Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

Abstract

Background: There is a strong correlation between the progress of viral hepatitis B and its natural history. It is important to know the characteristics of the carriers within a population. This study sought to determine the characteristics, according to gender, of patients seen in consultation to understand the evolution with regard to the natural history of the chronic hepatitis B virus infection.

Methods: This study, conducted from January 2009 to December 2014 at the Douala General Hospital, was cross-sectional. The study examined socio-demographic, historical and co-morbidity, co-infection, clinical, and biological parameters. Statistical analysis was performed using the Epi Info 34.3 software. Multivariate logistic regression was used for the inclusion of some confounding variables. The significance threshold was set at 5%.

Result: The size of the study sample was five hundred and seventy-three (573) patients, of which only 28 or 4.88% were receiving antiviral treatment. The average age was 40 years, with a median age of 33 years and an IQR [26 - 40]. The ALT level, which was 2 times higher than normal, stood at 21.63% in men versus 12.18% in women (p=0.0003). A significant presence of fibrosis was found in men, 17.89% of whom were affected as compared to 4.26% women (OR = 4.90, CI [1.08 - 22.20], p=0.02).

Conclusion: Patients with viral hepatitis B are predominantly male. Elevated transaminase levels and significant fibrosis are more common in men.

Keywords: Hepatitis B virus; Prevalence; Gender; Cameroon; Africa

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Abbreviations: HBV: Hepatitis B Virus; HBs Ag: Hepatitis B Surface Antigen; HBe Ag: Hepatitis B e Antigen; anti-HBe Ab: Hepatitis B e Antibodies; HCC: Hepatocellular Carcinoma; HDV: Hepatits Delta Virus; GGT: Gamma-Glutamyl Transpeptidase; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AFP: Alpha Foeto-Protein

Background

A third of the world population carries a trace of a present or past hepatitis B virus (HBV) infection [1]. HBV is a worldwide public health issue with close to 350 million chronic carriers [1-3]. In Cameroon prevalence varies according to population. It stands at 5.6% among medical and pharmacy students [4], 10.8% among blood donors [5], and 11.8% among pygmies [6]. The genotypic distribution in Africa is essentially made up of genotypes A and E [3]. In Africa, the HBV is essentially transmitted from mother to child [2]. The natural history of HBV is known and its evolution is closely linked thereto [2]. The European Association for the Study of the Live (EASL), in 2012, examined the different phases of the natural history of HBV as well as the dynamic nature of the infection [7]. There are five phases: the immune tolerance phase, the immune response phase, the inactive carrier phase, the HBeAg negative chronic hepatitis B, and the HBsAg negative phase [7]. Follow-up and treatment depend on these different phases of the disease. In Cameroon, more than two thirds of patients still pay all their medical expenses out of pocket. The treatment of viral hepatitis is subsidized since 2014 by the state, as part of a program, to the tune of USD 4 per month for lamivudine, USD 9 per month for tenofovir, and USD 93 per week for pegylated interferon. A quarter of patients worldwide die of an HBV complication, which could either be terminal cirrhosis or hepatocellular carcinoma (HCC) [1,3,7]. Research in Asia has shown that the presence of the HBe antigen (HBeAg) and a high viral load was linked to a risk of developing cirrhosis [2]. Risk factors associated with the occurrence of HCC are specific to the host, the virus, and the environment [2]. The risk score in terms of developing HCC, according to the REVEAL-HBV, takes into account the host's personal and family factors [8]. In both situations, the male gender is found to be a major risk factor in the development of hepatocellular carcinoma (HCC). In Cameroon, 65% of HCC carriers in a recent study were male [9]. No study has been conducted, in sub-Saharan Africa in general and in Cameroon in particular, on the characteristics of HBV carriers. This study sought to determine the characteristics, according to gender, of

Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

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2/6

patients seen in consultation to understand the evolution with regard to the natural history of the hepatitis B virus infection.

Methods

Study design, setting and population

This was a cross-sectional study conducted from January 2009 to December 2014, that is 5 years and 11 months. It involved examining records of patients of all ages who underwent consultation in the Douala general hospital (DGH) during this period. The Douala General Hospital is a first-category facility within Cameroon's health system. It has a capacity of 320 beds. Its Gastroenterology & Hepatology Unit has three hepatogastroenterologists. Patients received in consultation for hepatology are either referred by other colleagues or come to the hospital by themselves.

Data collection

The records of chronic HBV patients were included in the study. The following parameters were studied:

i. Socio-demographic data: age, gender, marital status, risk factors of HBV transmission, personal and family history;

ii. Clinical parameters, including diagnosis of compensated and decompensated cirrhosis, hepatocellular carcinoma, comorbidities such as diabetes, high blood pressure, alcohol consumption;

iii. Coinfection with the hepatitis Delta virus (HDV), Human Immunodeficiency Virus (HIV), and hepatitis C virus (HCV);

iv. Biological parameters: hemoglobin level, where there were two groups; less than 10 g/dl and above 10 g/dl, platelets with a group with less than 100,000 per mm3 and a group higher than 100,000 per mm3.

v. The liver function tests included prothrombin time (PT) – which was either lesser than 70% or greater than or equal to 70%-, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) level, and transaminases - that is Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT). The values of these biochemical parameters are determined on the basis of to the standard values of the laboratory of the DGH;

vi. The AFP test, which was less than 200 IU/ml or greater than 200 IU/ml;

vii. Viral markers were represented by the presence or absence of the HBe antigen (HBeAg) and the Hbe antibody (anti-HBe);

viii. The hepatitis B viral load was investigated through real-time PCR. The technique used was that of the COBAS TaqMan HBV test with a lower threshold at 20 IU/ml. The viral load was deemed low when lower than 2000 IU/ml and high when greater than or equal to 2000 IU/ml;

ix. Fibrosis and activity were measured through a non-invasive method, that is Fibrotest© and Actitest©; no liver biopsy was performed. Fibrosis and activity were correlated to the METAVIR score. The score for the stage of fibrosis was defined as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa, F3, septal fibrosis without cirrhosis; F4, cirrhosis. Concerning activity (A): A0 represented the absence of activity; A1, minimal activity; A2, moderate activity; A3, severe activity.

Definitions

Patients indicated alcohol consumption by 'yes' or 'no'. Alcohol level was not mentioned in the records. Obesity was defined as a Body Mass Index (BMI) greater than or equal to 30 kg/m2. Patients considered hypertensive and diabetic were already previously undergoing follow-up in cardiology and endocrinology respectively, where the diagnosis had already been made.

Patients with two positive HBs antigen(HBsAg) within 6-month period were considered as chronic carriers of the hepatitis B virus(HBV). Liver fibrosis was considered insignificant when it was strictly lesser than F2 and significant if it was greater than or equal to F2. Low activity was strictly lesser than A2 and high activity was greater than or equal to A2. The diagnosis of cirrhosis, whether compensated or decompensated, was made by the specialist who consulted the patient and indicated it in their record. It took into account the clinical, biological, and morphological signs of portal hypertension and liver failure. Decompensation was associated with the presence of ascites, edema of the lower limbs, jaundice, ascitic fluid infection, and gastrointestinal bleeding. The diagnosis of hepatocellular carcinoma was also made by the medical specialist and indicated in the record. It took into account the presence of nodules in the liver at the morphological level and the elevation of AFP above 200 IU/l.

Data analysis

The mean, median, and interquartile range were used to describe quantitative while frequency had a 95% confidence interval for qualitative variables. The Chi-Square test was used to compare qualitative data. Multivariate logistic regression was used for the inclusion of some confounding variables. Statistical analysis was performed using the Epi Info 34.3 software. The significance threshold was set at 5%.

Results

The size of the study sample was five hundred and seventy-three (573) patients. Twenty-eight (28), that is 4.88%, of these patients were under antiviral treatment (Figure 1). There was a predominance of the male gender, which, with 357 patients, represented 62.30% of the study population. The average age was 40 years, with a median age of 33 years and an IQR [26-40]. However, this distribution differed significantly according to gender: 192 of the 357 male patients, that is 53.78%, were older than the median age as against 78 out of 216 female patients, that is 36.11% ($p < 0.0001$) (Table 1). Majority of the patients resided in urban areas, with more male patients (93.98%) as compared to the females (88.80%) living in an urban setting ($p < 0.03$). Alcohol consumption was significantly more predominant among male patients, with 22.75%, as against females, with 7.44% ($p < 0.00001$). Regarding comorbidities, diabetes and hypertension were found in 1.97% against 0.93% and in 3.09% against 3.24%, respectively, of men and women ($p = 0.92$ and 0.33) (Table 1).
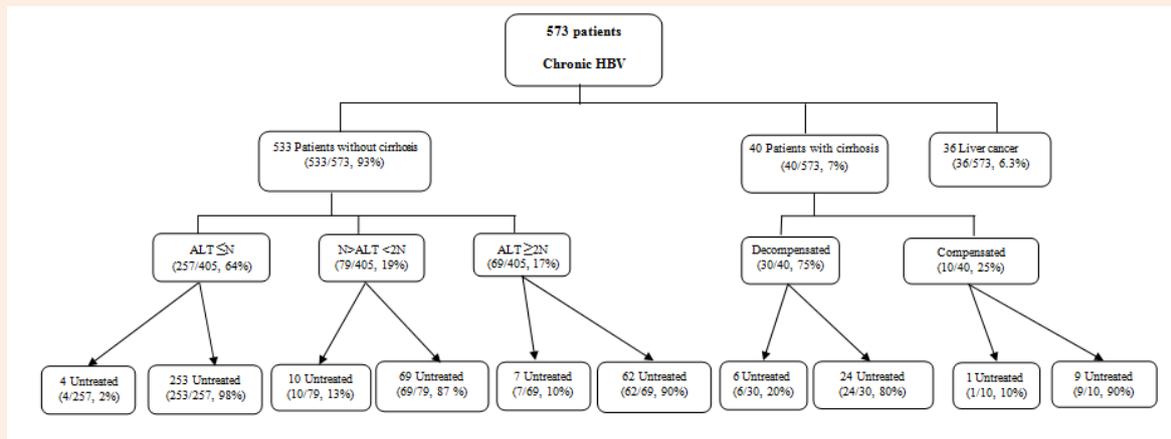
Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

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Figure 1: Clinical and biological profile of chronic HBV patients.

Table 1: Sociodemographic characteristics, history and comorbidities in the study population.

Variables		Male		Female		OR (CI 95%)	p-value
		n	%	n	%		
Sociodemographic characteristics							
Age based on the median (years)	<33	165	46.22	138	63.39	2.05 (1.45-2.91)	0
	>33	192	53.78	78	36.11		
Urban area residents		40/357	11.2	13/216	6.02	1.97 (1.02-3.77)	0.03
In a relationship		189/357	52.49	113/216	52.31	1.02 (0.73-1.43)	0.88
Health professional		71/357	19.89	50/216	23.15	0.82 (0.54-1.24)	0.35
History and risk factors							
Family HBV history		16/339	5.51	18/216	8.33	0.51 (0.25-1.04)	0.06
Blood transfusion		20/356	5.62	10/216	4.63	1.22 (0.56-3.67)	0.6
Jaundice		33/356	9.27	10/216	4.63	2.10 (0.78-1.91)	0.04
Scarifications		68/3357	19.04	35/216	16.2	1.22 (0.78-1.91)	0.38
Comorbidities							
Diabetes		7/356	1.97	2/216	0.93	2.14 (0.44-10.42)	0.33
HBP		11/356	3.09	7/216	3.24	0.95 (0.36-2.49)	0.92
Alcohol		81/356	22.75	16/215	7.44	3.66 (2.07-6.45)	0
Coinfection with the other viruses							
HIV		11/236	4.66	5/145	3.45	1.37 (0.46-4.02)	0.56
Hepatitis C virus		11/357	3.08	4/216	1.85	1.61 (0.50-1.51)	0.42
Hepatitis Delta virus		14/110	12.72	4/85	4.7	1.71 (0.53-5.41)	0.36

The disease was more often symptomatic in men, that is 65.55%, as compared to 55.56% in women (p = 0.01) (Table 2). When this was the case, jaundice was the symptom that varied most with regard to gender, that is 8.68% in men against 3.24% in women (p = 0.01) (Table 2). Finally, 15.52% of the men were obese as against 12.50% of the women (p = 0.3) (Table 2). Clinical signs such as hepatomegaly and peripheral edema were more significant in men with, respectively 16.5% and 14.35% against 4.76% and 2.78% in women (p = 0.48 and 0.24 respectively) (Table 2).

Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

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4/6

Table 2: Clinical characteristics of the study population.

Variables	Male		Female		OR (CI 95%)	p-value
	n	%	n	%		
Circumstance of detection of disease						
Symptomatic	234/357	65.55	120/216	55.56	1.52 (1.07-2.15)	0.01
Body Mass Index (BMI)						
Obese	55/116	47.41	31/64	48.44	1.04 (0.56-1.91)	0.8
Clinical signs						
Ascites	28/357	7.84	15/216	6.94	1.14 (0.59-2.18)	0.69
Jaundice	31/357	8.68	7/216	3.24	2.83 (1.22-6.56)	0.01
Hepatomegaly	59/357	16.53	31/216	14.35	1.18 (0.73-1.89)	0.49
Peripheral edema	17/357	4.76	6/216	2.78	1.75 (0.67-4.50)	0.2
Various diagnoses						
Cirrhosis	26/357	7.28	14/216	6.48	1.13 (0.57-2.22)	0.7
Decompensated cirrhosis	19/26	73.08	11/14	78.57	0.74 (0.15-3.46)	0.7
Liver cancer	28/356	7.87	8/215	9.72	2.20 (0.98-4.93)	0.04

On the paraclinical level, HBeAg was positive in 13.62% of men as against 9.32% of women (p = 0.25). Anti-HBe was present in 87.08% of men and 87.07% women (p = 0.99) (Table 3). Alanine aminotransferase (ALT) was 2 times higher than normal in 21.63% of men against 12.18% of women. This gender-related difference was significantly different in the study sample (p = 0.0003) (Table 3). There was no similar significant variation at the level of the viral load: 34.46% of men had a viral load greater than 2000 IU/ml as against 25.56% of women (p = 0.15) (Table 2). After completion of the non-invasive markers of liver fibrosis, 17.89% of men had a fibrosis higher than stage 2 as against 4.26% of women (p = 0.02) (Table 3).

Table 3: Biological, virological and histological characteristics of study population.

Variables		Male		Female		OR (CI 95%)	p-value
		n	%	n	%		
Biological markers							
Hemoglobin (g/dl)	<10	25/240	10.42	16/126	12.7	1.25 (0.60-2.44)	0.51
Platelets (/mm³)	<100000	30/237	12.66	8/124	6.45	2.10 (0.93-4.73)	0.06
PT(%)	<70	34/169	20.12	16/91	17.58	0.84 (0.44-1.63)	0.62
AST (IU/l)	<40	157/278	56.35	106/154	68.83		**0.01**
	40-80	53/278	19.06	26/154	16.88		
	>80	68/278	24.46	22/154	14.29		
ALT (IU/l)	<40	151/282	53.35	114/156	73.08		**0.003**
	40-80	70/282	24.82	23/156	14.74		
	>80	61/282	21.63	19/156	12.18		
GGT (IU/l)	>60	37/152	24.34	15/80	18.75	1.39 (0.71-2.73)	0.33
Albumin (g/l)	<30	19/91	20.88	12/48	25	1.26 (0.55-2.88)	0.58
AFP (IU/l)	>200	23/142	16.2	9/82	10.98	1.56 (0.68-3.57)	0.28
Viral markers							
HBeAg positive		29/213	13.62	11/118	9.32	1.53 (0.73-3.19)	0.25

Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

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5/6

Anti-HBe positive		182/209	87.08	101/116	87.07	1.01 (0.50-1.96)	0.99
Virological markers							
HBV DNA (IU/ml)	≥2000	51/148	34.46	23/90	25.56	1.53 (0.85-2.74)	0.15
Histological markers							
Activity	≥A2	7/95	7.37	2/47	4.26	1.78 (0.68-3.57)	0.47
Fibrosis	≥F2	17/95	17.89	2/47	4.26	4.90 (1.08-22.20)	0.02

Cirrhosis was diagnosed in 40 patients from the entire study population, that is 7.28% in men and 6.48% in women (p = 0.71) (Figure 1 & Table 3). It was decompensated in 73.08% and 78.57% of men and women respectively. Finally, 36 cases of liver cancer were recorded, that is 7.87% in men against 3.72% in women (p = 0.04) (Figure 1 & Table 3).

Discussion

This study found that the male gender was the main carrier of HBV. The patients were relatively young with a median age of 33 years. A predominant number of the male patients (93.98%) resided in urban areas. Very few patients were HBeAg-positive and, once again, those who were predominantly male with 13.62% of cases. Anti-HBe was found in 87.08% of the men. The men showed more elevated transaminase levels than the women, be it two higher than normal or over two higher than normal. Significant fibrosis (≥ F2) was more prevalent in men (17.89% of cases) than in women.

The main limitation of this study is that it is not multi-center and prospective, does not monitor patients over a longer period, and does not include certain viral markers such as genotype, HBsAg quantification. Yet, it has the merit of providing these particularities that can give us an idea about the fate of patients seen in consultation in order to act quickly for faster care or increased surveillance. Its other merits include the fact that a center in sub-Saharan Africa was able to gather all this data and, finally, that few studies in the world have been carried out on the characteristics of patients with HBV.

Chronic hepatitis B virus carriers in this study were predominantly male with 62.30%. According to the literature reviewed, the latter gender is the main carrier of the hepatitis B virus [4,5,10-12]. This is delicate because the male gender has been found to have a higher risk of developing complications such as cirrhosis and HCC [2,8,13,14]. In the recommendations, gender is not part of the criteria for the initiation of treatment [7]. It is important for gender to be taken into account in the criteria for treatment initiation. It constantly turns out to be a predictive factor linked to others such as those related to viruses in the carrier's family, and the environment in the development of complications, be it in terms of score [8] or natural history [2]. However, these observations should take into account the active or inactive nature of the disease.

Patients who consume alcohol were predominantly male (22.75% of the cases). In this study, alcohol consumption was not quantified. Therefore, we cannot conclude that such consumption was in toxic doses. Coinfection with HCV stood at 4.66% for male patients as against 1.85% for females. Progression to cirrhosis and development of HCC depends on environmental factors such as alcohol consumption and coinfection with other viruses (HIV, hepatitis C and Delta viruses) [2,11,12].

HBeAg was found in 13.62% and 9.32% of male and female patients respectively. The anti-HBe was predominant in the literature reviewed at a rate of close to 90% as compared to its antigen [10]. The natural history of HBV in the first two phases (immune tolerance and immune response) is characterized by the presence of HBeAg positive, then HBeAg loss in the inactive carrier phase and appearance of anti-HBe [2,3,7]. The presence of HBeAg alongside a high viral load increases progression to cirrhosis [2] and increases risk of developing HCC [8].

The ALT levels were more elevated in males, and more significant within the range of ALT levels falling between normal and two the normal (2N). Generally, ALT levels found are less than two the normal [11,12]. This can be explained by the close monitoring of chronic HBV carriers [7]. This monitoring is standardized every 3 to 6 months [7,14]. In this study, the dysfunction could be the result of environmental factors such as alcohol, which is also consumed predominantly by the men. Transaminase levels are a criterion for the initiation of treatment against HBV [7]. Transaminase elevations to the upper limit of normal or > 1 to 2 times the normal, require the initiation of hepatitis B antiviral treatment [7,14]. Elevated transaminase levels remain a risk factor in the development of complications such as cirrhosis and liver cancer [2,8].

Most patients had a viral load <2000 IU/ml, that is 68.91%, and were predominantly male (59.54%). Low viral load was not found to be a risk factor for progression to cirrhosis and development of liver cancer [2,8]. Conversely, a high viral load is a risk factor for the development of complications [2,8], explaining the recommendation that treatment should be initiated [7,14]. The fact that patients in this study mainly have low viral loads is a protective factor if one takes into account the data from the literature.

In this study, 2.88% of patients received hepatitis B antiviral treatment or based either on lamivudine, tenofovir or pegylated interferon. This proportion is very low like in the United States [11]. In our context, this may be explained by the fact that people did not have access to treatment at the time. Tenofovir, lamivudine, and pegylated interferon were introduced since 2014 as part of a government treatment program. This has made it possible to put many more patients under treatment.

Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis

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Liver cancer was more common in men as compared to women. In Cameroon, a 2014 study on liver cancer found that there was male predominance, but, in multivariate analysis, gender did not turn out as a risk factor for HCC [9]. Overall, in this study, liver cancer was found in 6.3% of patients, which is significantly higher than the findings of a study conducted in Brazil in 2014, which found liver cancer in 1.1% of patients [10]. Conversely, in this same study conducted in Brazil, 8.6% [10] of patients had cirrhosis, which is close to the 7% found in Cameroon. These results can be explained by the respect of the monitoring of patients with cirrhosis in the context of liver cancer screening [7]. In the natural history of HBV and in the REVEAL-HBV score predicting the occurrence of HCC, the male gender emerges as a key factor [2,8].

Conclusion

In this study, the HBV patients are predominantly male. The male gender is predominant in most of the factors found in the literature as those leading to the development of complications. We recommend carrying out observational multicenter cohort studies to identify factors for progression to complications in black African populations, but mostly to make specific recommendations for Africa with regard to the treatment of HBV.

Authors' Contributions

Study conception and design: SAFBE, HNL, DNN, GBNA

Data collection and analysis: SAFBE, HNL, DNN, GBNA, AM

Interpretation of data and drafting of the manuscript: SAFBE, HNL, DNN, GBNA, JJNN

Critical review of the manuscript: SAFBE, HNL, DNN, GBNA, JJNN, CT, ON, MSB, ECNN

Decision to submit the final draft: all authors

Ethics Approval and Consent to Participate

The study was granted ethical approval by the Institutional Review Board of the Douala General Hospital, Cameroon, and was performed in accordance with the guidelines of the Helsinki Declaration. As this is a retrospective study, patients' consent is not a requirement.

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