THE INFLUENCE OF PERIPORTAL (PIPESTEM) FIBROSIS ON LONG TERM RESULTS OF SURGICAL TREATMENT FOR SCHISTOSOMOTIC PORTAL HYPERTENSION

Álvaro Antônio Bandeira **FERRAZ**, Pedro Cavalcanti de **ALBUQUERQUE**, Edmundo Pessoa de Almeida **LOPES**, José Guido Corrêa de **ARAÚJO Jr.**, Anderson Henrique Ferreira **CARVALHO** e Edmundo Machado **FERRAZ**

ABSTRACT – ***Aim*** – To evaluate the degree of influence that periportal fibrosis has on clinical development and the long term results of surgical treatment on patients with hepatic-splenic schistosomiasis with previous gastrointestinal hemorrhages. ***Methods*** – During the period of 1992-1998, 111 patients underwent surgical treatment for the treatment of hepatic-splenic schistosomiasis with previous gastrointestinal hemorrhages. The degree of fibrosis was classified as: degree I – the portal spaces show a rich increase of young connective cells, a slight collagen production and a varying presence of inflammatory infiltrate. The periportal blade unchangeable (29/111); degree II – there is an expansion of the connective tissue with the emission of radial collagen septa, producing a star shaped aspect (38/111); degree III – the connective septa form bridges with other portal spaces or with the vein, with evident angiomatoid neo-formation (44/111). ***Conclusion*** – The patients with periportal fibrosis degree I present recurrent hemorrhages statistically less than patients with periportal fibrosis degrees II and III, and that the intensity of the periportal fibrosis is not the only pathophysiological factor of the esophageal varices, gastric varices, prevalence of post-operative portal vein thrombosis and hematological and biochemical alterations of the patients with pure mansoni schistosomiasis.

HEADINGS – Fibrosis, surgery. Hypertension, portal. Schistosomiasis.

INTRODUCTION

The behavior of schistosomiasis mansoni, an endemic disease in numerous countries[33], has undergone certain modifications throughout the last two decades. In Brazil, there has been an observed reduction in its prevalence of around 50%-70%[6], and consequently, also in its morbidity and mortality. However, despite this reduction, schistosomiasis mansoni still imposes a major socioeconomic impact on the areas where it is endemic, particularly in its hepatic-splenic form, because of the manner in which it attacks, economically active young people[31]. Within the region of 2% to 7% of infected patients go on to develop an advanced form of schistosomiasis – the hepatic-splenic form[18].

The evolutionary history of these patients comprises five major steps : 1) an appreciable contamination of the *Schistosoma mansoni;* 2) the fixation of live adult worms within the roots of the mesenteric veins; 3) the migration of the eggs deposited by the females and of dead worms towards the intra-hepatic portal roots in the liver, causing reactions both inflammatory and scarring, thus constituting Symmers fibrosis; 4) the development of portal hypertension; 5) the

Department of Surgery and Department of Internal Medicine – Gastroenterology, University Hospital, Federal University of Pernambuco, Recife, PE, Brazil.
Paper presented at the XXIV Brazilian Congress of Surgery, São Paulo, SP, 2001.
Address for correspondence: Dr. Álvaro Antônio Bandeira Ferraz – Av. Beira Rio 240 – ap. 2501 – Madalena – 50750 – 400 – Recife, PE, Brazil.

formation of esophageal varices, hypertensive gastropathy and colopathy[28, 32].

Periportal fibrosis, also known as Symmers fibrosis, was described in 1904[32] and constitutes a pathognomonic lesion of the hepatic-splenic region. It is characterized by wide fibroid strips that reach the branches of the portal vein from its entrance into the liver until its sub-divisions of the fourth degree branches[18].

The principal deciding antigenic factor of hepatic fibrosis is the presence of the *S. mansoni* eggs in the portal veins, which causes a granulomatous inflammatory reaction leading to the formation of fibroid tissue. During the sequence of events, there occurs a subsequent intra-hepatic, vascular neo-formation (the angiomatic, type), distributed around the portal ramifications that maintains the blood flow and preserves the hepatic cells[20]. It is for this reason that patients with schistosomiasis do not present hepatic insufficiency. This may also manifest itself in patients with mixed diseases, such as patients with schistosomiasis who acquire hepatitis B or C[18].

In such patients the global incidence of esophageal varices is within the region of 85%[3, 15, 23]. The natural history of esophageal varices during the hepatic-splenic phase of schistosomiasis mansoni considers that one third of the patients with hepatic-splenic schistosomiasis will not go on to develop upper gastrointestinal hemorrhages. This risk is greater in patients with thick varices and less in patients with thin varices[27]. Mortality during the first bleeding periods oscillates within the region of 11,7%[25]. This natural history data should be taken into consideration when dealing with a patient who develops gastrointestinal hemorrhages resulting from the rupture of esophageal varices. Due to their greater lethal risk, patients with cirrhosis should receive different therapeutic supervision to that of the patient with schistosomiasis.

Patients with schistosomiasis who present periods of gastrointestinal hemorrhaging should undergo surgical treatment, since they present good hepatic conditions and satisfactory post-surgical results[2, 21, 22, 26]. When not operated, recurrent hemorrhaging is frequent, unpredictable, with an increasing morbidity/mortality rate[2]. It is estimated that during the first year following the first bleeding, patients with schistosomiasis present recurrent hemorrhages at a rate of up to 80%[15]. Surgery is capable of correcting hematological alterations and is thereafter able to ensure the patient a good quality of life[22].

The treatment of hepatic-splenic schistosomiasis without previous hemorrhages is essentially clinical with the treatment of the parasitosis. In the presence of thick varices propanolol has a beneficial effect[30] however, endoscopic sclerotherapy or elastic ligature still as a controversial procedure. In the cases in which gastrointestinal hemorrhaging occurs, surgical therapy is indicated using shunt techniques or disconnections[23].

Since 1992, in the General Surgery Unit of the "Hospital das Clínicas" at the Federal University of Pernambuco, Recife, PE, Brazil, surgeries have been performed for hepatic-splenic schistosomiasis with previous gastrointestinal hemorrhages using splenectomy plus ligation of the left gastric vein (LLGV) plus devascularization of the great stomach curvature plus post-operative endoscopic sclerotherapy. With the presence of gastric fundus varices a gastrotomy and an obliterating running suture are also performed[21,22].

The identification of risk factors in the development of periods of gastrointestinal hemorrhages together with the clinical post-operative evolution (incidents of portal vein thrombosis, recurrent hemorrhages, development of gastric varices and a deterioration in hematological and biochemical data and mortality) could modify procedures and strategies when dealing with patients with schistosomiasis.

The objective of this study is to evaluate the degree of influence that periportal fibrosis has on clinical development and the long term results of surgical treatment on patients with hepatic-splenic schistosomiasis with previous gastrointestinal hemorrhages.

PATIENTS AND METHODS

During the period of 1992 and 1998, at the General Surgery Unit at the "Hospital das Clínicas" at the Federal University of Pernambuco, Recife, PE, Brazil, 111 patients underwent splenectomy plus LLGV plus devascularization of the great stomach curvature plus post-operative endoscopic sclerotherapy for the treatment of hepatic-splenic schistosomiasis with previous gastrointestinal hemorrhages. The study was analysed and approved by the Ethical Committee of the Federal University of Pernambuco.

In the patients who presented gastric varices in the pre-operative endoscopy (41/111) a gastrotomy and an obliterating running suture were also performed during the surgery. All patients were submitted to a hepatic wedge biopsy from the left lobe of the liver.

The progress of the patients was followed at the Portal Hypertension and Liver Clinic at the "Hospital das Clínicas", where patients underwent hematological and biochemical tests, upper digestive endoscopy, conventional ultrasonography, Doppler ultrasonography of the liver (with the objective of evaluating the portal flow).

All patients had previously been immersed in contaminated river water in endemic schistosomiasis mansoni areas, besides having suffered from gastrointestinal hemorrhages: hematemesis (99/111) or melena (12/111).

Inclusion and exclusion criteria in the current study are exposed in Figure 1.

FIGURE 1 – Inclusion and exclusion criteria in the current study

Criteria for inclusion	Criteria for exclusion
Over 16 years of age	Presence of mixed hepatic diseases
Previous history of gastrointestinal hemorrhages: hematemesis or melena	Other hepatic pathologies besides schistosomiasis
Presence of esophageal varices in pre-operative endoscopy	A history of alcoholism
Hematocrit higher than 22%	Pre-operative portal vein thrombosis
Prothrombin time no higher than 50% of the normal value	
Negative tests for hepatitis B and C	
Confirmation of pure schistosomiasis, by transoperative liver wedge biopsy	

Periportal fibrosis was evaluated from the hepatic wedge biopsies and classified according to the criteria defined by COELHO[13]. According to its intensity, the degree of fibrosis was classified as:

- degree I – the portal spaces show a rich increase of young connective cells, a slight collagen production and a varying presence of inflammatory infiltrate. The periportal blade and the reticulum are unchangeable.
- degree II – there is an expansion of the connective tissue with the emission of radial collagen septa, producing a star shaped aspect.
- degree III – the connective septa form bridges with other portal spaces or with the vein, with evident angiomatoid neo-formation.

According to the histologic degree of periportal fibrosis, the patients were categorized into three groups. Twenty-nine patients (26.1%) were included in group I (patients with periportal fibrosis degree I), 12 were male and 17 were female. In group II (patients with periportal fibrosis degree II), 18 were male and 20 were female, making a total of 38 patients (34.2%). And in group III (patients with periportal fibrosis degree III) 44 patients were analysed (39.7%), 24 were male and 20 were female.

The data was analysed statistically with the *t* test to establish differences between the averages, and the Q square and Fisher test were also used for comparing frequencies with a significance level of 95%.

RESULTS

The average time of patient follow-up varied depending on the group. The average follow up time for group I was 38.2 months, group II – 32.2 months and group III – 24.5 months. All patients underwent elective surgery outside any recent periods of gastrointestinal hemorrhages. Thirty-eight patients (34.2%) received trans-operative blood transfusions. The average age of the patients was 45.3, 44.8 and 45.4 for groups I, II and III, respectively. Hospital stay ranged from 5.4 days for group I, 6.6 days for group II and 8.1 days for group III.

Table 1 illustrates the relationship between the degree of periportal fibrosis and recurrent hemorrhaging, presence of pre-operative gastric varices and portal vein caliber.

Recurrent hemorrhaging occurred in 16 patients (14.4%) who were submitted to splenectomy plus LLGV plus devascularization of the great stomach curvature plus hepatic biopsy. Of these patients, eight (21.0%) were from group II and seven (15.9%) were from group III, with a higher statistical difference when these two groups were compared with group I, in which only one case of recurrent hemorrhaging was observed. All recurrent hemorrhaging was of the melena form.

Gastric fundus varices were observed in 36.9% of all patients, determining a gastrotomy and running suture during surgery. The incidence by group was 27.5%, 42.1% e 38.6% in groups I, II and III, respectively.

TABLE 1 – Relationship between the degree of periportal fibrosis and recurrent hemorrhaging, presence of pre-operative gastric varices and portal vein caliber

Periportal fibrosis degree	n	Recurrent hemorrhaging	Fundus gastric varices	Portal vein caliber
I	29	1 – 3.4%	8 – 27.5%	1.35 cm
II	38	8 – 21.0%*	16 – 42.1%	1.37 cm
III	44	7 – 15.9%*	17 – 40.9%	1.37 cm
Total	111	16 – 14.4%	41 – 36.9%	

* $P < 0,05$ in relation to the degree I

The presence of post-operative esophageal varices was relatively greater in group I (84.2%), but did not present any statistical differences that were greater than the other groups.

Not all patients submitted themselves to a postoperative Doppler ultrasonography, despite being solicited. In total, 68 patients underwent the Doppler and 9 of these (13.2%) revealed portal vein thrombosis. No relation between the degree of periportal fibrosis and the occurrence of portal vein thrombosis was demonstrated during the study (Table 2).

The patients who presented recurrent hemorrhaging and postoperative esophageal varices were treated with endoscopic sclerotherapy. Those who developed portal vein thrombosis were kept under rigorous observation, with regular sessions of sclerotherapy.

The pre and post-operative hematological and biochemical laboratory tests are illustrated in Tables 3 and 4. No significant differences were observed between groups I, II and III.

DISCUSSION

Periportal hepatic fibrosis is the most important and most characteristic anatomical finding of hepatic-splenic schistosomiasis mansoni[7]. This lesion was initially described by SYMMERS[32], in 1904, and in 1971 COELHO[19] classified it according to the intensity of the fibroid process in degrees I, II and III. Symmers fibrosis is constituted of fibroid strips resulting from the formation of granulomas, which distort the intra-hepatic portal architecture, determining the obstruction of the venous flow[20].

TABLE 2 – Relationship between the degree of periportal fibrosis and surgical results

	PERIPORTAL FIBROSIS		
	Degree I n = 29	**Degree II n = 38**	**Degree III n = 44**
Sex			
Male	12	18	24
Female	17	20	20
Age mean (years)	45.3	44.8	45.4
Hospital stay (mean – days)	5.4	6.6	8.1
Follow up (mean – months)	38.2	32.2	24.5
Postoperative esophageal varices	16 (19)	17 (26)	23 (31)
	84.2%	65.4%	74.2%
Portal vein thrombosis	3 (18)	4 (27)	2 (26)
	16.6%	14.8%	7.7%

TABLE 3 – Relationship between the degree of periportal fibrosis and pre-operative hematological and biochemical laboratory tests

	PERIPORTAL FIBROSIS		
	Degree I n = 29	**Degree II n = 38**	**Degree III n = 44**
Hemoglobin (g/dL)	10.8	9.8	10.1
WBC (mm^3)	5,271.4	3,059.5	4,478.2
Lymphocytes (mm^3)	1,058.7	696.5	801.4
Platelets (mm^3)	127,370	114,926	108,714
Prothrombin time (sec)	14.6	15.1	15.2
Glucose (mg/dL)	95.7	95.1	103.6
Urea nitrogen (mg/dL)	29.2	26.4	31.2
Creatinine (mg/dL)	0.8	0.8	0.8
Albumin (g/dL)	3.7	3.6	3.5
SGOT (UI/L)	29.6	34.8	42.5
SGPT (UI/L)	26.4	34.4	39.4
Bilirubin. total (mg/dL)	0.7	0.9	1.0
Bilirubin. direct (mg/dL)	0.3	0.4	0.4

TABLE 4 – Relationship between the degree of periportal fibrosis and postoperative hematological and biochemical laboratory tests (mean follow up 30 months)

	PERIPORTAL FIBROSIS		
	Degree I n = 29	**Degree II n = 38**	**Degree III n = 44**
Hemoglobin (g/dL)	13.5	12.1	12.6
WBC (mm^3)	7,026.7	6,765.4	6,792.8
Lymphocytes (mm^3)	2,256.6	2,258.8	1,841.1
Platelets (mm^3)	278,981	301,964	292,536
Prothrombin time (sec)	12.8	12.1	12.6
Glucose (mg/dL)	99.6	98.1	103.3
Urea nitrogen (mg/dL)	31.4	25.1	29.5
Creatinine (mg/dL)	0.7	0.7	0.7
Albumin (g/dL)	3.9	3.5	4.1
SGOT (UI/L)	44.2	50.6	56.2
SGPT (UI/L)	34.1	46.4	45.5
Bilirubin, total (mg/dL)	0.8	1.0	0.9
Bilirubin, direct (mg/dL)	0.3	0.3	0.3

Based on the fact that infected individuals who migrate from the endemic areas no longer develop the hepatic-splenic form, that individuals who already have this form of the disease have a better prognosis when out of the endemic area, and that patients clinically treated have better chances of regression than those who remain within the active transmission areas, it can be admitted that an inflammatory response principally depends on the degree of worm burden and the occurrence of re-infection[15]. Other substances, such as interleukins and cytokines also act on the process, although their mechanisms of action are not found to be completely elucidated.

The magnitude of periportal fibrosis is related to worm burden, to immunological and nutritional factors of the patient, and to an oxamniquine-based treatment[4, 8, 10, 12, 14, 24, 29]. The magnitude of the fibrosis could in this manner influence the natural evolution of the disease, and also the surgical results of patients with the hepatic-splenic form of the disease.

It was observed in this study that periportal fibrosis did not maintains a relationship with the gravity of schistosomiasis mansoni and with the clinical response to the surgical treatment by means of splenectomy plus LLGV plus hepatic biopsy.

Diagnosis of periportal fibrosis can be made through hepatic wedge biopsy or needle biopsy. According to a comparative study carried out on 183 patients by DIMMETTE[16], the wedge biopsy presented better diagnostic definition and was the preferred method. The hepatic wedge biopsy from the left lobe of the liver taken during surgery, is the best manner in which to evaluate the histological alterations of the portal spaces and the schistosomiasis granulomas[5, 16]. In this manner, this methodology of analysing the fibrotic alterations was possible because of the association of an intra-abdominal surgical procedure.

Recent studies[1, 17, 19] have revealed a new manner to diagnose periportal fibrosis by means of ultra-sound. This method has the principal advantage of being non-invasive and is easy to carry out. The use of ultrasound in the analysis and correlation of periportal fibrosis of the liver and the clinical evolution of patients has been increasingly used. However, there is no correlation between the degree of periportal fibrosis determined through ultrasonography and the histopathological analysis presented by COELHO[13].

All operated patients presented past episodes of upper gastrointestinal hemorrhages, clinically identified, via melena or hematemesis. In other words, despite presenting a severe form of schistosomiasis mansoni (the hepatic-splenic form), with a past of gastrointestinal hemorrhages, no predominant degree of periportal fibrosis was identified.

The degree of periportal fibrosis can result in very prominent pre-sinusoidal blockages and determine a higher level of portal hypertension[11]. The severity of the portal hypertension of these patients could, in an indirect manner, be measured by the caliber of the portal vein and from the presence of gastric fundus varices, identified before the surgical procedure. Once again however, no relation between the degree of periportal fibrosis and the caliber of the portal vein and the presence of gastric fundus varices was identified. Patients with a degree of periportal fibrosis type I presented a lower tendency of gastric fundus varices, which was not supported by the statistical analysis.

In the analysis of the surgical results, patients with periportal fibrosis degrees II and III presented a higher incidence of recurrent hemorrhages, 21% and 15.9% respectively, than the patients with fibrosis degree I (3.4%). Despite recurrent hemorrhages being higher in the fibrosis degrees II and III, the presence of postoperative esophageal varices in the patients with fibrosis degree I was statistically similar to the more advanced degrees. All patients, independent of level of periportal fibrosis, had to be submitted to post-operative endoscopy and sclerotherapy was carried out if they presented esophageal varices.

No relation between post-operative portal vein thrombosis and portal fibrosis was presented.

The hematological and biochemical laboratory tests between the degrees of periportal fibrosis, both in the pre and post-operative stages, did not present any differences. Despite the fact that the fibroid reaction was more intense in degree III, the neo-vascular angiomatic formation maintained the hepatic flow and preserved the hepatic functioning of these patients, which could justify the similarity of the laboratory tests of the different degrees[21, 22].

It can be concluded that patients with periportal fibrosis degree I present recurrent hemorrhages statistically less than patients with periportal fibrosis degrees II and III, and that the intensity of the periportal fibrosis is not the only pathophysiological factor of the esophageal varices, gastric varices, prevalence of post-operative portal vein thrombosis and hematological and biochemical alterations of the patients with pure mansoni schistosomiasis.

Ferraz AAB, Albuquerque PC, Lopes EPA, Araújo Jr JGC, Carvalho AHF, Ferraz EM. Influência da fibrose periportal no seguimento tardio de pacientes submetidos a tratamento cirúrgico da hipertensão portal esquistossomótica. Arq Gastroenterol 2003;40(1)4-10.

RESUMO – ***Objetivo*** – Avaliar a influência do grau de fibrose periportal no seguimento tardio de pacientes tratados cirurgicamente da esquistossomose hepatoesplênica com antecedentes de hemorragia digestiva. **Casuística e Métodos** – Foram analisados 111 pacientes submetidos ao tratamento cirúrgico da esquistossomose hepatoesplênica no período de 1992-1998. O grau de fibrose periportal foi classificado como: grau I (29/111): os espaços porta apresentam-se com riqueza de células conjuntivas jovens, discreta produção de colágeno e presença variável de infiltrado inflamatório. A lâmina periportal e o retículo são normais; grau II (38/111) – há expansão do tecido conjuntivo com emissão de septos colágenos radiais, dando ao mesmo um aspecto estrelado; grau III (44/111) – os septos conjuntivos formam pontes com outros espaços porta ou com a veia, havendo neoformação angiomatóide bem evidente. ***Resultados*** – O seguimento médio dos pacientes com fibrose grau I foi de 38,2 meses, 32,2 meses no grau II e 24,5 meses na fibrose periportal grau III. Pacientes portadores de fibrose periportal grau I apresentaram recidiva hemorrágica estatisticamente menor. A intensidade da fibrose periportal não influenciou a presença de varizes de fundo gástrico, prevalência de trombose portal pós-operatória e alterações bioquímicas e hematológicas. ***Conclusão*** – O grau de fibrose periportal tem influência na recidiva hemorrágica de pacientes portadores de hipertensão portal esquistossomótica submetidos a tratamento cirúrgico.

DESCRITORES – Fibrose, cirurgia. Hipertensão portal. Esquistossomose.

REFERENCES

1. Abdel-Wahab MF, Esmalt G, Milad M, Abdel-Razek S, Strikland GT. Characteristic sonographic pattern of schistosomal hepatic fibrosis. Am J Trop Med Hyg 1989;40:72-6.
2. Abrantes WL, Drumond DAF. Anastomose espleno-renal distal em esquistossomótico – revisão de 200 pacientes operados há 11 e 22 anos. In: Abrantes W, editor. Hipertensão portal – estado atual. Clin Bras Cir Col Bras Cir 1995;2:243-54.
3. Almeida STGC, Coutinho A, Ferreira-Filho H, Jucá N, Arouch DC. Estudo endoscópico e histopatológico da mucosa gastroduodenal em pacientes portadores de esquistossomose mansônica. In: 8º Seminário de Endoscopia Digestiva; 4ª Jornada Nordeste de Gastroenterologia; 1987; Salvador.
4. Andrade ZA, Grimaud JA. Morphology of chronic collagen resorption. A study on the late stages of schistosomal granuloma involution. Am J Pathol 1988;132:389-99.
5. Andrade ZA, Peixoto E, Guerret S, Grimaud JA. Hepatic connective tissue changes in hepatosplenic schistosomiasis. Hum Pathol 1992;23:566-73.
6. Andrade ZA. The situation of hepatosplenic schistosomiasis in Brazil today. Mem Inst Oswaldo Cruz 1998;93 Suppl 1:313-6.
7. Andrade ZA, Silva LM, Souza MM, Sadigursky M, Barbosa A, Oliveira IR. Role of the spleen on the pathogenesis of schistosomal periportal (pipestem) fibrosis of the liver: an experimental approach. Am J Trop Med Hyg 1998;59:557-62.
8. Assad KSH, Helmy MA, Zaki A, Mikhail MM, El Hai MA, El Sawy M. Some genetic, clinical and immunologic interrelations in *Schistosomiasis mansoni*. Ann Biol Clin 1993;51:619-26.
9. Bogliolo L. The anatomic picture of the liver in hepato-splenic schistosomiasis mansoni. Ann Trop Med Parasitol 1957;51:1-14.
10. Butterworth AE. Studies of human schistosomiasis: chemotherapy, immunity and morbidity. Ann Parasitol Hum Comp 1990;65:53-7.
11. Canto AL, Sesso A, Brito T. Human chronic mansonian schistosomiasis. Cell proliferation and fibre formation in the hepatic sinusoidal wall: a morphometric, light and electron-microscopy study. J Pathol 1977;123:35-44.
12. Cheever AW, Andrade ZA. Pathological lesions associated with *Schistossoma mansoni* infection in man. Trans R Soc Trop Med Hyg 1967;61:626-39.
13. Coelho RB. Lesões hepáticas secundárias. In: Coelho RB. Anatomia patológica das afecções hepáticas. Recife: Editora da UFPE; 1971. p.59-77.
14. Coutinho EM, Souza MM, Silva LM, Cavalcante CL, Araujo RE, Barbosa JAA, Cheever AW, Andrade ZA. Pathogenesis of schistosomal pipestem fibrosis: a low-protein diet inhibits the development of pipestem fibrosis in mice. Int J Exp Pathol 1997;78:337-42.
15. Cury AA. Hipertensão portal esquistossomótica – história natural. In: Abrantes W, editor. Hipertensão portal – estado atual. Clin Bras Cir Col Bras Cir 1995;2:121-36.
16. Dimmette RM. Liver biopsy in clinical schistosomiasis. Comparison of wedge and needle types. Gastroenterology 1955;29:219-34.
17. Domingues ALC, Lima ARF, Dias HS, Leão GC, Coutinho A. An ultrasonographic study of liver fibrosis in patients infected with *Schistosoma mansoni* in northeast Brazil. Trans R Soc Trop Med Hyg 1993;81:555-8.
18. Domingues ALC, Domingues LAW. Forma intestinal, hepatointestinal e hepatoesplênica. In: Malta J, editores. Esquistossomose mansônica. Recife: Editora da UFPE; 1994. p.91-109.
19. Domingues ALC. Ultra-sonografia na esquistossomose mansônica hepato-esplênica: avaliação da intensidade da fibrose periportal e da hipertensão porta [tese]. Recife: Universidade Federal de Pernambuco; 1998.
20. Ferraz AAB, Silveira MJ, Coelho ARB, Câmara-Neto RD, Araújo Jr GC, Ferraz EM. Surgical treatment of schistosomal portal hypertension. Int Surg 2001;86:1-8.

21. Ferraz AAB, Arruda SMB, Bacelar TS, Silveira MJC, Silva LMM, Cândido AC, Araujo Jr GC, Ferraz EM. Trombosis de la vena porta después de esplenectomia para hipertension portal esquistosómica. Rev Colombiana Cir 2000;15:1-7.
22. Ferraz AAB, Lopes EPA, Bacelar TS, Silveira MJC, Silva LMM, Ferraz EM. Tratamento cirúrgico da hipertensão portal esquistossomótica no HC-UFPE – análise de 131 casos. Rev Col Bras Cir 2000;27:332-7.
23. Ferraz EM, Ferraz AAB. Tratamento cirúrgico da hipertensão portal esquistossomótica. In: Malta J, editor. Esquistossomose mansônica. Recife: Editora da UFPE; 1994. p. 235-49.
24. Goes AM, Gazzinelli G, Rocha R, Katz N, Doughty BL. Granulomatous hypersensitivity to *Schistosoma mansoni* egg antigens in human schistosomiasis. III. In vitro granuloma modulation induced by immune complexes. Am J Trop Med Hyg 1991;44:434-43.
25. Kelner S, Ferraz EM, Wanderley F. Hematêmese: inquérito sobre desencadeamento por drogas contendo ácido acetilsalicílico na hipertensão porta esquistossomótica. An Fac Med Univ Pernamb 1964;24:153-65.
26. Kelner S, Ferreira PR, Dantas A, Lima-Filho JF, Souza AP, Carreiro Jr JC, Ferraz EM, Silveira M, Coelho AR, Camara-Neto RD, Domingues LA. Ligadura de varizes esôfago-gástricas na hipertensão porta esquistossomótica: avaliação de 25 anos. Rev Col Bras Cir 1982;9:140-6.
27. Kelner S, Silveira M. História natural das varizes do esôfago na esquistossomose mansônica hepatoesplênica. In: Kelner S, Silveira M, editores. Varizes do esôfago na esquistossomose mansônica. Recife: Ed. Universitária da UFPE; 1997. p 55-61.
28. Lima A, Magalhães V, Guimarães RX. Fatores que influenciam a morbidade da hepatopatia na esquistossomose mansoni. RBM Rev Bras Med 1991;48:738, 742, 745, passim.
29. Mohamed-Ali Q, Elwali NE, Abdelhameed AA, Margani A, Rahoud S, Elagib KE, Saeed OK, Abel L, Magzoub MM, Dessein AJ. Susceptibility to periportal (Symmers) fibrosis in human schistosoma mansoni infections: evidence that intensity and duration of infection, gender, and infection factors are critical in disease progression. J Infect Dis 1999;180:1298-306.
30. Primo I, Cordeiro F. Esclerose endoscópica das varizes de esôfago. In: Kelner S, Silveira M, editores. Varizes do esôfago na esquistossomose mansônica. Recife: Editora da UFPE; 1997. p.131-43.
31. Silveira RK, Silveira M, Kelner S. Prevalência de sexo, raça e grupo etário entre 3086 portadores de esquistossomose hepatoesplênica. In: Kelner S, Silveira M, editores. Varizes do esôfago na esquistossomose mansônica. Recife: Editora da UFPE; 1997. p.41-53.
32. Symmers WSTC. Note on a new form of liver cirrhosis due to the presence of the ova *Brilharzia haematobia*. J Pathol Bacteriol 1904;9:237-9.
33. World Health Organization. The control of schistosomiasis: second report of the WHO expert committee. Geneva; 1993. World Health Organization technical report series 830.

Recebido em 2/4/2002.
Aprovado em 23/9/2002.