ORIGINAL ARTICLE

AG-2020-182
doi.org/10.1590/S0004-2803.202100000-48

Histopathological, clinical and epidemiological features of hepatoportal sclerosis in a referral center for liver disease in Northeastern Brazil

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Received: 26 August 2020
Accepted: 9 February 2021

ABSTRACT – **Background** – Hepatoportal sclerosis (HPS) or obliterative portal venopathy (OPV), one of the differential diagnoses for non-cirrohtic portal hypertension, is characterized by the disappearance of the portal branches, portal and septal fibrosis, perisinusoidal fibrosis and regenerative nodular hyperplasia (RNH). It is a spectral disease that may progress to severe portal hypertension. Its etiopathogenesis is still little understood, especially in Brazil, it has been probably misdiagnosed due to its histopatological similarities with the hepatosplenic form of schistosomiasis. **Objective** – To analyze the profile of patients with HPS in Northeastern Brazil and to demonstrate the pathological characteristics of HPS. **Methods** – We retrospectively analyzed cases of OPV in liver biopsies and explants from a referral center for liver in Bahia – Brazil. The qualitative and quantitative analysis of the portal tracts and liver parenchyma was made so that comparisons could be done among the HPS findings of our population and the findings described by other authors. **Results** – From the 62 patients identified with HPS, 42% were male, while 58% were female. The average age at diagnosis was 48.3 years. From this group, we analyzed the liver biopsy of 10 patients whose diagnosis of schistosomiasis could be ruled out. From these 100% (10/10) presented dense portal fibrosis and portal venous obliteration. Liver parenchymal atrophy was present in 60% (6/10) of the patients, sinusoidal dilation was present in 30% (3/10), the presence of portal septa occurred in 50% (5/10) and dense portal fibrosis in all patients analyzed. Nodular regenerative hyperplasia was found in 30% (3/10) of the patients. **Conclusion** – HPS seems to be neglected and misdiagnosed in Brazil, due to its similarities with schistossomiasis. In our study dense portal fibrosis, obliteration of the portal vein branches, parenchymal atrophy, sinusoidal dilatation and parenchymal nodular hyperplasia were the main histopathological findings and were similar to that described in other countries.

Keywords – Hepatoportal sclerosis; obliterative portal venopathy; portal hypertension; schistosomiasis.

INTRODUCTION

Hepatoportal sclerosis (HPS) is a spectral hepatic vascular disease but may present with severe portal hypertension. In the literature, this disease is also described as idiopathic obliterative portal venopathy, idiopathic portal hypertension or porto-sinusoidal disease.

More than 50% of HPS cases have no clear etiology, but some etiopathogenic suspicions have arisen to explain the trigger of the disease development. Intestinal or systemic infections, whether viral (e.g.: HIV), bacterial or parasitic, are suggested to stimulate hepatic fibrogenesis and portal venous obstruction. In addition, the frequent association between autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, thyroiditis among others and HPS and the presence of anti-DNA antibody in some patients raises the suspicion that this may be an autoimmune component disease[1-4].

Besides that, some drugs such as azathioprine, 6-thioguanine and 6-mercaptopurine may be responsible for some cases, since it can cause portal vein branch fibrogenesis and the development of obliterative portal venopathy[1,3] Another condition strongly associated with this condition is genetic thrombophilia. In some thrombophilic patients, the appearance of micro-thrombi in the small and medium-sized branches of the portal vein of genetically susceptible patients is at the pathophysiological core of the entity[5] Some authors have suggested the establishment of anticoagulant therapy to decrease the rate of disease progression[6] In addition to clinical variability at the time of diagnosis, histopathological findings, which the description is the main objective of our study, are also quite heterogeneous[7]. The main ones are: dense portal fibrosis, disappearance of portal vein branches, presence of fibrous septa, nodular regenerative hyperplasia, sinusoidal dilation and perisinusoidal fibrosis.

From a clinical, laboratory, endoscopic and even histopathological point of view, this disease can be confused with the hepatosplenic or hepatic intestinal form of schistosomiasis, so it has been neglected for a long time. In fact, in the diagnostic practice in liver biopsies, there are a large number of cases diagnosed as portal fibrosis with no known cause, many with portal branch obstruction, some with portal hypertension. Given the high prevalence of schistosomiasis in Northeastern Brazil, the finding of portal fibrosis

Declared conflict of interest of all authors: none
Disclosure of funding: this paper was supported by *Fundação Maria Emília de Carvalho Freire*, Bahia, Brasil and *Fundação de Amparo à Pesquisa do Estado da Bahia* N. SUS0029/14.
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with obstruction of portal vein branches in patients, even in the absence of parasitological evidence in the past or *S. mansoni* eggs in portal tract, HPS can be easily misdiagnosed as hepatosplenic schistosomiasis. Now, when the prevalence of severe forms of schistossomiasis are dramatically decreasing in Bahia, the differential diagnoses between both diseases are mandatory.

Thus, this study aims to analyze the profile of patients with HPS in Northeastern Brazil and to demonstrate the pathological characteristics of HPS.

METHODS

A retrospective case series study was conducted assessing liver biopsies performed from 2002 until 2018. The cases were selected after a liver biopsy and explants survey from the IMAGEPAT-pathological anatomy laboratory archives to create a database and biorepository of paraffin tissue blocks and slides. We then reviewed the liver biopsy reports from the IMAGEPAT archive diagnosed with portal septal fibrosis, whether or not associated with other findings.

For data collection, a database was created containing the following information: biopsy registration number, data, patient data (gender, age, ethnicity, procedure), clinical suspicion, and available laboratory data. All biopsies with diagnosis of the portal fibrosis were reviewed by two pathologists with experience in liver pathology. The hematoxylin and eosin (HE), silver, perls and red picrosirious were used.

After selecting cases compatible with HPS, patients' medical records were evaluated to rule out the possibility of schistosomiasis.

Cases with parasitological stool positive for *S. mansoni* eggs, residence in endemic areas for schistosomiasis, presence of egg or egg rests on biopsy, serology and / or positive skin test for schistosomiasis were excluded.

According to results of the previous study[8], we review ten cases focused on: portal fibrosis intensity, presence of septal fibrosis, portal vein obstruction, hepatic artery branch hyperplasia, ductular reaction, periportal venous vessels and portal vein branch thrombosis.

In hepatic parenchyma, we assed the presence of sinusoidal dilation and congestion, hepatic atrophy signs, hepatocyte necrosis and apoptosis, as well as we evaluated the evidence of hepatic parenchyma extinction appraising the approximation of vascular structures, such as portal tracts and central veins and evidence of nodular regenerative hyperplasia of liver parenchyma indicating changes in hepatic circulatory dynamics. After that, we compared, through literature review, the findings of our sample with those described in the literature.

Statistical analysis was descriptive, using SPSS statistics® version 24.0.

This project was approved under the Research Ethics Committee of the Gonçalo Muniz Research Center – CPqGM / Fiocruz – BA under number 757.935.

RESULTS

We identified 868 biopsies diagnosed with portal fibrosis by the following etiologies: viral hepatitis, steatohepatitis, cirrhosis, schistosomiasis infection, chronic cholestasis and autoimmune hepatitis. Within these 868 pathological exams, 7.14% (62/868) had corresponding findings with HPS. The sample consisted of 36 (58%) female patients and 26 (42%) male patients. The mean age of the patients at the time of diagnosis of HPS was 48.3±16.7 years. The mean values of aspartate aminotrasferase (AST) were 71.9±66.0 U/L, alanine aminotrasferases (ALT) were 73.8±71.0 U/L, gamma glutamyltransferase (GGT) 246.1±281.2 U/L and alkaline phosphatase (ALP) were 197.7±176.9 U/L. (TABLE 1).

TABLE 1. Clinical and pathological characteristics of patients diagnosed with hepatoportal sclerosis.

Variable	N=10 Patients that had slides reviewed	N=52
Gender		
Male n	50%	42 %
Female n	50%	58%
Age	49.8±12.5	47.6±17.6
AST	38.2±6.7	71.9±66.0
ALT	68.0±30.0	73.8±71.0
ALP	93.8±38.9	246.1±281.2
GGT	168.0±131.7	197.7±176.9
Parenchymal atrophy	60%	–
Sinusoidal dilation	30%	–
Presence of fibrous septa	50%	–
Dense portal fibrosis	100%	–
NRH	30%	–

AST: aspartate aminotransferase; ALT alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase; NRH: nodular regenerative hyperplasia.

From the 62 exams that presented HPS on liver biopsy, only 16% (10/62) had the slides reviewed. These ten patients, AST 38.2±6.7 U/L, ALT 68±30.04 U/L, ALP 93.8±38.9 U/L and GGT 168±131.7 U/L (TABLE 1). The main finding of hepatoportal sclerosis is the obliterative portal venopathy (OPV), characterized by dense portal fibrosis and obliteration of the portal vein branches, which was present in 100% of our sample. Approximation between portal spaces and centrilobular veins was present in 60% of the patients. Sinusodal dilation was found in 30% of the patients. Interlobular fibrous septa occurred in 50% of the analyzed slides. Parenchymal nodular hyperplasia was observed in 30% (FIGURE 1).

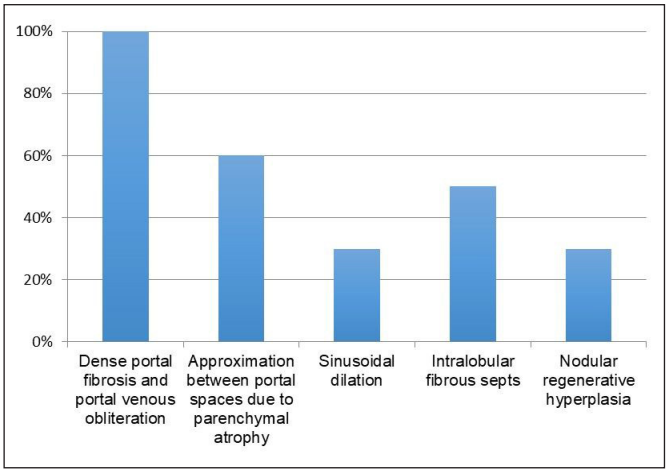

FIGURE 1. Characterization of histopathological findings found in patients diagnosed with hepatoportal sclerosis.

The main characteristics of the portal tract in the HPS found were the fibrous thickening and occlusion of the intrahepatic portal vein branch, as well as intrahepatic proliferation of the portal vein branches (FIGURES 2.A and B).

Another common finding found in liver biopsies is parenchymal atrophy and consequent approximation of vascular structures with alteration of the liver's typical lobar architecture (FIGURE 2.C).

It was also verified dilated sinusoids and perisinusoidal fibrosis, frequently found in HPS. (FIGURE 2.D). Nodular regenerative hyperplasia (NRH) was also observed in some patients (FIGURE 2.E).

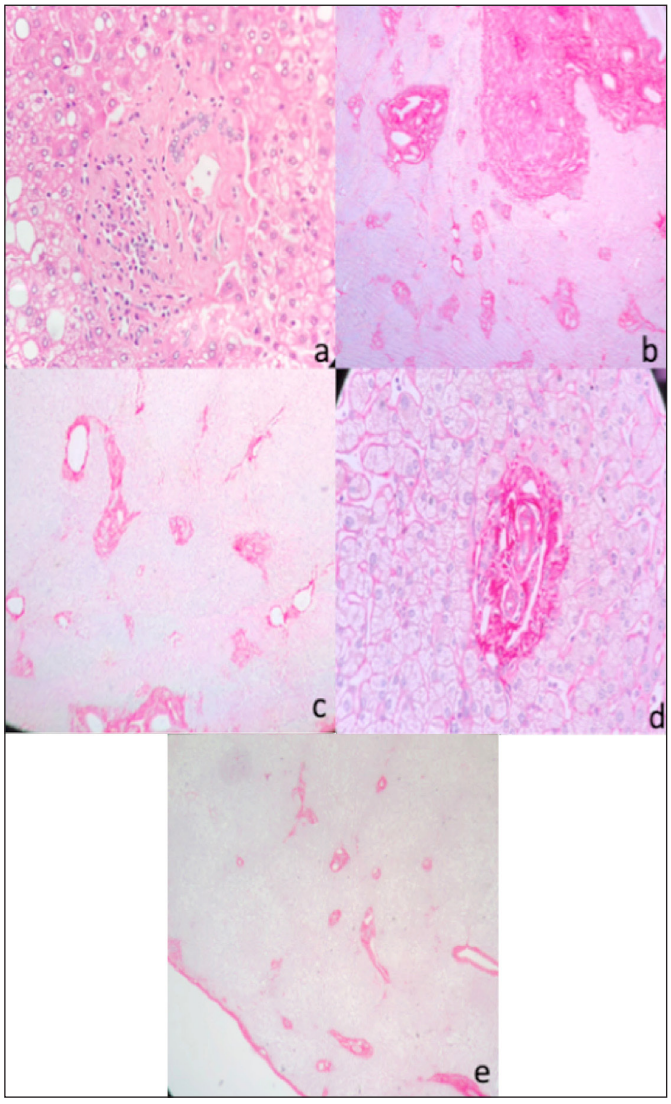

FIGURE 2. Optical microscopy with the main histopathological findings of hepatoportal sclerosis.
A. HE stained portal spaces showing portal tract retraction. **B.** Picrosirius-stained showing numerous sclerosed portal tracts with retraction of the portal spaces and important widening of others. **C.** Picrosirius-stained showing the approximation of hepatic vascular structures (portal space and centrilobular veins) secundary to parenchymal atrophy. **D.** Portal space with sclerosis and disapparance of the portal vein branch, consistente with POV, is observed, as well as, perissinusoidal fibrosis and sinusoidal dilation, especially in the upper left quadrant of the image. **E.** Slide showing POV, approximation of vascular structures and formation of parenchymal nodules in the absence of fibrosis, consistent with NRH.

DISCUSSION

There are few studies on hepatoportal sclerosis as well as many confusion because variable nomenclature in different countries. In India this disease is known as non-cirrhotic portal fibrosis, while in Japan, it is called idiopathic portal hypertension[9]. In the United States, Europe and Brazil, regions with highest prevalence of the disease[7], the most used name is hepatoportal sclerosis[10].

Besides the nomenclature, the clinical and pathological characteristics of the patients analyzed in the studies are also quite different. In addition, although it is a spectral disease, most studies focuses on complications of portal hypertension such as esophageal varices, upper gastrointestinal bleeding and hypersplenism[11].

In 2002, a study involving 151 patients, observed that 62.2% of the patients were women, with an average age of 30.5 years. The annual report of the Japanese Research Committee on Portal Hemodynamic Abnormalities found a ratio of three women for each man affected by the disease with a mean age of 44.5±15.8 for women and 51.8±11 years for men[12]. The data found in the literature are very close to the findings in our study, where 42% of the patients were male while 58% were female. In addition, the average age was 48.3±16.7 years, with a maximum age of 72 years and a minimum of 2 years. The peak of incidence was also around the fifth and sixth decade of life.

Serum levels of transaminases and canalicular enzymes in patients with HPS also vary widely between studies of the disease. In India, 45.5% of patients had AST above the upper normal level[13]. Another study, in Spain, found the mean serum AST values to be 40.4 U/L, while the mean values for ALT were 40.7 U/L. The mean levels of GGT and AF were, respectively, 78.2 U/L and 318.6 U/L[14].

Again the values found in our study approached the data found in the literature about the subject. The mean AST of our patients was 60.7±56.4 U/L (normal range: 5 to 40 U/L) ALT 71.7±63.9 U/L (NR: 7 to 56 U/L), ALP 243.1±246.7 (NR: 40 to 126 U/L) and GGT 169.9±152.9 (NR: 7 to 60 U/L).

Histopathological findings, as aberrant portal vessels, sinusoidal dilatation, abnormal parenchymal veins, nodular regenerative hyperplasia, and portal fibrosis, as described by Guido et al.[15] are crucial for the HPS diagnosis, since there is no specific laboratorial or clinical markers and portal hypertension are not always present at the time of diagnosis[16]. The most updated consensus on the subject determines that the diagnosis should be made when biopsy presents obliterative portal venopathy, disorganized vasculature, portal tract fibrosis and absence of hepatocellular lesion or established cirrhosis[17]. The presence of all findings is not required to make the diagnosis. Some authors showed that the frequency of dense portal fibrosis finding was 100% among the patients analyzed[18,19].

The mechanism of portal vein branch fibrosis induction seems to be related to the activation of fibroblasts located in the portal tract causing them to increase TGF-β expression and thus triggering an increase in extracellular matrix deposition. The fibrosis of the portal vein branches, also called OPV, presents histologically with retraction or widening of the portal tract. Irregular thickening of the intimate portal vein tunic occurred in 75% of patients. Nodular parenchymal hyperplasia was found in 40% of patients. The presence of interlobular fibrous septa was found in 95% of the patients. In another study, portal vein sclerosis was described in 98% of patients, hypoplastic portal tracts in 63% of patients, NRH in 47% of patients, interlobular fibrous septa in 14% of patients, sinusoidal dilation in 98% of patients and perisinusoidal fibrosis in 94%[20-22].

Some author suggest that the degree of NRH was related to the severity of portal vein sclerosis[21].

The NRH also develops after changes in hepatic blood flow, which produces repeated processes of atrophy of regions where there is decreased blood supply followed by compensatory hyperplasia of regions where flow remains normal, resulting in the aspect seen in FIGURE 2.E[23]. Sinusoidal dilatation and perisinusoidal fibrosis are pathological processes that have the same triggering factor in their pathophysiology: capillarization and increase of the arterial fraction of blood that reaches the sinusoids. Arterial blood reaches the sinusoids exerting a higher pressure and a higher flow velocity, as a result of this there is a sinusoidal endothelial cell defenestration and development of the basal lamina characteristic of the capillaries (FIGURE 2.D).

All the histological findings of our study were very close to most of the histopathological features described in the literature. Portal fibrosis and obliteration of portal vein branches were present in 100% of the patients studied. Sinusoidal dilation occurred in 30% of patients, the presence of interlobular fibrous septa occurred in 50% of patients and parenchymal nodular regenerative hyperplasia was present in 30% of patients. Data not yet found in the literature was the frequency of approximation between vascular structures due to parenchymal atrophy, which was present in 60% of the patients in our study. The reason for this process seems to be the decrease in blood supply from the portal vein – which would normally be 70% – secondary to the progressive increase in fibrosis and the establishment of a continuous process of local ischemia[24]. In addition, there is a shortage in the production and distribution of growth factors that induce hepatocyte replication. The most important growth factor is undoubtedly the hepatocyte growth factor (HGF). It is mainly produced by stellate cells and has the ability to stimulate the proliferation, maturation and movement of hepatocytes. Its lower production results in hepatic parenchymal atrophy. In addition to HGF, other substances such as epidermal growth factor (EGF), transformed alpha growth factor (TGFα), insulin-like growth factor (IGF–1), have decreased production and activity in the liver, which contributes to aggravation of parenchymal atrophy[25].

Interestingly, during our slide studies and analysis, the characteristic histopathological findings of HPS are not evenly distributed throughout the liver tissue examined. There are no justifications in the literature for the occurrence of this anarchic distribution.

Despite the limitations, as e.g. few cases diagnosed and losses of clinical information, this study brought initial considerations about HPS in our country. There are few data in Brazil concerning this disease, mainly its differential diagnosis with schistossomiasis. We suppose many cases of HPS in Brazil are strongly misdiagnosed as *S. mansoni* infection. Our group recently described three cases of HPS that seemed to me associated with DILI. The patients were previously exposed to tees and alimentary supplements which contained many herbs. We postulated that, HPS could be a consequence of DILI induced by them[26].

We need more studies in order to define risk factors, etiology, prevention methods, less invasive methods of diagnosis, new treatment models and prognosis of patients with hepatoportal sclerosis, so that knowledge about the disease may be disseminated, and reduce its neglect and underdiagnosis.

CONCLUSION

In our study dense portal fibrosis, obliteration of the portal vein branches, parenchymal atrophy, sinusoidal dilatation and parenchymal nodular hyperplasia were the main histopathological findings and were similar to that described in other countries.

Hepatoportal sclerosis is a neglected and underestimated disease in Brazil, where it may be easily misdiagnosed as schistossomiasis. The complete analysis of all patients in our data bank, as well as the analysis of possible etiologies will contribute to better understanding this disease in our country.

Authors' contribution

Araújo C: data collect and text writing. Nunes VS, Santos G: text writing. Freitas LAR: data collect. Schinoni MI, Paraná R: reviewer.

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Araújo C, Nunes VS, Santos G, Freitas LAR, Schinoni MI, Paraná R. Características histopatológicas, clínicas e epidemiológicas da esclerose hepatoportal em um centro de referência para doenças do fígado no Nordeste do Brasil. Arq Gastroenterol. 2021;58(3):276-80.

RESUMO – **Contexto** – Esclerose hepatoportal (EHP) ou venopatia portal obliterativa (VPO), um dos diagnósticos diferenciais para a hipertensão portal não cirrótica, é caracterizada pelo desaparecimento dos ramos portais, fibrose portal e septal, fibrose sinusoidal e hiperplasia nodular regenerativa (HNR). A EHP é um doença espectral, que pode progredir para hipertensão portal severa. Sua etiopatologia é ainda pouco compreendida, especialmente no Brasil, onde ela é provavelmente subdiagnoticada devido as suas similaridades com a forma hepatoesplênica da esquistossomose. **Objetivo** – Analizar o perfil dos pacientes com EHP no Nordeste do Brasil, e demontrar as características patológicas da EHP. **Métodos** – Analisamos restrospectivamente os casos de VPO em biópsias hepáticas e explantes de um centro de referência em fígado na Bahia, Brasil. A análise qualiquantitativa dos tratos portais e parênquima hepático foi realizada, permitindo a comparação entre os nossos paciente e os achados descritos por outros autores. **Resultados** – Entre os 62 paciente identificados com EHP, 42% era do sexo masculino, 58% era do sexo feminino. A média de idade no diagnótico foi 48,3 anos. Desse grupo, analizamos a biópsia hepática de 10 pacientes nos quais o diagnóstico de esquistossomose pode ser excluído. Desses pacientes, 100% (10/10) se apresentou com fibrose portal densa e obliteração venosa portal. Atrofia do perênquima hepático estava presente em 60% (6/10) dos pacientes, dilatação sinusiodal em 30% (3/10) a presença de septos portais ocorreu em 50% (5/10) e fibrose portal densa foi achada em todos os pacientes. Hiperplasia nodular regenerativa foi encontrada em 30% dos pacientes. **Conclusão** – A EHP parece ser negligenciada e subdiagnosticada no Brasil, devido as suas similaridades com esquistossomose. Em nosso estudo, fibrose portal densa, obliteração dos ramos da veia porta, atrofia do parênquima, dilatação sinusoidal e hiperplasia nodular do parênquima foram os principais achados histopatológicos e foram semelhantes aos descritos em outros países.

Palavras-chave – Esclerose hepatoportal; venopatia portal obliterativa; hipertensão portal; esquistossomose.

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