Biological Profile of Chronic Hepatitis B and its Predictive Factors According to Liver Histological Activity at the Renaissance Hospital, N'Djamena, Chad

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Research Article

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Abstract

Background: No study in black Africa has investigated the profile of chronic hepatitis B according to the new European association for the study of the liver (EASL) classification. The aim of the study was to determine the biological profile of chronic HBsAg carriers according to the EASL classification of chronic hepatitis B.

Method: This is a prospective cross-sectional study carried out in the gastroenterology outpatient department at the Renaissance Hospital in N'Djamena from January, 2018 to July, 2019. All patients with chronic HBsAg were included and documented for at least one year. Patients with hepatitis C, hepatitis D or HIV or alcoholic were excluded. The biological profile was determined according the EASL classification: HBeAg-positive chronic infection, HBeAg-positive chronic hepatitis, HBeAg-negative chronic infection, HBeAg-negative chronic hepatitis and HBsAg-negative phase. Factors associated with presence of significant liver fibrosis were founded by logistical regression.

Results: 106 patients were included. The average age were 42.4 years old. The sex ratio was 1.43. The median of the transaminase were 24 IU/ml (AST) and 21 IU/ml (ALT). 61 patients had HBeAg-negative chronic infection (59.8%) and 37 patients had HBeAg-negative chronic hepatitis (36.2%). HBeAg-positive chronic infection and HBeAg-positive chronic hepatitis were both seen in 2% of the cases. Significant liver fibrosis was independently associated with the ALT levels (Odds ratio=1.038 [1.009-1.068]; p=0.009).

Conclusion: Chronic HBeAg-negative B infection is the main form in chronic HBsAg-positive carriers. Transaminases are a predictive factor for the presence of hepatic fibrosis.

Background

Hepatitis B virus (HBV) infection is endemic in Sub-Saharan Africa (1) and is the main cause of liver cirrhosis and hepatocellular carcinoma (2). These progressive complications are linked to the chronic forms of the virus. The natural history of these chronic forms is complex, evolving in several phases which can overlap (3). The HBV treatment is variable depending on whether or not there is significant histological liver damage (4, 5). The European Association of the Study of the Liver (EASL) currently recognizes five phases; HBeAg-positive or negative chronic infection, HBeAg-positive or negative chronic hepatitis and HBsAg-negative phase (6). These five forms are distinguished by the presence of the HBeAg or of the anti HBe antibody, the HBV DNA level, the transaminase values, and the presence or absence of liver inflammation or liver fibrosis. HBeAg positive chronic infection represents the classical early phase of infection known as the immune tolerant phase, which is characterized by the presence of HBeAg, elevated levels of HBV replication, normal transaminases, minimal histological lesions and lack of clinical signs of liver inflammation. The presence of HBeAg, elevated levels of HBV DNA replication (greater than 2000 IU/ml), elevated transaminases and moderate or severe histological lesions characterize HBeAg positive chronic hepatitis or phase two. The third phase called HBeAg negative chronic infection B (formally inactive phase) with low levels of HBV DNA replication, normal

transaminases, absence of HBeAg and minimal histological damage. HBeAg negative chronic hepatitis in which transaminases are permanently elevated or fluctuating, HBV viral load is elevated and moderate to severe histological lesions.

Phase 5 is the loss of the HBsAg characterized as negative, the presence of the anti-HBc antibody with or without detection of the anti-HBs antibody; which is also called the occult hepatitis B where the transaminases are normal and the HBV DNA is generally undetectable but not always. The distribution of each of these forms in a given population of chronic HBsAg carriers has not been largely studied (7). No study in black Africa has investigated the profile of chronic viral hepatitis b according to the new EASL classification. The objective of our study was to determine the distribution of the different forms of chronic hepatitis B according to the definition of EASL. Therefore, this cross-sectional study was done in the gastroenterology consultation department at the Renaissance University Hospital in Ndjamen, Chad.

Methods

This is a cross-sectional study carried out from January 2018 to July 2019 at the Renaissance University Hospital in N'djamena. It included all patients seen in the gastroenterology outpatient department for chronic carriers of HBsAg, documented for at least one year. Patients co-infected with HIV, hepatitis C or hepatitis D or alcohol abuse were excluded from the study. During the first consultation, the following parameters collected from all the patients included; age, sex, HBeAg/anti-HBe antibody, transaminase levels, hepatitis B viral load and FibroTest ActiTest score. The enzyme linked immunosorbent assay (ELISA) technique was used for the serological markers; HBsAg and Ag/anti-HBe couple. The transaminase levels were assayed by a VIDAS automated system. Hepatitis viral load (detection threshold of HBV DNA = 10 IU/L). The FibroTest-ActiTest score (BioPredictive, Paris, France) was used for the non-invasive and biological evaluation of fibrosis and liver activity according to the METAVIR score. Fibrosis (F2) and activity (A2) were significant from a score corresponding to F2 and A2. The abnormal ALT/AST levels were defined as greater than 40 IU/L. An enzyme linked immunosorbent assay

(ELISA) of an enzyme linked solid phase immunosorbent was used for the qualitative detection of HBsAg, HBeAg, anti-HBe and anti-HCV (RecombiLISA ELISA, CTK Biotech, San Diego,

California, USA). Anti-HDV was detected by ELISA, Adaltis anti-HDV kit in Rome, Italy.

The quantitative determination of HBV DNA was carried out by real time PCR using the

COBAS 8800 Roche test (quantification range from 10 – 1,000,000,000), version 2.0 of Roche

Diagnostics in Mannheim, Germany. The biological profile of hepatitis B was determined in four forms according to the FibroTest-ActiTest score, the presence or the absence of HBeAg, the viral load and the level of transaminases:

1. HBeAg positive chronic infection; presence of HBeAg, elevated viremia, high ALAT in the norm, and minimal or absence of liver necrotic inflammation and fibrosis.

- 2. HBeAg positive chronic hepatitis; presence of HBeAg, very high viremia, high ALT, and fibrosis score greater than or equal to 2.
- 3. HBeAg negative chronic infection; absence of HBeAg, low viremia, normal ALT, minimal or absence of necrotic inflammation or fibrosis and minimal disease progression.
- 4. HBeAg negative chronic hepatitis; absence of HBeAg, high viremia, high ALT, and necrotic inflammation and fibrosis.

Statistical analysis

The categorical variable were classified as a percentage; those continuous on average with their standard deviation. The proportion of different types of chronic hepatitis B has been determined. The factors influencing the presence of significant fibrosis were calculated in a univariate analysis and then a logistic regression was made to identify the independent variables. SPSS version 20 software (Chicago, USA) was used for statistical tests.

Results

We included 102 patients and their ages ranged from 3 to 63 years old. The male/female sex ratio was 2.9, the level of ALT ranged from 7 IU/L to 323 IU/L, the viral load varied from 1 to 8.6 log while 16 patients (15.7%) had biochemical activity. Among patients with anti-HBe negative antibodies, 25.5% (n=25) had a viral load greater than 2000 IU/L. Two of the four HBeAg positive patients had a VHB DNA between 4 to 7 logs (66.7%). Moreover, according to the FibroTest-ActiTest score, fibrosis and activity were found in 37 and 14 patients respectively. In patients with HBeAg negative, virological and biochemical activity was noted in 25.5% (n=25) and 14.3% (n=14), respectively. Table 1 presents the characteristics of the samples.

Table 1
sample characteristics

Variables	Characteristics
Age *	34.6±12.8
Male	75 (73.5%)
Anti-HBe antibodies positive	98 (96.1%)
Alanine amino transferase *	31.9 ± 39.4
Viral B load logarithm *	3.2 log ± 1.6
Liver fibrosis score n (%)	
F0	37 (36.3%)
F1	28 (27.5%)
F2	23 (22.5%)
F3	8 (7.8%)
F4	6 (5.9%)
Liver activity score n (%)	
A0	82 (80.4%)
A1	6 (5.9%)
A2	7 (6.9%)
A3	7 (6.9%)
Patient HBeAg-negative n (%)	
Virological activity	25 (25.5%)
Biochemical activity	14 (14.3%)
* mean ± standard deviation	

HBeAg negative chronic infection was observed in 61 patients (59.8%). Table 2 shows the biological profile of the chronic HBsAg carriers in our study.

Table 2

Biological profile of chronic hepatitis B

Biological profile	Effectif	Pourcentage
HBeAg-negative chronic infection	61	59.8%
HBeAg-positive chronic infection	2	2%
HBeAg-positive chronic hepatitis	2	2%
HBeAg-negative chronic hepatitis	37	36.2%
Total	106	100%

The ALT level was independently associated with the presence of significant liver fibrosis (Odds ratio =1.038 (1.009-1.068); $p=0.009$). In the study, tables 3 shows the factors associated with the presence of significant hepatic fibrosis.

Table 3

Demographic and biological predictive factors of the presence of histological activity in multivariate analysis.

Variable	<i>p</i>	Odds Ratio (95%CI)
Age	0.369	1.021 (0.976 - 1.069)
Male	0.062	4.035 (0.930 - 17.503)
Alanine amino-transferase level	0.009	1.038 (1.009 - 1.068)
Load log Viral B level	0.226	1.265 (0.865 - 1.851)
Anti-HBe-positive versus HBeAg-positive	0.556	0.366 (0.013 - 10.398)
CI = confidence interval		

Discussion

The predominance of HBeAg negative forms, young adulthood and males were usually found in Sub-Saharan Africa [8]. The predominance of HBeAg negative forms was also found in Asia and Europe but in lower proportions [7,9,10]. In South Asia, a quarter of children with chronic

HBsAg were still HBeAg positive during adolescence; the spontaneous loss of HBsAg being faster in Africans where only 10% of them remained HBsAg positive in their thirties [11-13].

This geographical variation was often explained by the difference in genotypes but also by the difference in the modes of transmission; materno-fetal in Asia and early childhood in Africa

[12, 13]. HBeAg negative chronic infection (59.8%), also known as inactive carriage of HBV, was the major form in our sample, which was followed by chronic HBeAg negative chronic hepatitis. HBeAg positive

forms (infection or hepatitis) were marginal with 2% each while the data in the literature were variable. Hadziyannis et al [15] had also reported the prevalence of

HBeAg negative chronic infection. Makvandi et al found 7% HBeAg positive chronic infection, 19.7% HBeAg positive chronic hepatitis, 40.8% HBeAg negative chronic hepatitis and 32.3%

HBeAg negative chronic infection [7]. In Asia, Wang et al analyzed 166 patients with chronic hepatitis B and found 43 (25.9%) cases of HBeAg positive chronic infection (immunotolerance), 71 (42.77%) cases of chronic hepatitis (activity phase) and 52 (31.32%) cases of inactive carriers [16]. Assis et al in Brazil, determined the natural history stage of 110 patients (average age 42.95 ± 12.52) and reported 6 (3.4%) cases of HBeAg positive chronic infection, 16 (9.1%) cases of HBeAg positive chronic hepatitis, 50 (28.6%) cases of HBeAg negative chronic hepatitis and 38 (21.7%) cases of HBeAg negative chronic infection [17].

Chan et al in Hong Kong, had reported 117 (18.8%) cases of HBeAg negative chronic infection in a longitudinal study after an average follow-up of 99 ± 16 months [18]. In a retrospective study in Senegal, Diallo et al had observed 26% of inactive HBV carriers among 442 chronic

HBV carriers (34.6% of patients were included for lack of financial means) [8]. In USA,

Spradling et al reported 7% of inactive carriers and 0.6% of immunological tolerance in a study that included 1598 patients, where only 55% of whom were included [19]. In Cuba, Marlen et al found 7% of inactive carriers in a cohort study of 146 chronic HBV carriers [20]. According to Guardiola et al, the majority of subjects with chronic HBeAg negative carriers were inactive carriers [21]. Respectively, 75% and 56% of the patients had normal transaminases and a HBV

DNA less than 2000 IU/ml. In our study, these proportions were 85% and 75%, respectively.

During a Fibroscan, 54% of the patients had no histological fibrosis activity [21]. The Fibrotest-Actitest score was zero in 36% of our patients. The only factor in our study associated with the presence of significant fibrosis activity was the high level of transaminases. The predictive nature of transaminases for the presence of significant hepatic fibrosis is recognized by several authors [10, 12, 22, 23].

Conclusion

According to the EASL classification, the biological profile of chronic hepatitis B is dominated by HBeAg-negative chronic infection. The level of transaminases is predictive of the presence of significant hepatic fibrosis.

Abbreviations

ELISA: An enzyme linked immunosorbent assay

EASL: European association for the study of the liver

HBV: Hepatitis B virus

DNA: desoxy nucleic acid

Declarations

- Ethics approval and consent to participate

The administrative authorization of the Renaissance Hospital was obtained and the study was consistent with Helsinki Declaration. All patients had given their consent to participate.

- Consent for publication

All patients had given their consent for publication.

- Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

- Competing interests

All authors declare no conflicts of interest related to this article.

- Funding

None of the personal or funding interests declared.

- Authors' contributions

TMS, MAB, DSA and AC contributed equally to manuscript rewriting and data analysis; TMS, MAB, and AC, assisted in collecting patient data; TMS, MAB, DSA AC contributed to designing the study, providing clinical data, and reviewing the drafts and final versions of the manuscript. All authors have read and approved the manuscript.

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Not applicable

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