Treatment and education reduce the severity of schistosomiasis periportal fibrosis

**Paula Carolina Valença Silva[1],[2], Tallita Veríssimo Leal[2],
and Ana Lúcia Coutinho Domingues[3]**

[1]. Programa de Pós-Graduação em Medicina Tropical, Universidade Federal de Pernambuco, Recife, PE. [2]. Curso de Enfermagem, Universidade Federal de Pernambuco, Vitória de Santo Antão, PE. [3]. Departamento de Medicina Clínica, Centro de Ciências da Saúde, Universidade Federal de Pernambuco, Recife, PE.

ABSTRACT

Introduction: This study evaluates the factors associated with the development of severe periportal fibrosis in patients with *Schistosoma mansoni*. **Methods:** A cross-sectional study was conducted from April to December 2012 involving 178 patients infected with *S. mansoni* who were treated in the Hospital das Clínicas of Pernambuco, Brazil. Information regarding risk factors was obtained using a questionnaire. Based on the patients' epidemiological history, clinical examination, and upper abdomen ultrasound evaluation, patients were divided into 2 groups: 137 with evidence of severe periportal fibrosis and 41 patients without fibrosis or with mild or moderate periportal fibrosis. Univariate and multivariate analyses were conducted using EpiInfo software version 3.5.5. **Results:** Illiterate individuals (30.1%) and patients who had more frequent contact with contaminated water in towns in the *Zona da Mata of Pernambuco* (33.2%) were at greater risk for severe periportal fibrosis. Based on multivariate analysis, it was determined that an education level of up to 11 years of study and specific prior treatment for schistosomiasis were preventive factors for severe periportal fibrosis. **Conclusions:** The prevailing sites of the severe forms of periportal fibrosis are still within the *Zona da Mata of Pernambuco*, although there has been an expansion to urban areas and the state coast. Specific treatment and an increased level of education were identified as protective factors, indicating the need for implementing social, sanitary, and health education interventions aimed at schistosomiasis to combat the risk factors for this major public health problem.

Keywords: Schistosomiasis mansoni. Periportal fibrosis. Epidemiology.

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 region[1-3].

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 cases[4-6].

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 aspects[7]. The risk for developing the most severe hepatosplenic form of schistosomiasis increases according to the severity of the fibrosis[6,8].

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 transmission[9]. 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 morbidity[10]. 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 disease[5,11].

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[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).**
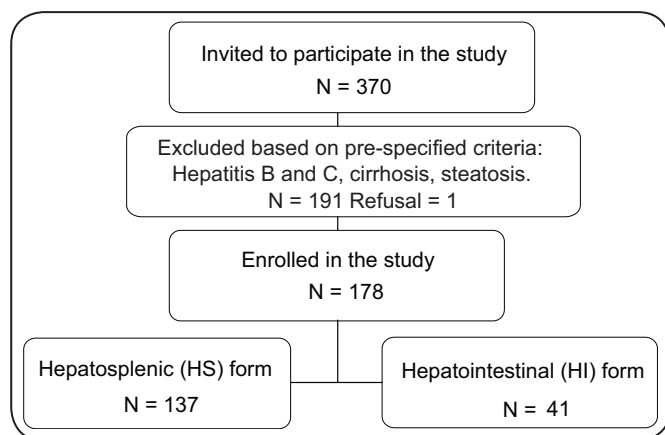

FIGURE 1 - Diagram depicting patient enrollment and classification.

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[14]) or those with no fibrosis and patients with HS schistosomiasis with advanced periportal fibrosis (pattern E or F from Niamey's classification[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[7,8].

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® 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[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**.
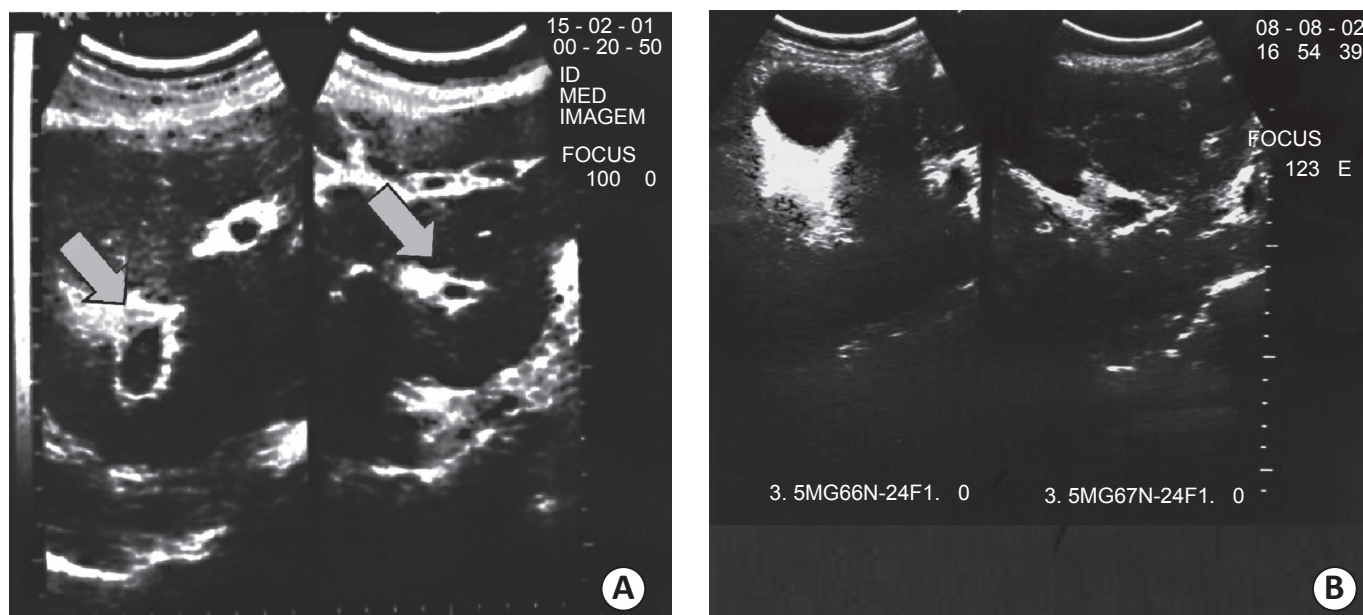
FIGURE 2 - Ultrasound features of periportal fibrosis patterns E (A) and D (B), according to Niamey's classification.

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 | | Group 2 | | | | |
	n	%	n	%			
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; *χ2 : chi-square.

TABLE 2 - Univariate analysis of the association between alcoholism, contact with contaminated water, specific treatment, and the periportal fibrosis pattern in Pernambuco, Brazil, 2012.

Variables	Periportal fibrosis groups				PR	95%CI	p-value*
	Grupo 1		Group 2				
	n	%	n	%			
Alcoholism							
yes	12	8.7	6	14.6	0.85	0.61-1.20	0.207
no	125	91.3	35	85.3			
total	137	100.0	41	100.0			
CCW							
MRR	4	2.9	7	17.0	0.49	0.22-1.08	0.014
Zona da Mata	53	38.6	6	14.6	1.21	1.05-1.40	0.029
Coast	5	3.6	2	4.8	0.96	0.59-1.56	0.584
others	75	54.7	26	63.4	1		
total	137	100.0	41	100.0			
Last exposure time*							
≤ 1 year	15	11.2	1	2.4	1		
≥ 1 to 15 years	41	30.4	14	34.1	0.80	0.65-0.97	0.089
> 15 to 25 years	26	19.2	10	24.3	0.77	0.61-0.98	0.077
≥ 25 years	53	39.2	16	39.0	0.82	0.68-0.98	0.114
total	135	100.0	41	100.0			
Specific treatment**							
oxamniquine	09	6.9	2	5.5	1		
praziquantel	112	84.8	26	72.2	0.99	0.74-1.33	0.658
did not undergo	11	8.5	8	22.2	0.71	0.44-1.14	0.175
total	132	100.0	36	100.0			
Last treatment***							
≤ 1 year	32	26.4	10	32.2	1		
≥ 1 to 15 years	83	68.5	19	61.2	1.07	0.88-1.30	0.633
≥ 15 to 25 years	6	5.0	2	6.4	0.98	0.64-1.52	0.626
total	121	100.0	31	100.0			

CCW: contact with contaminated water; MRR: Metropolitan Region of Recife; PR: prevalence ratio; CI: confidence interval; n: number of studied individuals; *2 cases with no information were excluded; **10 patients (5 cases/5 controls) with no information were excluded; ***26 patients (16 cases/10 controls) with no information were excluded; *χ2: chi-square.

Clinical and ultrasound evaluation

Liver abnormalities were identified in 170 patients who were attributed to *S. mansoni* according to Niamey's protocol[14]. 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, 76 (55.4%) had episodes of severe gastrointestinal bleeding,

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,

TABLE 3 - Final multiple logistic regression model for the advanced periportal 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).

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 'last time of 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.

DISCUSSION

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

It has been shown that specific treatment for *S. mansoni* can contribute to decreasing infection levels and improving clinical conditions such as hepatosplenomegaly and PPF[15-17]. As a result, the regression of PPF may prevent the emergence of portal hypertension, highlighting the importance of PPF diagnosis by obtaining accurate methods for monitoring this disease[18]. However, a higher education level might lead the patient to seek early treatment and could prevent reinfections.

Ultrasound examination and Niamey's classification[14] were used to diagnose the clinical forms and the PPF stages, which are currently the most widely used techniques for this purpose in both field and hospital studies[4].

This study was hospital-based; individuals generally present with more severe clinical forms in hospital studies when compared to field studies. There were many HS schistosomiasis patients with advanced fibrosis and even HI individuals presenting the more advanced fibrosis pattern D when compared to pattern C. Only 8 individuals did not exhibit fibrosis. In an

area with a low prevalence of this disease, most of the population did not show fibrosis, and only 4.6% had fibrosis pattern C[18].

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[19,20]. 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[19,21,22]. In addition, studies have described recent transmissions of schistosomiasis throughout this region and even in the City of Recife[19].

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[23].

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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