough because periportal fibrosis is not uniformely distributed in the liver parenchyma. We tried to correlate ultrasonographical findings to serum markers of hepatic fibrosis.

Type III collagen is a major collagen synthesized in liver disease. Serum levels of the amino-terminal propeptide of procollagen type III (P-III-NP) are elevated in both acute and chonic liver diseases. Some studies showed a positive correlation between P-III-NP and morphometrically measured degree of liver fibrosis (Gabrielli *et al.* 1989). Most authors regard P-III-NP as the most reliable serum marker for ongoing fibrosis in the liver rather than as an indicator of the fibrotic extent (Wu & Danielsson 1995). Procollagen-III-peptide as a serum marker for hepatic fibrosis has been evaluated in some schistosomiasis patients (Bolarin *et al.* 1984; Roberts *et al.* 1986; El Mohandes *et al.* 1987; Zwingenberger *et al.* 1988a 1988b; Tanabe *et al.* 1989; Mincis *et al.* 1990; Fayol *et al.* 1991; Shahin *et al.* 1992). In most of these studies criteria for the diagnosis of hepatosplenic schistosomiasis and/or exclusion of other diseases were not given. When children were included, it was not considered that interstitial procollagen turnover attributed to growth exceeds that of the diseased liver (Trivedi *et al.* 1986). Only three studies (El Mohandes *et al.* 1987; Fayol *et al.* 1991; Shahin *et al.* 1992) correlated P-III-NP levels with the histopathological pattern in liver biopsies. In one study, patients with higher histological grading showed significantly higher P-III-NP levels, although patients with no organ involvement also had elevated P-III-NP levels (Shahin *et al.* 1992). In *S. japonicum* infection P-III-NP was found to be correlated with the development of hepatic fibrosis and portal hypertension as diagnosed by ultrasound (Ohmae *et al.* 1992).

Hyaluronan is mainly synthesized by hepatic stellate cells and taken up and degraded almost exclusively in hepatic sinusoidal endothelial cells. As serum levels are elevated mostly in chronic liver disease, increased hyaluronan might be a sensitive indicator for prediction of cirrhosis and of progression in primary biliary cirrhosis. Circulating hyaluronan levels in patients with PBC and chronic viral C hepatitis correlated better with the severity of liver fibrosis than P-III-NP (Guéchot *et al.* 1994). Additionally, like laminin, hyaluronan levels correlated positively with portal venous pressure (Gressner 1991). In summary, serum hyaluronan appears to be associated more with liver function and portal hypertension than with the degree of the fibrotic process (Wu & Danielsson 1995). It has not been examined in patients with schistosomiasis.

Laminin is a major component of the basal membrane. Markedly increased serum levels were found in patients with

posthepatitic and postalcoholic fibrosis and cirrhosis and correlated with the extent of fibrotic transition in the liver. Serum laminin might also be a noninvasive indicator of increased portal venous pressure (Gressner 1991; Kropf *et al.* 1991), as a strong positive correlation between serum laminin level and the portal venous pressure has been established (Gressner *et al.* 1988b). Fourteen patients with 'hepatosplenic schistosomiasis' examined in Brazil had elevated serum laminin levels compared to 10 patients with 'hepato-intestinal disease' (Parise & Rosa 1992).

In our study no correlation between P-III-NP, hyaluronan or laminin with ultrasound findings could be established. For this comparison we used the ultrasound findings described by the Managil classification because the Cairo classification could not adequately describe our 12 cases with severe fibrosis and because its usefulness has been questioned by several other authors (Nooman *et al.* 1995; Boisier *et al.* 1995; Lanuit *et al.* 1996; Kardorff *et al.* 1997; Yazdanpanah *et al.* 1997; Gerspacher-Lara *et al.* 1997). Even in the 7 patients with unequivocal hepatic fibrosis diagnosed by ultrasound (grade 3 according to Managil classification), no elevation of these markers was present. Similar to our results, there was no association between sonographic features and P-III-NP in a recently published study from Tanzania, whereas a correlation was found between procollagen-IV-peptide and severe liver pathology (Kardorff *et al.* 1997). In this study, however, a relatively high percentage of ultrasonographic diffuse liver abnormalities, which are considered unusual for schistosomiasis, have been described and no information on the presence or absence of hepatitis was given. The discrepancy concerning P-III-NP in different studies may be due to the fact that sometimes cases with symptomatic portal hypertension were included. We could not find the high prevalence of increased laminin levels described in Tanzania (Kardorff *et al.* 1997); the reason for this discrepancy remains unclear. In summary, our results indicate that the measurement of P-III-NP, hyaluronan or laminin in serum is not a sensitive method to detect early periportal fibrosis in schistosomiasis. The alternative interpretation of our results, namely that the measurement of connective tissue metabolites in serum is sensitive whereas ultrasound is insensitive, seems unlikely because the serological markers were insensitive even in unequivocal sonographical findings of hepatic fibrosis. The conclusions from this study in Senegal must not be generalized to schistosomiasis mansoni elsewhere because the pathogenesis in West Africans may be different from, e.g. that in Sudan or East Africa.

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