Treatment and education reduce the severity of schistosomiasis periportal fibrosis

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INTRODUCTION

Schistosoma mansoni is a major public health problem worldwide that has great social and economic impact. The disease affects over 200 million people around the world. Approximately 6 million people are infected in Brazil, particularly in the Northeast region1-3.

One characteristic of this disease is the capacity to cause an inflammatory response against the Schistosoma mansoni eggs deposited in the host’s liver. This process can lead to periportal fibrosis (PPF) due to the deposition and accumulation of extracellular matrix, causing the host to develop portal hypertension that leads to splenomegaly and the emergence of varicose veins in the esophagus. Rupture of these esophageal varices with subsequent severe gastrointestinal bleeding occurs in 12 to 15% of patients, which leads to death in approximately 20% of cases4-6.

The disease presents in various clinical forms, with 5% to 10% of individuals developing severe liver and spleen lesions the hepatosplenic form described above of which schistosomal fibrosis is among the most important aspects7. The risk for developing the most severe hepatosplenic form of schistosomiasis increases according to the severity of the fibrosis6,8.

One factor related to PPF is the infection intensity. Several factors are related to the occurrence of schistosomal infection, including exposure time, frequency of contact with contaminated water, and age at infection. Different contacts with contaminated water bodies (natural waters, stream waters, water reservoirs) may determine different epidemiological patterns of infection and transmission9. Thus, understanding the evolution of the various clinical forms of schistosomiasis involves understanding a set of factors, such as poor housing and sanitation conditions, economic and sociocultural activities related to the use of contaminated water in rural areas, lack of health education, low adherence to control programs, and lack of an effective vaccine, all of which have contributed to morbidity10. Other factors, such as the exacerbation of the host’s immune response, concomitant infections, virulence of the S. mansoni strain, and nutritional status of infected individuals, should be taken into account when determining an individual’s susceptibility to developing the severe clinical form of the disease5,11.

Currently, the mechanism of liver fibrosis has been an object of extensive research, but much work still remains to better understand the complex mechanisms related to the inhibitory...
and activating pathways involved in schistosomal fibrosis. Thus, understanding the causal factors that can affect the clinical outcome of this disease remains a challenge\textsuperscript{11-13}. Therefore, this study aims to describe the epidemiological and clinical factors and to evaluate the factors associated with the development of moderate to severe PPF.

**METHODS**

A cross-sectional study examining associations between several factors and the development of moderate to severe PPF was conducted from April to December 2012 and involved 178 patients infected with *S. mansoni* aged over 18 years and treated in the Gastroenterology Outpatient Clinic of Hospital das Clínicas/Universidade Federal de Pernambuco (HC/UFPE), a reference center for the treatment of schistosomiasis.

**Selection of patients**

All patients infected with *S. mansoni* examined during the study period were included. We excluded individuals with other previous liver-associated diseases, such as liver cirrhosis, steatosis, hepatitis B or C, and other clinical forms of diagnosed schistosomiasis. In total, 178 individuals were selected for the study and were divided into two groups. Group 1: 137 cases of individuals with the hepatosplenic (HS) form of the disease and Group 2: controls 41 cases of individuals with the hepatointestinal (HI) form of the disease (Figure 1).

The two groups were prospectively selected during the study period according to the following criteria: patients with HI *schistosomiasis* without splenomegaly and with mild or moderate periportal fibrosis (pattern C or D from Niamey’s classification\textsuperscript{14}) or those with no fibrosis and patients with HS schistosomiasis with advanced periportal fibrosis (pattern E or F from Niamey’s classification\textsuperscript{14}) with splenomegaly or previous history of splenectomy. All of these patients had a history of contact with contaminated water, a positive stool test for *S. mansoni*, or prior treatment for schistosomiasis.

The sample size was calculated using statistical software (EpiInfo version 3.5.5, Atlanta, U.S) to allow 80% power at a 5% significance level. Considering an expected frequency of PPF severity of 8% and a 4% margin of error with a 95% confidence level, the sample size was estimated to be 180 individuals\textsuperscript{15}.

The variables related to risk factors for developing PPF were arranged in two groups: the socioeconomic and demographic variables, including gender, age, education level, family income, alcoholism, and site of contact with contaminated water; and the clinical variables, including history of severe gastrointestinal bleeding, hepatomegaly, splenomegaly, and specific treatment. The instrument used for investigating these factors was a pre-coded, structured questionnaire applied to individuals by a single operator.

**Ultrasound evaluation**

The diagnosis of the clinical form of disease was determined using the patient’s clinical history and a clinical examination. An ultrasound evaluation of the upper abdomen was also performed by a single operator at the Gastrointestinal Endoscopy Unit of CH/UFPE using a Siemens Acuson X 150\textsuperscript{5} device with a 3.5-MHz convex transducer to confirm the diagnosis and rule out other liver diseases (Figure 2). The parameters used to define the PPF pattern were based on Niamey’s classification\textsuperscript{14}: C - peripheral; D - central; E - advanced; and F - very advanced.

**Statistical analysis**

Data from the questionnaires were tabulated twice. Univariate and multivariate analyses were conducted using EpiInfo software version 3.5.5. For evaluating the association of selected factors and the fibrosis pattern, prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using the fibrosis pattern as a dependent variable and the selected factors as independent variables. The potentially confounding variables with the factors of interest were examined using a non-conditional logistic regression analysis. The association was regarded as significant when p < 0.05.

**Ethical considerations**

All clinical and ultrasound examinations were performed according to a standardized protocol. The study was conducted within the standards required by the Declaration of Helsinki and was approved by the Research Ethics Committee of the Center for Health Sciences of Universidade Federal de Pernambuco under the Protocol 437/11.

**RESULTS**

The sample consisted of 178 individuals (Figure 1), 41.8% of which were male and 58.2% of which were female. The average age was 54 years and ranged from 18 to 89 years. The risk factors for developing PPF were illiteracy (PR 1.46, 95% CI 1 to 2.13, p = 0.026) and site of contact with contaminated water, particularly in the towns within the Metropolitan Region of Recife (PR 0.490, 95% CI 0.22 to 1.08, p = 0.014) and in the *Zona da Mata* of *Pernambuco* (PR 1.21, 95% CI 1.05 to 1.40, p = 0.029). The initial evaluations and tests of the associations between the explanatory variables and the PPF pattern are presented in Tables 1 and 2.
TABLE 1 - Univariate analysis of the association between sociodemographic variables and the pattern of periportal fibrosis in Pernambuco, Brazil, 2012.

| Characteristics   | Periportal fibrosis groups |          |          | PR    | 95%CI | p-value* |
|-------------------|----------------------------|----------|----------|-------|-------|----------|
|                   | Grupo 1 | n | % | Group 2 | n | % | PR | 95%CI | p-value* |
| Gender            |         |   |    |         |   |    |     |       |         |
| male              | 58      | 42.3 | 16 | 39.0    | 1.03 | 0.88-1.21 | 0.8439 |
| female            | 79      | 57.7 | 25 | 61.0    |      |          |        |
| total             | 137     | 100.0 | 41 | 100.0   |      |          |        |
| Age (years)       |         |   |    |         |   |    |     |       |         |
| 18 to 40          | 22      | 16.0 | 8  | 19.5    | 1   | 0.76-1.30 | 0.825  |
| 41 to 60          | 73      | 53.2 | 18 | 44.0    | 1.09 | 0.90-1.31 | 0.467  |
| ≥ 61              | 42      | 30.6 | 15 | 36.5    | 1   |          |        |
| total             | 137     | 100.0 | 41 | 100.0   |      |          |        |
| Education         |         |   |    |         |   |    |     |       |         |
| illiteracy        | 28      | 20.4 | 4  | 9.7     | 1.46 | 1-2.13   | 0.026  |
| 1 to 8 years      | 97      | 70.8 | 29 | 70.7    | 1.28 | 0.89-1.86 | 0.178  |
| 9 to 11 years     | 12      | 8.7  | 8  | 19.5    | 1   |          |        |
| total             | 137     | 100.0 | 41 | 100.0   |      |          |        |
| Family income     |         |   |    |         |   |    |     |       |         |
| < 1 minimum wage  | 21      | 15.3 | 2  | 4.9     | 1.17 | 0.81-1.70 | 0.556  |
| 1 to 3 minimum wages | 109 | 79.5 | 37 | 90.2    | 0.96 | 0.67-1.38 | 0.596  |
| ≥ 4 minimum wages | 7       | 5.1  | 2  | 4.9     |      | 1        |        |
| total             | 137     | 100.0 | 41 | 100.0   |      |          |        |

PR: prevalence ratio; CI: confidence interval; \( \chi^2 \): chi-square.
Clinical and ultrasound evaluation

Liver abnormalities were identified in 170 patients who were attributed to *S. mansoni* according to Niamey’s protocol. In the control group, there was PPF in the peripheral pattern in 11 (26.8%) individuals and in the central pattern in 22 (53.7%); 8 (19.5%) of these patients had no fibrosis. In the cases, the advanced pattern was detected in 110 (80.2%) cases, and the very advanced pattern was detected in 27 (19.8%) cases. With regard to the clinical variables, among the HS individuals, 59 (43.1%) were splenectomized, and 83 (60.5%) showed no hepatomegaly on physical examination.

On multivariate analysis, there were inverse associations between education level (up to 11 years of study) and specific treatment with the advanced PPF pattern, indicating that these variables may be protective factors. Table 3 shows the odds ratios (ORs) associated with the variables that remained in the final logistic regression model. For the final analysis, we selected 9 variables (education, time of last contact with contaminated water, site of last contact with contaminated water, alcoholism, specific treatment, last treatment time, *etc.*) as explanatory variables for the conditional logistic regression analysis.
### DISCUSSION

Protective associations were identified between the education level up to 11 years of study and prior specific treatment and the advanced perportal fibrosis pattern.

It has been shown that specific treatment for *S. mansoni*, family income, last specific treatment, age, and gender. This analysis was used to evaluate the association between the PPF pattern (dependent variable) and the selected variables (independent variables).

The variables with *p* < 0.20 in the univariate analysis were included in the logistic regression model. We had to exclude patients in both groups due to lack of information for this analysis. The exclusions occurred in the analysis of the variables ‘time of last specific treatment’ - 16 cases/10 controls; ‘specific treatment for *S. mansoni*’ - 5 cases/5 controls and ‘time of last contact with contaminated water’ - 2 cases.

TABLE 3 - Final multiple logistic regression model for the advanced perportal fibrosis pattern.

| Variables | Adjusted OR* | 95% CI | p-value |
|-----------|--------------|--------|---------|
| Education |              |        |         |
| illiteracy | 1            |        |         |
| ≥ 11 years | 0.7198       | 0.5491-0.9434 | 0.0172 |
| Treatment for SM |      |        |         |
| treated (PZ/OX) | 0.7612 | 0.5819-0.9956 | 0.0464 |
| not treated | 1            |        |         |

*Adjusted OR: odds ratio adjusted through the variables: time of last contact with contaminated water; site of last contact with contaminated water; alcoholism; specific treatment for SM; family income; age group; and gender. OR: odds ratio; CI: confidence interval; PZ: praziquantel; OX: oxamniquine; SM: schistosomiasis mansoni; P-model = 0.0364.

Specific treatment for *S. mansoni*, family income, last specific treatment, age, and gender). This analysis was used to evaluate the association between the PPF pattern (dependent variable) and the selected variables (independent variables).

We observed an improvement in the education level in the patients from rural areas compared with previous studies, possibly due to Brazilian socioeconomic growth in recent years. It is well known that control measures such as sanitation and education are gradually improving in Brazil; these measures contribute to a decrease in schistosomiasis transmission. In addition, better economic conditions for all individuals in northeastern Brazil may help to solve this public health problem, which still affects many states in the region, particularly Pernambuco. In addition, studies have described recent transmissions of schistosomiasis throughout this region and even in the City of Recife.

This study demonstrated that the prevailing sites with severe forms of schistosomiasis are still within the Zona da Mata of Pernambuco by evaluating the towns with higher frequencies of contact with contaminated water, although there has been an expansion of the disease to urban areas, especially within the Metropolitan Region of Recife and near the coast. The development of the severe form requires a high parasitic load, which means that the individual has undergone repeated contact with the infection focus over a long time. This is more frequently observed in the Zona da Mata than in the current foci in the metropolitan region of Recife and the coast of Pernambuco. Contact with these more recent foci is less intense. Moreover, it has been shown that HS schistosomiasis needs 5 to 15 years for the infection to establish itself.

The high (55.4%) frequencies of gastrointestinal bleeding and prior splenectomy (43.1%) for the treatment of portal hypertension in these patients and the significant percentage of patients with no prior treatment (30.7%) reinforce the need for a systematic approach to the specific treatment of all cases with a positive diagnosis, particularly those with a diagnosis of the hepatosplenic form with advanced PPF. Evaluation and monitoring of esophageal varices and improvements in hospitals located in endemic areas to provide emergency care for HS schistosomiasis patients are needed to decrease the morbidity and mortality of this parasitic disease.

In conclusion, the risk factors evaluated in this study reinforce the impact of this disease in endemic areas of the State of Pernambuco, once again drawing attention to the fact that treatment and education constitute preventive factors for this disease. These data also indicate the need to implement social, sanitary, and health education interventions aimed at schistosomiasis to decrease or prevent disease occurrence, which is still a major public health problem.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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