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Research Article

Epidemiological Aspects of Hepatitis B and Prognostic Factors of Cirrhosis in Patients with Chronic Hepatitis B in the Western Amazon

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Abstract

Background and Aims: viral factors and host factors were associated with disease progression of chronic hepatitis B (CHB) to cirrhosis. We studied 672 patients HBs Ag+ followed at the Hepatitis Referral Centers of Rio Branco (AC), Brazil, from 2000 to 2009 to evaluate the clinical and epidemiological characteristics, and associated factors the progression to cirrhosis.

Methods: Clinical and epidemiological features of 672 patients with CHB cadastrado at Hepatitis Referral Centers of Rio Branco (AC), Brazil, from January 2000 to December 2009 were evaluated retrospectively. For the associated factors the progression to cirrhosis, the dependent variable was cirrhosis and independent variables were the exposures of interest. Unadjusted and adjusted odds ratios were estimated by conditional logistic regression, and the confidence interval was set at 95% (95% IC).

Results: The average follow-up was 52.7 ± 12.8 months. A total of 8.5% (57/672) of patients progressed to cirrhosis, with an incidence rate of 26.8/1000 person-year. The variables independently associated with progression to cirrhosis were: male gender (OR = 2.2, 95% CI, 1.1 to 3.7); co-infection with HCV (OR = 4.6, 95% CI: 1.2 to 17.8); co-infection with HDV with HBe Ag+ (OR = 4.0 , 95% CI, 1.3 to 1.9); co-infection HDV with anti-HBe+ (OR = 7.1 , 95% CI, 1.2 to 17.8); and Gamma GT serum levels > 2 ULN (OR = 2.7 , 95% CI, 1.3 to 5.4).

Conclusion: Male gender, concomitant infection with HCV, HDV and GGT serum levels were independent progression factors to cirrhosis in patients with CHB.

ABBREVIATIONS

CHB: Chronic Hepatitis B; HCV: Hepatitis C Virus; HDV: Hepatitis D Virus; GGT: Gama Glutamil Transferase

INTRODUCTION

Infection with hepatitis B virus (HBV), with 360 million chronic carriers, 1.2 million deaths annually is a major cause of acute liver disease, chronic, cirrhosis and hepatocellular carcinoma worldwide [1,2], where 5% of these patients are infected with the hepatitis delta (HDV) viruses, predominantly in the Mediterranean Basin European and North African [3]. In South America, the VHD is restricted to the Amazon region. In Brazil, in areas hyper endemic for HBV, the prevalence of total antidelta, varies from 1.7% to 66.6% depending on the population studied [4-7]. The parenteral, perinatal, sexual and vertical transmission (household interpersonal contact) is the main modes of transmission, and its frequency differs according to the pattern of prevalence of HBV [8-11]. Among the factors associated with disease progression have: the viral factors (diversity of genomes, mutations and viral load), host factors (age, changes intrans aminases, histological staging exacerbations flares recurring) and external factors alcohol, drugs-hepato toxins and co-infection with HDV, HCV and HIV [12-18].The risk of developing cirrhosis is higher in those with associated infection HCV and HDV [19-27]. The incidence for cirrhosis in HBe Ag positive patients is 1.6/ 100 person/years in the countries of East Asia and 3.8 in European

countries, with cumulative incidence at five years of 8% and 17% in HBe Ag negative, the incidence is 2.8 in Asia and 9.7 in Europe, with cumulative incidence at 5 years of 13% and 38%, respectively and in inactive carriers is below 0.1/100 person years [25].

MATERIALS AND METHODS

Study population

Of 672 CHB patients followed at the Hepatitis Referral Centers Rio Branco from January 2000 to December 2009 were enrolled in this study and evaluated retrospectively. Cirrhosis was defined as presence of F4 in liver biopsy or signs of liver insufficiency or portal hypertension, i.e., presence of jaundice, vascular spiders, splenomegaly, abdominal collateral circulation, ascites, palmarerythema, gynecomastia, flapping and coagulopathy. Ultrasound and upper endoscopy results, i.e., decreased liver size, dilatation of the portal veinandor splenic, esophageal and or gastric varices, or hypertensive gastropathy.

Serologic, molecular and biochemical tests

To sorology HVB, HVC, HVD were used commercialserologykits(Abbott, Roche DiagnosticorSanofi-Pasteur). The HBV-DNA was investigated using commercial kits lab Roche® (AMPLICOR HBVMONITORTM). Automated biochemical tests for Automatic Biochemical Analyzer-Dade Behring-Dimension AR. The resultswere expressed ashow manytimesthe enzymeswere increasedrelative to the upperlimitof normal (ULN). Forplatelets, the normality valuewas ≥150x10mm^3. The Metavir score was used to stage the disease [28].

Statistical Analysis

The following clinical and serological variables at baseline were evaluated with descritive analysis. Pearson's chi-square or Fischer's exact test when appropriate, were used for comparisons of categorical variables, and Kruskal-Wallis test for continuous variables. The cirrhosis incidence rate was estimated using as the numerator cases of cirrhosis and, as denominator, the total person-time at risk for the event in years. The conditional logistic regression model were used to factors associated with the evolutionof CHB, to estimatetheodds ratiosunadjusted and adjustedwithconfidence intervalsof 95% ($CI_{95\%}$).Variables linked to cirrhosis, as defined above, with a p-value < 0,20 in bivariate analysis, were included in a final model with stepwise backward procedure. The importance of the variables for the final model was assessed using the likelihood ratiotest, considering significant for p ≤ 0.05. For the analysis, we used SPSS version 15. Informed consent was obtained from each patient.This study was approved by the Ethics Committees in Research of the HC of Acre and the School of PublicHealth-USP.

RESULTS AND DISCUSSION

Of the 672 patients studied, 70.7% were miscellaneous, 3.0% Indian, 65.3% had up to eight years of study. The intra-familial transmission was reported in 70.8% of patients.Sharing sharp objects 78.8% (451/572), toothbrush 39,5% (223/564) and the use of glass syringe 49.6% (284/573) was the most frequent type of exposure, showing that the epidemiology of HBV in the Amazon has specific peculiarities[9,10,5,29]. The serological profile at the basiline was 83.6% (562/672) antiHBe positive, characterizing a short immunotolerance phase, because half of the patients are HBeAg negative in the second decade of life, differing from what happens in Asia [18]. The total follow-up was 2.127 person-years, with progression to cirrhosis in 8.5% (57/672) at the end of the period, the incidence rate for the period was 26.8/1,000 person-years (Table 1), does not differ from studies in other countries, despite ethnic and viral diferences [25,14].

This study the status of HBe Ag and viral load was not associated with risk of progression to cirrhosis, demonstrated in most longitudinal studies with patients CHB, implying that other factors are influencing the evolution to cirrhosis in this population, i.e., different genotype, associated with HDV, which would exert a suppressive effect on HBV [12,14,15,30,23], (Table 2,3). The (Table 4) shows the variables associated with progression of CHB to cirrhosis with p <0.05 in the bivariate analysis. The final model variables with the likelihood ratio test with p ≤ 0.05. In this cohort, male gender, infection associated with HCV, HDV, and gamma GT were the factors associated with

Table 1: Distribution of cases of chronic hepatitis B, and person-year incidence rate of cirrhosis from 2000 to 2009, Rio Branco, Acre, Brazil.

Year	Incidence of Hepatitis		Incidence of cirrhosis		Incidence rate/1000
	n	Person-year	Person-year	Person-year	Person-year
2000	23	178.0	8	48.43	44.9
2001	23	162.9	2	14.5	12.27
2002	22	135.9	7	38.09	51.85
2003	47	263.9	5	19.25	19.01
2004	62	307.0	6	33.83	19.54
2005	65	243.33	4	12.84	16.46
2006	76	243.92	7	24.82	28.80
2007	86	212.17	2	4.92	9.43
2008	114	199.92	2	4.42	10.05
2009	154	180.33	10	11.83	55.55
Total	672	2127.29	57	212.93	26.8

Table 2: Bivariate analysis on risk factors associated with progression to cirrhosis in chronic carriers of hepatitis B. The Center of Tropical Infectious Diseases, from 2000 to 2010. Rio Branco, Acre, Brazil.

Variable	No cirrhosis n=615(91,5%) n (%)	Cirrhosis n=57(8,5) n= (%)	OR	IC95%	p-Value
Gender					0,003
Male	267(43,4)	36(63,2)	1,0		
Female	348(56,6)	21(36,8)	2,2	1,3-3,9	
AgHBe marker[1]					0.169
No	517(86.0)	45(80.4)	1.0		
Yes	84(14.0)	11(19.6)	1.5	0.7-3.0	
Anti-HBe marker[1]					0.098
No	84(14.0)	12(21.4)	1.0		
Yes	517(86.0)	44(78.6)	0.6	0.3-1.1	
HCV co-infection[2]					0.012
No	563(97.9)	51(91.1)	1.0		
Yes	12(2.1)	5(8.9)	4.6	1.6-13.6	
HDV co-infection[3]					<0.0001
No	458(80.2)	20(35.7)	1.0		
Yes	113(19.8)	36(64.3)	7.3	4.1-13.1	
Serological profile[4]					<0.0001
AgHBe (+) delta (-)	61(10.8)	5(8.9)	1.0		
Anti HBe (+) delta (-)*	247(43.7)	12(21.4)	0.6	0.2 – 1.7	
Anti HBe (+) delta (-)**	146(25.8)	3(5.4)	0.2	0.1 – 1.1	
AgHBe (+) delta (+)	21(3.7)	7(12.5)	3.9	1.4 – 10.7	
Anti HBe (+) delta (+)	90(15.9)	29(51.8)	4.1	1.1 – 14.2	
HBV viral load (UI/ml)[5]					0.059
Indetectable	158(27.5)	17(32.7)	1.0		
60 – 2000	186(32.4)	23(44.2)	1.1	0.6 – 2.2	
> 2000	230(40.1)	12(23.1)	0.5	1.1 – 14.2	
Liver biopsy[6]					
Activity					0.005
A0, A1	132(75.4)	13(48.1)	1		
A2, A3	43(24.6)	14(51.9)	3.3	1.4-7.6	
Fibrosis					<0.0001
F0,F1, F2	145(82.9)	10(37.0)	1	1	
F3, F4	30(17.1)	17(63.0)	8.2	3.4-19.7	

Tests not performed for: (1) "e" antigen and antibody against the antigen "e" B virus -15 patients, (2) antibody to hepatitis C virus - 41 patients, (3) Antibody delta virus - 45 patients (4) antigen antibody "ë" and delta virus antibody - 51 patients; (5) Viral load CV-Hepatitis B - 46 patients, (6) Liver biopsy 470 patients (mild inflammation A0, A1, moderate to severe inflammation A2, A3) and (mild fibrosis F0, F1, F2, and advanced fibrosis F3,F4); (*) HBV-DNA≤ 2000IU / ml; (**) HBV DNA> 2000IU / ml.

progression to cirrhosis after adjustment for follow-up time. Various studies have shown that CHB associated with HCV would cause increase in effect cytopathic with worse prognosis and higher risk of fulminant hepatitis in the acute phase and more advanced disease such as cirrhosis and HCC [12,14,15,20,21,31,]. Concurrent infection with VHD, is relevant in the Amazon, with occurrence of outbreaks of disease icterohemorrhagic and high prevalence of chronic liver disease and hepatocellular carcinoma, described more than four decades. The VHD would cytopathic effect, with unusual and peculiar histological features, with the presence of cells morula and cytoplasmic virus multiplication. International studies show a clinical course associated with rapid progression to fibrosis with early hepatic decompensation and increased risk for development of hepatocellular carcinoma, possibly related to the genotype and independent of the HBeAg status. In CHB associated with VHD observed a complex and dynamic pattern of viral dominance, with the VHD often suppressing HBV replication and early seroconversion of HBeAg,

Table 3: Bivariate analysis baseline biochemical markers associated with progression to cirrhosis in chronic carriers of hepatitis B. The Center of Tropical Infectious Diseases, from 2000 to 2010. Rio Branco, Acre, Brazil.

Variable	No cirrhosis n=615(91,5%) n (%)	Cirrhosis n=57(8,5) n (%)	OR	IC95%	p-Value
ALT (U/L)*					<0.0001
Normal	224(37.5)	6(10.5)	1.0		
>1 a 5 x ULN#	311(52.1)	31(54.4)	3.7	1.5 – 9.1	
>5 a 10 x ULN	47(7.9)	14(24.6)	11.1	4.1 – 30.4	
>10 x ULN	15(2.5)	6(10.5)	14.9	4.3 – 51.9	
Mean	69(±104.0)	110(66.4)			
Min/Max	7/1240	25/303			
Platelets count (x10^3 mm)**					<0.0001
≥150	514(86.1)	36(63.2)	1.0		
< 150	83(14.0)	21(36.8)	3.6	2.0 – 6.5	
Mean	212(64.9)	182(±82.8)			
Min /Max	22/533	63/451			
Albumin (g/dl)***					0.009
≥3,5	523(91.8)	45(80.4)	1.0		
<3,5	47(8.2)	11(19.6)	2.7	1.3 – 5.6	
Mean	4,2(±0.51)	3.9(±0.58)			
Min/Max	1.9/7.4	2.6/5.3			
Gamma GT(U.L)****					<0.0001
< 2 ULN	478(81.8)	22(40,7)	1.0		
≥2 ULN	106(18.1)	32(59,3)	6.5	3.7 – 11.7	
Mean	49(±62.2)	118(±117,2)			
Min/Max	7/621	15/561			
Leukocytes (mm^3)*****					0.175
≥3000	559(93.6)	51(89,5)	1.0		
<3000	38(6.4)	6(10,5)	1.7	0.7-4.3	
Mean	6296(±2143)	5094(±2066)			
Min/Max	1000/13200	1033/10900			

tests not performed for: * 18 patients, 18 patients **; *** 46 patients; **** 34 patients; ***** 18 patients, #LSN - Upper limit of normal

Table 4: Final model of multivariate analysis to investigate factors associated with progression to cirrhosis in patients with chronic hepatitis B.

Risk factors	Unajusted OR	Ajusted OR	IC 95%	p-Value
Gender				0.05
Female	1.0	1.0		
Male	2.2	1.9	1.1 – 3.7	
Follow-up (Years)				0.05
1	1.0	1.0		
2	0.4	0.3	0.1 – 1.8	
3– 4	1.9	1.3	0.5 – 3.4	
> 5	3.7	2.0	0.8 – 4.9	
Co-infection with HCV				0.004
Yes	1.0	1.0		
No	4.6	4.6	1.2 – 17.8	
Anti-HDV/Anti-HBe markers				<0.0001
HBeAg (+) delta (-)	1.0	1.0		

Anti HBe (+) delta (-)[1]	0.6	0.8	0.2 – 2.6	
Anti HBe (+) delta (-)[2]	0.2	0.4	0.1 – 1.8	
HBeAg (+) delta (+)	3.9	4.0	1.3 – 11.9	
Anti HBe (+) delta (+)	4.1	7.1	1.2 – 17.8	
Gamma GT(baseline)				<0.0001
< 2 ULN	1.0	1.0		
≥2 ULN	7.5	2.7	1.3 – 5.4	

(1) HBV viral load ≤ 2000IU / ml; (2) HBV viral load> 2000IU / ml.S

there is a strong association with the pre-core mutant hepatitis B virus, despite the inhibition of HBV, suggesting that patients with CHB, they would have pre-core mutant prior to Super Infection [3,6,24,26,32-47]. The greatest risk of progression to cirrhosis was aged 30 to 39 years, attributed possibly to the pattern of infection in the Amazon region, i.e., HBV genotype F associated with genotype III HDV, differing from other studies that shows progression to cirrhosis in older patients, which result from the replication of the HDV persistently with the highest level of cytotoxic CD4 + T cells in the liver than in the blood, which accumulate with age [12,16,25,41,44,48-53]. But studies are needed to define the importance of gamma-glutamyl transpeptidase (GGT) as a factor for progression to cirrhosis or prognosis of CHB. The (GGT) present within hepatocytes and biliary epithelial cells in is considered a marker of hepatocellular injury high sensitivity and low specificity [54-57]. Since it can is altered by use of medications, alcohol and various systemic diseases, such as metabolic syndrome [58].

CONCLUSION

Male gender, concomitant infection with HCV, HDV and Gamma GT were independent factors associated with progression of CHB to cirrhosis in this population.

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