

# Biological Profile of Chronic Hepatitis B Infection 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:** the profile of chronic viral hepatitis B has been little studied in Chad. The factors predictive of the presence of hepatic fibrosis are not well known. The aim of the study was to determine the biological profile of chronic HBsAg carriers according to the new European 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 are known alcoholic patients and were excluded from the study. The biological profile was determined according to four forms; 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:** The average age of the patients were 42.4 years old. The sex ratio was 1.43 in favor of men and a total number of 106 patients were included. The median of the transaminase concentrations 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 found in chronic HBeAg-positive carriers. Transaminases are a predictive factor for the presence of hepatic fibrosis.

## Introduction

Hepatitis B viral (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 chronic occult hepatitis [6]. These five forms are distinguished by the presence of the HBeAg or of the antiHBe antibody, the HBV DNA level of 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 antiHBs 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]. 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.

## Materials And 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 were excluded from the study. During the first consultation, the following parameters collected from all the patients included; age, sex, HBeAg/antiHBe 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/antiHBe 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. HDV RNA was performed with a quantitative one-step reverse transcriptase (RT-PCR) chain reaction, Roche, LightMix kit in Meylan, France. 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.

In case of discrepancy, if the fibrosis score is less than 2 and the HBeAg is positive, the patient is classified as HBeAg positive chronic infection and HBeAg negative chronic infection if HBeAg is negative. If the fibrosis score is greater than or equal to 2, the patient is classified as HBeAg positive chronic hepatitis if HBeAg is positive and if HBeAg is negative, it is classified as HBeAg negative chronic hepatitis.

## Statistical analysis

The categorical variables 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.

### Ethics

The administrative authorization of the Renaissance Hospital was obtained and the study was consistent with Helsinki Declaration.

## 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 antiHBe 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, from 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 studied. 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. 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, Table 3 shows the factors associated with the presence of significant hepatic fibrosis.

Table 1  
sample characteristics

| <b>Variables</b>             | <b>Characteristics</b> |
|------------------------------|------------------------|
| Age *                        | 34.6 ± 12.8            |
| Male                         | 75 (73.5%)             |
| Anti-HBe positive antibodies | 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  |                        |

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 négative chronic hepatitis | 37       | 36.2%       |
| Total                            | 106      | 100%        |

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  $42.95 \pm 12.52$ ) 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  $99 \pm 16$  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

The biological profile of chronic viral hepatitis B is dominated by HBeAg negative chronic infection. The level of transaminases is predictive of the presence of significant hepatic fibrosis.

## Declarations

Ethical approval and consent to participate

The study was consistent with the Helsinki Declaration.

Consent to publication

All authors approved the manuscript prior to submission.

Availability of supporting data

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

Competing interests

The authors declare that they have no competing interests

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None of the personal or funding interests declared.

## Authors' contributions

Ali Mahamat Moussa, Assi Constant, Mayanna, Doffou Stanislas Adjeka, Ali Adam Ahamat and Mahamat Ali Bolti contributed equally to manuscript rewriting and data analysis; Tahir Mahamat-Saleh, Ali Mahamat Moussa, Mahamat Ali Bolti, Assi Constant, assisted in collecting patient data; Tahir Mahamat-Saleh, Ali Mahamat Moussa, Mahamat Ali Bolti, Assi Constant contributed to designing the study, providing clinical data, and reviewing the drafts and final versions of the manuscript.

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