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Etiology of liver cirrhosis in Brazil: chronic alcoholism and hepatitis viruses in liver cirrhosis diagnosed in the state of Espírito Santo

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OBJECTIVES: To report the etiology of liver cirrhosis cases diagnosed at the University Hospital in Vitoria, Espirito Santo, Brazil.

METHODS: The medical charts of patients with liver cirrhosis who presented to the University Hospital in Vitoria were reviewed. Chronic alcoholism and the presence of hepatitis B or C infections (HBV and HCV, respectively) were pursued in all cases.

RESULTS: The sample consisted of 1,516 cases (male:female ratio 3.5:1, aged 53.2 ± 12.6 years). The following main etiological factors were observed: chronic alcoholism alone (39.7%), chronic alcoholism in association with HBV or HCV (16.1%), HCV alone (14.5%) and in association with alcoholism (8.6%) (total, 23.1%), and HBV alone (13.1%) and in association with alcoholism (7.5%, total 20.6%). The remaining etiologies included cryptogenic cases (9.8%) and other causes (6.0%). The mean patient age was lower and the male-to-female ratio was higher in the cirrhosis cases that were associated with alcoholism or HBV compared with other causes. Intravenous drug abuse and a history of surgery or blood transfusion were significantly associated with HCV infection. Hepatocellular carcinoma was present at the time of diagnosis in 15.4% of cases. Chronic alcoholism associated with HCV infection was significantly associated ($p<0.001$) with reduced age (at the time of cirrhosis diagnosis) and increased prevalence of hepatocellular carcinoma ($p=0.052$).

CONCLUSION: Alcoholism, HCV and HBV are the main factors associated with liver cirrhosis in the state of Espirito Santo. Chronic alcoholism associated with HCV infection reduced the age of patients at the time of liver cirrhosis diagnosis.

KEYWORDS: Liver Cirrhosis; Hepatitis B Virus; Hepatitis C Virus; Alcoholism.

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INTRODUCTION

There are few reports on the etiology of liver cirrhosis in Brazil. A systematic search in PUBMED (January 2012, search limited to human studies) using the keywords ''liver cirrhosis Brazil'' yielded 409 publications; however, none focused on the etiology of cirrhosis in relation to chronic alcoholism and hepatitis B and C infection in all patients. There are reports of anatomic studies of liver cirrhosis in large series of autopsies with descriptions of patient morphological features, but these reports did not include information about the etiology of the associated chronic liver disease (1). Additionally, three studies reported mortality from liver cirrhosis; these studies were based on the analysis of death certificates, and none investigated the etiology (2-4).

In Vitoria, the capital of the state of Espirito Santo, the University Hospital Cassiano A Moraes (HUCAM) is a referral hospital for patients with liver disease. Since 1993, all patients presenting with chronic liver disease to the HUCAM Gastroenterology outpatient clinic have been evaluated for chronic alcoholism, hepatitis B (HBV, evaluated with HBsAg) and hepatitis C (HCV, evaluated with anti-HCV). The aim of this study was to review the cases of liver cirrhosis diagnosed at HUCAM between 1993 and 2011 to identify the etiology of cirrhosis, particularly as it related to alcoholism and HBV and HCV. This investigation was justified for many reasons: (a) in PubMed, there is a lack of

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Table 1 - Etiology in 1,516 liver cirrhosis cases.

Etiology*	N (%) [M:F ratio]	Age (mean ± SD)			*p*-value** (MxF)
		All cases	Male	Female	
Chronic alcoholism	602 (39.7) [13.3:1]	51.6 ± 10.8#	51.8 ± 10.8	0.6 ± 10.7	0.508
HCV	221 (14.5) [0.97:1]	56.9 ± 11.7	55.6 ± 12.1	58.1 ± 11.3	0.108
HCV plus alcoholism	131 (8.6) [7.2:1]	50.3 ± 11.8##	49.8 ± 9.8	52.9 ± 10.1	0.249
HBV	199 (13.1) [4.4:1]	51.7 ± 13.8	51.0 ± 13.7	54.7 ± 14.3	0.143
HBV plus alcoholism	114 (7.5) [66:1]	50.2 ± 11.4###	50.3 ± 11.4	45.5 ± 6.3	0.554
Other causes	92 (6.0) [0.4:1]	55.0 ± 17.7	57.0 ± 17.4	54.2 ± 17.9	0.495
Cryptogenic	149 (9.8) [1.4:1]	60.1 ± 14.1	59.9 ± 13.8	60.4 ± 14.5	0.840

*Five cases were HBV and HCV positive, and three had chronic alcoholism and HBV and HCV infection. M = male; F = female; HCV = hepatitis C virus; HBV = hepatitis B virus. **Age comparison between males and females. # Mean patient age for chronic alcoholism and HBV *versus* HCV, Other causes and cryptogenic: $p<0.05$; chronic alcoholism *versus* HBV, $p = 0.461$. ## Mean patient age for HCV *versus* HCV plus alcoholism, $p<0.001$. ### Mean patient age for HBV *versus* HBV plus alcoholism, $p = 0.338$.

information published on the etiology of liver cirrhosis in Brazil; (b) the study population is representative of liver cirrhosis occurring in the state because HUCAM is a referral hospital that treats patients from all municipalities; and (c) although there are geographical variations in the environmental factors associated with liver cirrhosis, the state of Espirito Santo has a population with demographic characteristics that are similar to the Brazilian population at large.

PATIENTS AND METHODS

The study population consisted of 1,516 patients with liver cirrhosis who presented to the Gastroenterology Department of HUCAM between December 1993 and December 2011. We only included those cases that simultaneously performed the evaluations of chronic alcoholism and hepatitis B and C infections.

All of the laboratory testing was performed with commercial kits at the routine hospital laboratory. Persistent infection with HBV and HCV was assessed by the evaluating HBsAg and anti-HCV antibodies in serum, respectively. HCV infection was confirmed by detecting the virus in the plasma with a polymerase chain reaction (PCR). According to criteria used by the HUCAM Gastroenterology Department, patients were diagnosed with chronic alcoholism when the ethanol ingestion was >80 g per day in men and >40 g per day in women for ten years or longer.

Liver cirrhosis was diagnosed according to clinical data in addition to either a positive radiologic or pathologic result (i.e., computerized tomography [CT] scan, nuclear magnetic resonance imaging, ultrasonography, endoscopy or liver biopsy).

In addition, the patient age, gender, intravenous drug abuse, history of surgery and blood transfusion, sexual risk behavior (defined as more than one sexual partner per year without protection) and the presence of associated hepatocellular carcinoma (HCC) at the time of diagnosis of cirrhosis were recorded in all cases. HCC was diagnosed using the following criteria: (a) typical pattern in two imaging methods; (b) one suggestive image plus increased plasma levels of alpha-fetoprotein (>200 ng/ml); or (c) histopathology (5).

The statistical analysis was performed using the SPSS for Windows, version 1.9 (IBM, USA). A *p*-value of <0.05 was considered significant.

This research was approved by the Ethics Committee of the Health Sciences Center of the Federal University of Espirito Santo.

RESULTS

The male-to-female ratio of the 1,516 patients included in this study was 3.5:1, and the average age was 53.2 ± 12.6 years (52.4 ± 12.0 years for males and 56.1 ± 13.9 years for females, $p<0.001$). The ethnic distribution based on skin color was 69.5% Caucasian and 29.8% Afro-descent, with no gender distribution difference.

The main etiologies of liver cirrhosis, the mean patient ages and the gender distribution according to the etiology are summarized in Table 1. Chronic alcoholism was the most frequent etiology (39.7%), followed by HCV alone (14.5%) and HBV alone (13.1%). Other causes of cirrhosis included non-alcoholic steatohepatitis (67 cases, 4.4%), primary biliary cirrhosis (12 cases, 0.8%) and autoimmune hepatitis (10 cases, 0.7%); sclerosing cholangitis, secondary biliary cirrhosis and metabolic diseases were less frequent, totaling 0.1% of cases. In 9.8% of cases, the cirrhosis was considered cryptogenic.

In 16.1% of the cases, chronic alcoholism was associated with HCV or HBV infection. Both the average patient age and male-to-female ratio differed significantly between the cases of alcoholic cirrhosis and cryptogenic cirrhosis or cirrhosis associated with viruses ($p<0.001$). Moreover, when viral infection was associated with chronic alcoholism, the demographic profile of HBV- or HCV-associated cirrhosis changed; patient age at the time of diagnosis decreased in the HCV cases

Table 2 - Risk factors associated with HCV, HBV or chronic alcoholism associated with liver cirrhosis.

Risk factors	HCV	HBV	Alcoholism	*p*-value*
Blood transfusion				
Yes	172	31	47	
No	161	271	509	<0.001
Surgery				
Yes	191	75**	107	
No	141	137	449	<0.001
I.V. drug abuse				
Yes	75	5	18	
No	137	297	537	<0.001

*HCV *versus* HBV or Alcoholism; **HBV *versus* alcoholism, $p<0.001$ for surgery and $p>0.05$ for blood transfusion or I.V. drug abuse.

($p<0.001$), although the observed age reduction was not significant in the HBV cases ($p=0.338$). However, the male-to-female ratio increased in HBV and HCV cases ($p<0.001$).

The patient history of surgery or blood transfusion and intravenous drug abuse in relation to disease etiology is summarized in Table 2. These factors were significantly associated with cirrhosis related to HCV infection compared with frequencies in cirrhosis associated with alcoholism or HBV ($p<0.001$). Sexual risk behavior did not show any relationship with etiology (data not shown).

At the time of the cirrhosis diagnosis, 15.4% of patients were simultaneously diagnosed with HCC (Table 3). This association was significantly higher in the cirrhotic cases associated with HBV and HCV, as well as the cryptogenic cases, compared with the alcoholic cirrhosis cases ($p<0.001$). However, this association increased when viral infection was associated with chronic alcoholism (HBV or HCV alone 81/420, HBV and alcoholism or HCV and alcoholism 63/245, $p=0.052$).

DISCUSSION

We believe that this is the first Brazilian study to investigate the etiology of liver cirrhosis associated with alcoholism and hepatitis B and C viruses in a significant sampling of patients.

When compared with the data reported in the literature (6-8), our study population had a lower mean patient age and higher male-to-female ratio. These differences may be related to the uniqueness of our study population; there were a large number of cirrhotic cases associated with chronic alcoholism and HBV. Importantly, when associated with these two conditions, cirrhosis usually occurs more often at an earlier age and in men (8,9). In fact, as summarized in Table 1, the mean patient age was lower, and the male-to-female ratio was higher in those cases associated with alcoholism or HBV compared with the other etiologies, including HCV, as well as in the cryptogenic cases ($p<0.05$).

The results demonstrated that alcohol abuse was the main etiology of cirrhosis in this case series; this observation supported prior reports of the high prevalence of alcohol abuse in the state of Espirito Santo (27.8% in men and 10.8% in women in metropolitan Vitoria in 2008 according to the Health Ministry) (10). Furthermore, in this study, the criteria defining patients as chronic alcoholics were even stricter than for those patients considered at risk of developing chronic liver disease (11).

Table 3 - Presence of hepatocellular carcinoma at the time of diagnosis among 1,516 liver cirrhosis cases.

Etiology	Associated hepatocellular carcinoma N of HCC/N of cirrhosis (%)
Chronic alcoholism	49/602 (8.1)*
HBV (all cases)	88/313 (28.1)
HBV alone	51/199 (25.6)
HBV plus ethanol	37/114 (32.4)
HCV (all cases)	56/352 (15.9)
HCV alone	30/221 (13.5)
HCV plus ethanol	26/131 (19.8)
Cryptogenic	30/149 (20.1)
Other causes	9/92 (9.7)

*Chronic alcoholism *versus* HBV (all cases) or HCV (all cases) or cryptogenic etiology. $p<0.001$; chronic alcoholism *versus* other causes, $p=0.595$.

It is difficult to compare the data on the etiology of cirrhosis presented herein with the data observed worldwide because there are few reports on the etiology of cirrhosis in which the three main risk factors (alcoholism, HBV and HCV infections) were investigated simultaneously. A systematic literature review on alcohol abuse and chronic liver disease showed that 32% of cirrhosis was associated with chronic alcoholism (12). In Europe, particularly in Ireland, UK (6), Italy (13) and Eastern Europe (14), chronic alcoholism is recognized as an important cause of liver cirrhosis. Reduced alcohol consumption, paralleling a decreased incidence of and mortality from liver cirrhosis, has been reported in several European countries (14), confirming chronic alcoholism as an important etiological factor of liver cirrhosis. In Latin America, studies in Mexico (8) and Chile (15) showed that alcohol was the most frequent cause of cirrhosis in 39.5% and 46.3% of cases, respectively. However, it is possible that there is an over-diagnosis of alcoholic cirrhosis in some countries that have underestimated HBV and HCV infection, as it was recently emphasized with respect to the etiology of liver cirrhosis in Mexico (16).

A review of published papers on the impact of HBV and HCV on the etiology of liver cirrhosis and hepatocellular carcinoma worldwide demonstrated a large variation in the occurrence of HBV- and HCV-associated liver cirrhosis. The contribution of HBV in the etiology of cirrhosis ranged from 5% in Japan to 57% in China, Mongolia, South Korea and Taiwan. The frequencies of HCV-related cirrhosis ranged from 16% in Africa to 62% in Japan (17). In this study, HBV and HCV alone or in association with chronic alcoholism was present in 43.7% of cases (13.1% and 7.5%, respectively, for HBV and 14.5% and 8.6%, respectively, for HCV). In the MEDLINE literature search, no reports were found on the prevalence of HBV or HCV in cases of liver cirrhosis in Brazil. However, two national surveys showed a common association between HCV and HBV infection and HCC but with variable proportions in different regions of the country (18,19). Our data showing a high prevalence of HBV-associated cirrhosis further support the existing data that demonstrate the prevalence of HBV in the state of Espirito Santo (20). Moreover, HBV-associated HCC is frequently diagnosed at the University Hospital in Vitoria. The contribution of HBV and HCV in the etiology of liver cirrhosis in other Brazilian regions may be similar to that observed in the two national surveys of hepatocellular carcinoma; a country-wide high prevalence of HCV and the increased frequency of HBV in areas where high or intermediate chronic HBV infection has been reported, particularly in the north and central west regions and in the state of Espirito Santo.

In cirrhotic cases of viral etiology, the mean patient age was decreased when those cases were associated with chronic alcoholism. The average patient age was significantly lower in the cases with HCV plus chronic alcoholism compared with cases of HCV alone, which supported the premise that chronic alcoholism was an accelerating factor in the evolution of fibrosis in chronic hepatitis C (21,22). In relation to HBV, the effects of associated chronic alcoholism in progression of liver fibrosis are less clear. Chronic alcoholism facilitates the proliferation of the virus in experimental models of HBV infection (23); however, few studies have investigated the progression of lesions in

patients with chronic hepatitis B associated with chronic alcoholism (24). Alcohol abuse in patients with chronic hepatitis B has been associated with increased mortality (25) and increased risk for HCC (26). Moreover, studies in Japan (27) and Brazil (28) have demonstrated a significantly lower mean age of patients when HBsAg-positive HCC was associated with chronic alcoholism compared with the HBsAg-positive cases without chronic alcoholism. In cases reported here, the mean patient age at the time of diagnosis was decreased in the cases of HBV infection associated with chronic alcoholism compared with cases of HBV infection alone. However, the difference was not statistically significant, which suggested that chronic alcoholism impacted the progression to liver cirrhosis in patients with chronic hepatitis B less than in patients with chronic hepatitis C.

In evaluating the risk factors for viral infection, the history of surgery and blood transfusion and the use of intravenous drugs were significantly associated with hepatitis C virus infection; this correlation supported other findings in the literature (29).

Among other etiological factors associated with liver cirrhosis, the most frequent included non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis and autoimmune hepatitis. More rare etiologies included sclerosing cholangitis, secondary biliary cirrhosis and metabolic diseases. The frequency of cirrhosis associated with NASH reflected the increasing prevalence of steatohepatitis associated with obesity and dyslipidemia, which has been observed worldwide (30). Further investigations are needed to verify whether the observed low frequencies of cirrhosis associated with autoimmune injury are caused by difficulties in diagnostic resources or by the low prevalence of these conditions in this community. The prevalence of primary biliary cirrhosis and autoimmune hepatitis varies worldwide (31,32).

The prevalence of cryptogenic cirrhosis, which was similar to that observed in Mexico (8), was higher than that observed in developed countries, such as the United States and Japan (7,33). The prevalence of cryptogenic cases may be at least partially related to the underdiagnosis of some etiologies in the first ten years of this study because of limited diagnostic capabilities and particularly, steatohepatitis, given its recent rapidly increasing prevalence.

The presence of hepatocellular carcinoma at the time of diagnosis in 15.4% of cirrhosis supports the high risk of tumor development in patients with liver cirrhosis (26). As shown worldwide (26), our observations confirmed that patients with cirrhosis associated with HBV or HCV were at high risk for developing hepatocellular carcinoma, with the risk increasing in association with chronic alcoholism.

In conclusion, this analysis evaluated a large number of liver cirrhosis cases that were diagnosed at the University Hospital in the state of Espirito Santo and simultaneously investigated chronic alcoholism and HBV and HCV infection. We showed that chronic alcohol consumption alone was the most frequent etiologic factor and that when associated with HBV or HCV, decreased the age at diagnosis and increased the frequency of associated hepatocellular carcinoma. These results confirmed that alcohol abuse was an important factor in worsening the evolution of chronic hepatitis B and C infection. Brazil is a large country; therefore, the data presented here may not be applicable to other states in the country given the regional differences in environmental and behavioral factors associated with the etiologies of liver cirrhosis, particularly hepatitis viruses and chronic alcoholism. Further studies on the etiology of liver cirrhosis from other Brazilian regions are needed to improve the understanding of the etiology of end-stage liver disease in our country.

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■ AUTHOR CONTRIBUTIONS

Gonçalves PL reviewed the files, analyzed the data and wrote the draft of the manuscript. Zago-Gomes MP, Mendonça AT and Marques CC participated in the file review. Gonçalves CS analyzed the data. Pereira FE planned the study, participated in the result analysis and reviewed the final manuscript.

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