HEPATOSPLENIC MORBIDITY IN SCHISTOSOMIASIS JAPONICA: EVALUATION WITH DOPPLER SONOGRAPHY

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Abstract. In Southeast Asia, schistosomiasis japonica is an important cause of hepatic fibrosis and gastrointestinal hemorrhage. Reliable methods to investigate portal hypertension (PHT) clinically and epidemiologically on community level are lacking. Doppler sonography is an established tool for investigating PHT in hospital settings. In Leyte, The Philippines, 137 individuals underwent color Doppler sonography, stool examination, and serology for hepatitis B and C, liver cell injury and cholestasis. A total of 85% of the study population had been infected with Schistosoma japonicum. Sonographically, periportal liver fibrosis was seen in 25% and reticular echogenicities (network pattern) in 44%. Portal blood flow was decreased or portosystemic collaterals were present in 10% (adults throughout) and correlated with periportal fibrosis, but not with network lesions. Chronic viral hepatitis was rare. Thus, hepatic lesions are frequent in adults but not in children in areas endemic for S. japonicum. Periportal liver fibrosis indicates a risk of PHT, and network pattern fibrosis apparently does not. Doppler sonography is suitable for research under tropical field conditions.

Infection with the trematode Schistosoma japonicum currently affects about one million people, mainly in the Philippines and China.1-2 Chronically infected individuals may develop liver fibrosis with portal hypertension (PHT), potentially resulting in life-threatening upper gastrointestinal hemorrhage.3 For individual case management as well as for public health priority setting under conditions with limited resources, presymptomatic detection of this serious complication in endemic communities is vital. Since clinical signs are unspecific and unreliable, the use of ultrasonography has been evaluated. A wide range of abnormalities has been described, and conflicting results were obtained concerning criteria for diagnosis, staging, and differentiation from other prevalent hepatopathies.4-10

In 1996, a World Health Organization expert committee on ultrasonography in schistosomiasis determined that there is no clear evidence as to which sonographic features of schistosomiasis japonica are related to portal hypertension and thus to an increased risk of fatal outcome (Richter J and others, unpublished data). We therefore carried out a study in a longstanding S. japonicum focus in The Philippines to define the range of hepatosplenic ultrasound findings and to relate these to the state of S. japonicum infection, to indicators of concomitant liver disease, and to Doppler sonographic measurements of portal perfusion. The latter has been shown to be a prognostic indicator of the risk of gastrointestinal hemorrhage and of overall survival of portal hypertensive patients.11,12 For the first time, this study demonstrates the applicability of this advanced ultrasound technique within the setting of a field study under tropical conditions.

STUDY AREA, STUDY POPULATION, AND METHODS

The study was performed in Jaro District in northeast Leyte, The Philippines, in 1997. A schistosomiasis control program had been active in the area until 1985 and from 1991 to 1994, but due to financial constraints, the scope of the control program became very limited after 1994.1 Leyte is not endemic for malaria.

The study population included those who were infected with Schistosoma japonicum, 137 individuals in total. All were examined for liver fibrosis and portal hypertension, and their liver function tests were recorded. The study was carried out with a SonoAce 7700 Trident color Doppler scanner (Medison Co., Ltd., Seoul, South Korea) equipped with a 3 MHz curved array transducer. Each participant was asked to submit a stool sample. B-mode and Doppler sonography were performed within 1 week of the stool examination.

Individuals were enrolled into the study in the order in which they presented for a mass treatment campaign. Previous documented history of S. japonicum infection and alcohol intake (none, occasionally, frequently, daily) were recorded. Duplicate, 50-mg Kato-Katz slides were prepared from one stool sample. Schistosoma japonicum egg counts were expressed as eggs per gram of stool (epg). Individuals with a negative fecal egg count were asked to submit a second stool sample. B-mode and Doppler sonography were performed with a SonoAce 7700 Trident color Doppler scanner (Medison Co., Ltd., Seoul, South Korea) equipped with a 3 MHz curved array transducer. For some work breaks needed during midday heat to prevent equipment overheating, technical difficulties concerning ultrasonography were not encountered. The follows were recorded: shape, length, and echostucture of the liver; echogenic periportal thickening (PPT) using the definitions and grading of Doehring-Schwerdtfeger and others;13 diameter and maximum blood flow velocity of the main portal vein (P V max) and the splenic vein (S V max); presence of portosystemic collateral vessels; spleen length; and presence of ascites.

Organometric data were transformed into body height–adjusted standard deviation scores (SDS, Z-score) using German normative data14,15 because no local reference data were available. The normal interval of the SDS of any organometric measurement was −2.0 to +2.0. The lower limit of normal P V max was 15 cm/sec.16 Both a decrease of P V max below this threshold and the presence of portosystemic collaterals were regarded as indicative of PHT.

The following parameters were measured in venous blood samples from all consenting participants using commercial routine assays: alanine aminotransferase (ALT, [reference value] ≤ 30 U/L) to monitor hepatocellular injury, cholinesterase (CHE, ≥ 3.5 kU/L) to monitor hepatic protein synthesis capacity, γ-glutamyl-transferase (GGT, ≤ 30 U/L) and total bile acids (TBA, ≤ 20 gmol/L) to monitor bile duct injury and cholestasis, and antibody to hepatitis C virus (negative), and antibody to hepatitis B core antigen (anti-HBc) (negative). Those found positive for anti-HBc were
examined for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B e antigen. Due to the variable amount of material available, not all analyses could be performed on all sera. All villagers were treated with praziquantel (Shin Poong Pharmaceutical Co., Ltd., Seoul, South Korea), 50 mg/kg body weight, in a single oral dose. Other diseases detected during the study were either treated immediately or the patients were referred to local health care providers.

**Ethical considerations.** The study was explained to the village population by local health care personnel in the local language. It was stressed that all villagers would receive treatment irrespective of their individual decision about participation in the study. Participants were enrolled only with their explicit approval, or with that of parents in the case of children. The study was reviewed and approved by the Institutional Board of the Research Institute of Tropical Medicine, Manila. Sonography including color Doppler is considered to be free of any relevant health risk. Blood sampling was done under aseptic conditions by professional personnel and could be refused by any study participant.

**Statistical analysis.** The SPSS for Windows 6.1 software (SPSS, Inc., Chicago, IL) was used for data processing and analysis. Data were tested for a normal distribution by the Kolmogorov-Smirnov test. Comparisons were done using the Mann-Whitney U test, the chi-square test, the Kruskall-Wallis H test, and analysis of variance where appropriate. Differences with a *P* value < 0.05 were considered statistically significant.

**RESULTS**

Ultrasound examinations were carried out on 137 individuals; 52% were female, 8% were ≤ 10 years old, 13% were 11–20 years, 79% were > 20 years old, and the median age was 34 years. Stool samples were obtained from 118 study participants. Forty-one (35%) excreted *S. japonicum* ova, most of them (n = 35) less than 100 epg. Median and maximum egg output was 30 and 1,740 epg, respectively. On questioning, 109 individuals reported that *S. japonicum* infection had been diagnosed in them after stool examination earlier in their life. Overall, 117 individuals (85% of the study population) were infected or previously infected.

**Laboratory findings.** The ALT were increased in only one of 123 individuals (47 U/L). The TBA levels were abnormal in 56 of 129 individuals (43%); high values > 100 μmol/L to a maximum of 219 μmol/L were found in nine individuals. Similarly, GGT was increased in 60 (49%) of 123 persons to a maximum of 302 U/L. In those reporting frequent or daily alcohol consumption (26% of the adults), the prevalence of abnormal GGT levels was increased (73% versus 40%, χ² = 10.4, *P* = 0.001). The CHE level was decreased to < 3.5 kU/L in 18 (15%) of 123 individuals to a minimum of 1.2 kU/L. Forty of 123 individuals were positive for anti-Hbc. Ten of these (8% of the total sample) were also positive for HBsAg. However, none of them had increased ALT levels. Antibodies to hepatitis C virus were detected in one of 124 individuals tested who had otherwise normal laboratory findings and no abnormalities on sonography.

**Sonographic indicators of portal hypertension.** Ascites was not detected in any individual. The portal system could be sufficiently evaluated by Doppler sonography in 125 persons. The P V max was reduced below the limit of 15 cm/sec in eight individuals, and abnormal portosystemic collateral vessels were visualized in six individuals. Twelve persons (10%) presented with both or either of these portal hypertension signs; they were all adults > 20 years old. In affected persons, the mean spleen length was higher (11.8 cm versus 8.7 cm; *F* = 20.5, *P* < 0.001), and splenic and portal vein diameters were larger (8.5 mm versus 5.6 mm; *F* = 22.9, *P* < 0.001, and 11.2 mm versus 9.7 mm; *F* = 5.5, *P* = 0.02, respectively) than in those without PHT. Signs of PHT were statistically unrelated to active *S. japonicum* egg output.

**Abnormalities of hepatic echostructure.** Sonographically, two distinct patterns of hepatic abnormalities were identified: increased echogenic PPT and the network pattern. The prevalence of echogenic PPT was 25%. Findings resembled those observed in patients with schistosomiasis mansoni, ranging from moderate wall thickening of the portal bifurcation region only (grade I) to massive echogenic streaks along the whole portal tree with obliterated lumina (grade III) (Figure 1). Findings that first appeared as focal echogenic lesions (Figure 1A) usually could be identified as cross-sections of thickened portal branches (Figure 1B). Grade I was seen in 22 persons (17%), grade II in nine (7%), and grade III in two (2%). For further analysis, grades II and III were combined as severe (compared with no = grade 0 or mild = grade 1) PPT, which was present only in adults with one exception. The PPT grading did not correlate with laboratory parameters. In severe PPT, the spleen and splenic vein were larger, the P V max was lower, and the overall prevalence of sonographic signs of portal hypertension was much higher than in those without or with mild PPT (Table 1).

A frequent finding (prevalence = 44%) was a network of echogenic lines within the liver parenchyma, usually involving the entire liver. These lines did not follow portal tracts but seemed to connect the liver capsule with hepatic veins and their tributaries. In advanced cases (prevalence = 29%), the echogenic lines seemed to split the liver into multiple, sharply delineated, regular lobules or blocks with a central vessel that could be identified as a portal branch (Figure 2). Thus, the echogenic lines of the network were clearly distinct from periportal fibrosis bands that follow the portal tracts.

With two exceptions, the network was seen only in adults. Its presence was unrelated to active *S. japonicum* infection and to a history of alcohol intake. Those with an advanced network had a higher rate of increased GGT (65% versus 38%; χ² = 7.7, *P* = 0.02) and of decreased CHE (24% versus 10%; χ² = 4.0, *P* = 0.05) than those without it. There was no correlation between the presence of network and hepatomegaly or splenomegaly, portal or splenic vein dilatation, or indicators of portal hypertension.

**DISCUSSION**

In schistosomiasis japonica, hepatic involvement may lead to major and potentially life-threatening complications. Thus, presumptomatic diagnosis and epidemiologic knowledge of liver involvement is of crucial importance for the
Figure 1. Grade III periportal thickening. A, longitudinal section of a left liver lobe. Segmental portal branches are completely obliterated by fibrosis, appearing like focal echogenic lesions. B, transverse section of the identical area. Fibrotic streaks now clearly identified as segmental portal branches.
infected individual, as well as for control programs and public health priority setting.

Ultrasonography carried out with portable scanners under field conditions has become an accepted tool to detect hepatosplenic involvement in schistosomiasis mansoni. Ultrasonographic features have been shown to correlate with histology, the presence and grade of esophageal varices, and with the risk of upper gastrointestinal hemorrhage.

Available literature on the ultrasonography of schistosomiasis japonica is scarce. Descriptions and definitions of findings vary widely; most investigators have found major abnormalities only in adults, and mentioned echogenic PPT and a network pattern of fibrosis as typical findings. The prognostic relevance of either lesion for survival or risk of bleeding has not been defined. Moreover, it remains unclear whether other prevalent hepatic injuries, such as alcohol abuse or chronic viral hepatitis, might alter the presentation of S. japonicum-related liver disease.

FIGURE 2. Longitudinal scan of a right liver lobe. An echogenic network dissects the liver into blocks of intact parenchyma. In one of these (center of the image), a portal branch is seen in cross-section.
Doppler sonographic measurements of portal perfusion have been shown to correlate with the presence and degree of esophageal varices, the probability of gastrointestinal bleeding and, in patients with cirrhosis, with survival.\(^{1,12,27}\) In the present study, Doppler sonography was used for the first time in the setting of a population-based field study within an endemic area to investigate schistosomiasis-related portal hypertension.

Our findings confirmed that both periportal and network pattern echogenicities are usually seen only in adults, suggesting that longstanding infection over many years is necessary to induce major liver fibrosis.\(^{9}\) The echogenic bands of the network were connected to the liver capsule and appeared to be augmentations of interlobar and interlobular septa; they encircled blocks of parenchyma that often contained a central portal branch. Such bands have been identified histologically as dense fibrous tissue containing ova.\(^{28}\) Contrast-enhanced computed tomography liver scans have produced strikingly similar images.\(^{26}\)

Our data clearly show that severe echogenic PPT but not network fibrosis is correlated with sonographic indicators of portal hypertension, namely reduced portal blood flow velocity, presence of portosystemic collaterals, dilatation of the splenic vein, and splenomegaly. Thus, we assume that the degree of PPT but not the presence of network fibrosis is a prognostic indicator for upper gastrointestinal bleeding and probably for survival. This finding is important for any future clinical or epidemiologic investigations of \(S.\) \(japonicum\)-related morbidity using ultrasonography, since advanced PPT can be easily identified even with basic sonographic equipment.\(^{17}\)

Conversely, network fibrosis showed some correlation with increased GGT and with impaired hepatic protein synthesis quantified by serum CHE levels. Ohmae and others found marginally lower CHE levels and significantly higher TBA levels in patients from the same region with network fibrosis compared with others with normal liver scans or PPT only.\(^{7}\) Thus, network fibrosis may be associated with an increased risk of cholestasis or hepatocellular dysfunction, and may be prognostically important in another respect than PPT.

We deliberately asked the first individuals presenting for a mass treatment campaign to participate in this study because we expected a higher prevalence of morbidity in these than in the general population, which was welcome given the purpose of this survey. However, prevalence rates of findings in this cohort should not be considered representative for the total population.

Since no regional reference data for ultrasound of liver and spleen were available for this Philippine population, European standard values were used. This may have caused systematic underreporting of organomegaly. However, this bias affected all individuals, and did not influence the results of subgroup comparisons presented in this paper. For future studies, the establishment of regional reference charts for ultrasound organometry of course is desirable.

In summary, this study shows that Doppler sonography can be successfully applied to investigate schistosomiasis-related portal hypertension under field conditions. We present clear evidence that portal hypertension in hepatosplenic schistosomiasis \(japonica\) is related to severe echogenic PPT but not to network pattern fibrosis. The latter, however, may be associated with cholestasis and impaired hepatocellular function. Future studies using the Doppler methodology in representative population samples will define the real prevalence and epidemiologic importance of signs of portal hypertension in endemic areas, and they will contribute to a much more precise clinical definition of risk groups needing special attention and aggressive therapy.

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