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Diagnosing schistosomiasis-induced liver morbidity: implications for global control

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SUMMARY

Background: Subclinical morbidity due to schistosomiasis was evaluated in 565 patients, and the enhanced liver fibrosis (ELF) test was assessed for the first time as a potential screening tool for disease.
Methods: The prevalence and intensity of infection were determined by Kato–Katz thick smear stool examination at baseline and 2 years after curative treatment. The degree of hepatic fibrosis was assessed by ultrasound. Non-invasive serum biomarkers of hepatic fibrosis were also evaluated.
Results: The baseline human prevalence and infection intensity were found to be moderately high at 34% and 123 eggs per gram, respectively. However, hepatic parenchymal fibrosis occurred in 50% of subjects, with grade II fibrosis in 19% and grade III in 6%. The ELF score and higher serum levels of tissue inhibitor of metalloproteinase 1 (TIMP-1) and hyaluronic acid (HA) correlated with the grade of liver fibrosis.
Conclusions: The findings of this study demonstrated that praziquantel treatment had a short-term impact on both the prevalence and intensity of infection, but less of an impact on established morbidity. Higher TIMP-1 and HA serum levels, and an ELF cut-off score of 8 were found to be correlated with the grade of liver fibrosis; these values may, therefore, assist physicians in identifying individuals at greater risk of disease.

1. Introduction

Schistosomiasis is a major public health problem that afflicts approximately 240 million people worldwide[1] and causes approximately 70 million disability-adjusted life years lost.[2] Preventive chemotherapy has been endorsed and advocated by the World Health Organization (WHO) for the global control of schistosomiasis.[3] Since its inception in 1979, much optimism has surrounded mass drug administration (MDA) for the worldwide control of schistosomiasis, for which praziquantel (PZQ) has served as the cornerstone drug. Numerous studies have claimed that preventive chemotherapy (i.e., 40 mg/kg PZQ) given once or twice yearly can significantly reduce the prevalence and intensity of infection and control morbidity in the long term.[3]

Schistosomiasis was first reported in the Philippines in 1906. Approximately 865 000 people are currently infected and a further 12 million are at risk of infection.[3,4] Major endemic foci (80%) are in the poorest regions of the Visayas (Samar and Leyte) and Mindanao.[3,4] The current national control program comprises annual free MDA (40 mg/kg PZQ) in all schistosomiasis-endemic communities with a prevalence of >10%. The Philippines National Schistosomiasis Control Program has recently reported that the human prevalence has declined to less than 3% nationally.[5] However, contradictory reports claim the program is failing because of poor drug compliance, poor drug coverage, infrequent monitoring and evaluation, and rapid re-infection rates.[4–6] Moreover, newly published data have revealed very high prevalence rates in both humans and bovines in endemic areas

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throughout the country.[4–6] There are now advanced schistosomiasis cases and disease-related deaths being reported by the National Department of Health for Mindanao, Samar, Leyte, and Oriental Mindoro.[4]

Hepatic fibrosis is the major cause of morbidity and mortality among people with chronic schistosomiasis. Schistosomiasis-induced liver fibrosis in the field setting is best assessed with a portable ultrasound.[6] The instrument has been reliable for detecting and assessing the degree of parasite-induced liver abnormalities and for monitoring pathology regression following anti-schistosome treatment.[6] Despite inter-observer variability related to its use,[8] several studies have confirmed its usefulness in evaluating hepatosplenic schistosomiasis in the field over the past 30 years.[6,9–17] The potential of non-invasive markers to complement the imaging assessment of organ morbidity has been studied before.[5] Among the most promising for assessing schistosome-induced liver fibrosis are hyaluronic acid (HA), collagenous proteins, matrix metalloproteinases, and intercellular adhesion molecules.[5,14,15]

In this study, the clinical morbidity due to schistosomiasis at baseline and at 2 years after curative treatment was evaluated among 565 residents of a known endemic area in Northern Samar, the Philippines. Furthermore, the enhanced liver fibrosis (ELF) test was assessed as a potential field screening tool for advanced disease.

2. Methods

2.1. Study area

The study area comprised 18 schistosomiasis-endemic barangays in the municipalities of Laoang and Palapag, Northern Samar, the Philippines. Residents of this area are typically poor rice farmers with family incomes far below the national average. Over 50% of the population lives below the poverty line, and the water supply, sanitation, and hygiene are rudimentary.[7] The area is non-endemic for malaria but has had an active schistosomiasis control program for more than over three decades, including an MDA program that commenced in 2008. All individuals aged 5–65 years are offered free annual treatment (40 mg/kg of PZQ) in accordance with the Department of Health Administrative Order 2007–0015.[7]

2.2. Study procedures

A cross-sectional schistosomiasis survey involving approximately 20 000 individuals was conducted in 2012 in order to determine the prevalence, intensity of infection, and morbidity associated with the disease (Figure 1).[7] The baseline prevalence and intensity of infection were determined by Kato–Katz thick smear stool examination. Individuals were asked, over the course of a week, to provide two stool specimens from which six 50 g Kato–Katz thick smears were prepared on microscope slides according to established methods.[20] Slides were examined under a light microscope by experienced laboratory technicians, who counted the number of *Schistosoma japonicum* eggs per slide. For quality control, 10% of all slides were randomly selected and re-examined by a senior microscopist at the Research Institute for Tropical Medicine, Manila. *S. japonicum* egg counts were expressed as eggs per gram (epg) of stool.[18] The intensity of infection was graded according to WHO criteria: light infection, 1–99 epg; moderate infection, 100–399 epg; heavy infection, ≥400 epg.[19]

For a more accurate assessment of schistosome-induced hepatosplenic morbidity, ultrasonographic studies were performed on a subset of individuals with symptoms and signs suggestive of schistosomiasis. All subjects (n = 736) who reported gastrointestinal and/or neurological symptoms (i.e., fatigue, malaise, abdominal pain, blood per rectum, hematemesis, diarrhea, jaundice, dizziness, headache, and seizures) and/or were clinically assessed to have morbidity (i.e., palpable liver and spleen, varices, ascites, etc.) based on physical examination were initially selected for the ultrasound investigation. However, only those with baseline stool and ultrasound examination results were included in the final analysis (n = 565). The degree of hepatic fibrosis was assessed by ultrasound examination using a portable gray-scale ultrasonogram equipped with 3 MHz curve array transducer (SONOACE X1; Madison Co., Ltd, Seoul, South Korea). Liver size was measured in millimeters along the mid-sternal line (MSL) and mid-clavicular line (MCL) for the left lobe and right lobe, respectively. Spleen size was measured in millimeters along the left mid-axillary line (MAL). Hepatic fibrosis grading was adopted

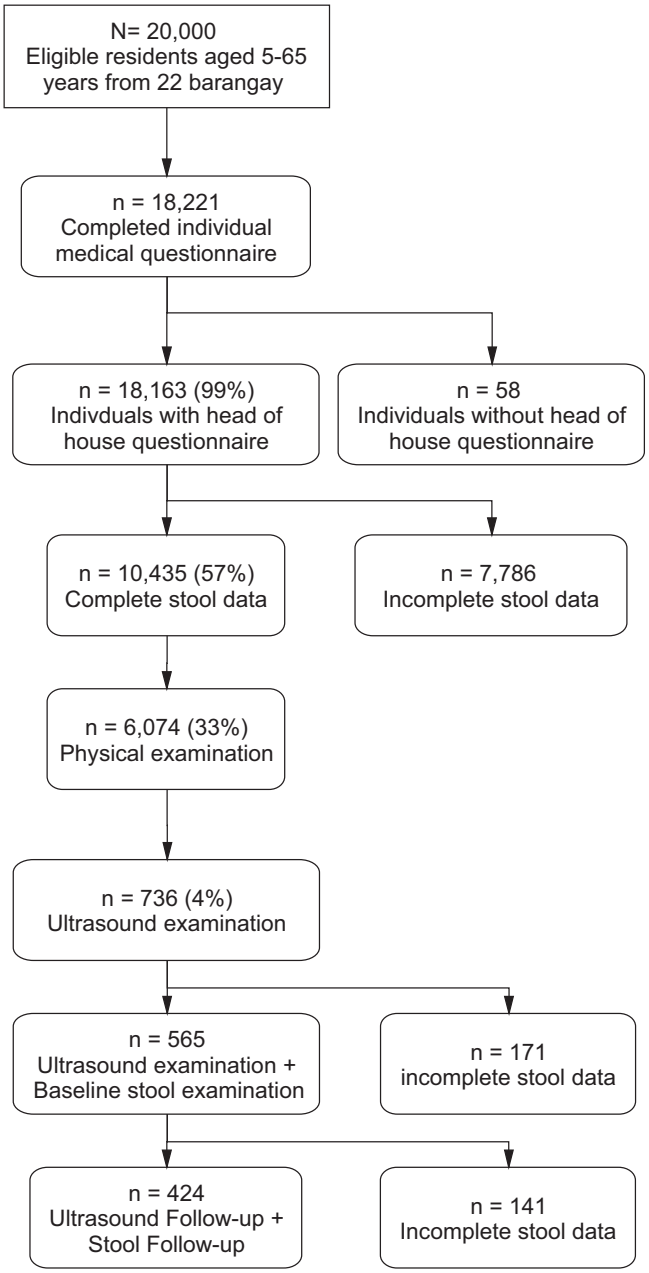

Figure 1. Study profile and compliance among 18 221 residents from 22 schistosomiasis-endemic barangays in Palapag and Laoang, Northern Samar, the Philippines. All inhabitants aged 5–65 years were invited to participate in the questionnaire and provide two stool samples for parasitological examination. A subset of patients (n = 736) were selected for ultrasound investigations.