Original article

Chronic viral HBeAg-negative hepatitis B: Epidemiological, clinical and biochemical characteristics in an outpatient descriptive cohort in Burkina Faso

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ABSTRACT

Introduction: Our study aimed to describe epidemiological and diagnostic features in an outpatient's cohort with chronic HBeAg-negative hepatitis B.

Patients and methods: A cross-sectional descriptive study with a retrospective data collection was implemented from January 2004 to April 2016 in the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo (CHU-YO) in Burkina Faso.

Results: Overall 325 HBeAg negative patients met the inclusion criteria. The sex ratio was 1.5 and the mean age 38.7 years. The most frequent circumstance of diagnosis was the health check-up (54.5%). The mean HBsAg concentration and viral load were 7861.6 IU/mL and 32 237.20 IU/mL, respectively. Low or moderate inflammatory activity was found in 44% and 24% of patients, respectively at the liver biopsy; 32% presented a portal fibrosis with some septa (F2). 43.9% and 41.6% had low (A1) or moderate (A2) inflammatory activity, respectively at the hepatic fibrosis blood test, while 59.1% and 20.4% had low (F1) or moderate (F2) fibrosis stage, respectively. Of the five biochemical and virological profiles among the untreated patients, the profile 1 represented 67.2% of the sample.

Conclusion: The proportions of negative HBeAg in chronic hepatitis B patients are increasing in Burkina Faso. Most of the patients have a high viral load, a low to moderate inflammatory activity or fibrosis stage.

Introduction

Five types of agents including viruses A, B, C, D and E are involved in viral hepatitis.^{1,2} More serious than hepatitis A, better known than hepatitis C or E, more frequent than hepatitis D which is only a very inconsistent co-infection or superinfection, hepatitis B appears to be the most important disease in the viral hepatitis series. Viral hepatitis B (VHB) is an inflammatory disease of the liver caused by the hepatitis B virus (HBV). It constitutes a major public health problem both in terms of its seriousness and its evolution towards chronicity, as well as the number of affected subjects and the diversity of its clinical forms. The World Health Organization (WHO)³ estimated that two billion people including ten to thirty million infections per year, would be infected during their life-course. Also according to WHO in 2015, around 257 million people suffered from chronic hepatitis B worldwide with a high

frequency in African countries and more than 800,000 people died from it.

In Burkina Faso, the prevalence of HBs antigen (HBsAg) is estimated at 9.1%.⁴ The HBV transmission is predominantly vertical (mother-to-child) or horizontal (sexual and other close contact).⁵ Despite the existence of an effective vaccine recommended by WHO, the number of patients chronically infected with the hepatitis B virus is still important in Sub Saharan Africa. In this area, the infection is often acquired at birth leading easily to the chronic carriage because of the immune-tolerance.^{5,6} Following the immune-tolerance phase the immune reactivation with a negativation of the HBeAg with or without appearance of anti-HBe antibodies (Ab) corresponds to the infection control phase. However, due to a pre-C/C mutation, HBeAg may no longer be secreted despite the presence of antiHBeAb. This situation has become very frequent (87% in Europe and 50–80% in Asia and the Mediterranean

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zone).^{6,7}

In Burkina Faso, Sombié⁸ in 2010 found a proportion of 77.7% for chronic hepatitis B HBeAg-negative patients. This form is at risk of a long-term progression toward serious fibrosis, cirrhosis or hepatocellular carcinoma (HCC). It should prompt a discussion on an antiviral treatment initiation with the objective to obtain a HBs seroconversion.⁹ The gastro-enterology department of the university teaching hospital Yalgado Ouédraogo follows up a cohort of thousands of chronic hepatitis B patients. Still in Burkina Faso, little is known regarding the clinical and biological profile of the HBeAg-negative patients. Describing the profile and specific features of HBeAg-negative patients may improve the patients' monitoring while allowing a customization of the provided care. Our study aimed to describe the epidemiological and clinical features in an outpatient's cohort with chronic HBeAg-negative hepatitis B.

Patients and methods

Study type and duration

A cross-sectional descriptive study with a retrospective data collection was implemented from January 2004 to April 2016.

Data source, sampling and sample size

Our study took place at the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo (CHU-YO) in Burkina Faso. The patients were selected from a larger outpatients' cohort. We included patients aged at least 15 years, with positive HBsAg for more than six months and a negative HBeAg and whose latest laboratory tests including the alanine-amino-transferase (ALT) and/or the HBV DNA, were $\leq$ one year. Patients with decompensated cirrhosis or primary liver cancer were excluded. The sample size included 325 patients.

The study overview

A monthly, then quarterly and semi-annual monitoring of the ALT was carried out. Serum creatinine and serum phosphorus were performed every six months in patients taking treatment. A lab analysis for HBsAg, HBeAg and HBV-DNA was performed every six months or one year. HBsAg was detected by the Determine™ technique (Abbott) and Elisa (Vidas®). The HBsAg was quantified using HBs Ag II quant II Cobas: 0.05 IU/mL to 52,000 IU/mL ($\log_{10}$: 2.11). Quantification of HBV-DNA was performed by real-time PCR (Roche Cobas Taq Man, sensitivity threshold 20 IU/mL). An ultrasound and/or abdominal CT scan were performed annually in the absence of cirrhosis and every six months otherwise. Liver activity and fibrosis were assessed by a liver biopsy or a liver fibrosis blood test (FibroMeter®). Antiviral therapy was indicated in patients with a liver activity and/or fibrosis ≥ 2 . In the context of an increase in ALT greater than twice the upper limit of the normal range in a patient with a detectable viral load, treatment was started regardless of the status of hepatic fibrosis. The complete virological response was defined as undetectable HBV-DNA obtained within one year of treatment.

Data management and statistical analysis

Data were collected using a data collection form. The relevant variables included socio-demographic, clinical, biological and virological characteristics. We implemented basic descriptive univariate analysis on the relevant variables, displaying means and proportions. The treatment compliance was assessed over the last three months by a visual analogue scale (VAS) from 0 to 10 (0: no treatment taken at all, to 10: no treatment skipped). Three adherence groups were defined including a high adherence group (HAG where no dose was missed, mean VAS score of 10 over the last four weeks), moderate adherence group (MAG: overall

compliance over the last 4 weeks between mean VAS score 8.1 to 9.9) and the low adherence group (LAG with a mean VAS score ≤ 8 over the last four weeks). The data were analysed with Epi Info 7 software.

Ethics

This study was implemented in the context of a medical doctorate thesis. The data collecting forms were anonymised. The study obtained the required authorizations from the hospital management team. It was a retrospective collection of routine data of the gastro-enterology department.

Operational definitions

We categorized five biochemical and virological profiles:

- first profile: HBV-DNA < 2000 IU/ml and ALT still within the normal range (inactive carriage);
- second profile: a high HBV-DNA $> 20,000$ IU/ml and ALT consistently above the normal range;
- third profile: a fluctuating viral replication and ALT values without any normalization window;
- fourth profile: a succession of periods of elevated ALT followed by spontaneous normalization and a fluctuating viral replication;
- fifth profile: the immune-tolerance phase with an HBV-DNA $> 20,000$ IU/ml and ALT consistently within the normal range.

Study results

From January 2004 to April 2016, we recruited 1133 patients with chronic viral hepatitis B. Overall 325 (28.7%) patients were HBeAg negative and met the inclusion criteria.

Sociodemographic and clinical characteristics

Our study population consisted of 60% of men, meaning a sex ratio of 1.5 (Table 1). The mean age was 38.7 years. The youngest patient was 16 and the oldest 74. The 25- 44 year-old age group represented 67% of the patients. Employees in the formal public or private sector, were the most represented with 197 (60.6%) of the patients. Married participants represented 61.8%. In terms of lifestyle, occasional alcohol consumption was found in 134 (41.2%) patients and 17 (5.2%) patients were

Table 1
Basic socio-demographic characteristic.

Basic socio-demographic characteristics	Frequency	Percent (%)
Gender		
Male	195	60
Age group		
16–24	19	5.8
25–34	101	31.1
35–44	117	36.0
45–54	63	19.4
≥ 55	25	7.7
Employment		
Pupils/Students	62	19.1
Formal sector	197	60.6
Informal sector	66	20.3
Marital status:		
married	210	61.8
Lifestyle		
Alcohol consumption	134	41.2
Smoking	17	5.2
No alcohol no smoking	174	53.6
Family history:		
HBsAg + or HCC	53	16.3
Circumstance of diagnosis		
Health checkup	177	54.5
Blood donation	109	33.5
Antenatal visit	16	4.9
Diagnostic	23	7.1

smoking. A family history of HBsAg carriage or primary liver cancer was found in 53 (16.3%) patients.

The most frequent circumstance of diagnosis in our series was the health check-up (54.5%). The health check-up can be broken-up in the health check-up per se, but also prenatal health check-ups, hepatitis B screening campaigns and family screening around a newly diagnosed HBsAg-positive patient, the annual occupational medical check-up and finally the HBV pre-vaccination assessment. The second circumstance of discovery was the blood donation (33.5% of the participants). The physical examination was normal in 319 (98.2%) patients and suggestive of cirrhosis in the others.

Biochemical and virological tests

The mean HBsAg concentration from 188 (57.8%) patients was 7861.6 IU/mL (range from 2 IU/mL to $\geq 52,000$ IU/mL). The mean viral load (from all participants) was 32 237.20 IU/mL (range: 0 to 91 086 744 IU/mL). HBV DNA was detectable (greater than 20IU/mL) in 258 patients (79.4%). ALT concentration was controlled every month for six months in 241 untreated patients and was normal in 78% of them. Table 2 indicates the distribution of patients according to the ALT changes.

HBV serology was positive in 19/121 tested partners and 17.5% of the HBsAg negative spouses received the hepatitis B vaccination. HBsAg was also tested positive in 5/109 children and 23.1% of the HBsAg negative children were also immunized against HBV. The viral hepatitis C and D tests were positive in 4/310 and 1/184 patients respectively, while the HIV test was positive in 3/305 participants.

We observed the five biochemical and virological profiles among the untreated patient population (Fig. 2). The profile 1 represented 67.2% of the sample. The mean age of these inactive carriers was 38 (range: 16 to 63) years. Patients with profile 5 had a mean age of 39.4 (ranges: 27; 52) years.

Ultrasound, endoscopy and biopsy investigations

The Abdominal ultrasound was normal in 276 (84.9%) patients. The results are summarized in Fig. 1.

Thirteen patients performed the digestive endoscopy which found two cases of a grade II esophageal varices (15.4%) and one case of bulbar ulcer, acute gastritis, esophageal mycosis and congestive antritis, respectively. The liver biopsy from 25 patients (Table 3) showed low or moderate inflammatory activity in 44% and 24% of patients, respectively, and a portal fibrosis with some septa (F2) (32%). A total of 132 (40.6%) patients performed the hepatic fibrosis blood test (Table 3); 43.9% and 41.6% had low (A1) or moderate (A2) inflammatory activity, respectively while 59.1% and 20.4% had low (F1) or moderate (F2) fibrosis stage, respectively.

Discussion

Socio-demographic and professional characteristics

The sex-ratio was 1.5. This male predominance was reported by many authors^{10,11} and clearly indicated that VHB became chronic more often in men than in women. The mean age of our patients was 38.7 years. Usually, patients in resource-limited settings are younger than those in developed countries, as transmission is predominantly perinatal in LMICs.

Table 2

Distribution of patients according to the transaminases (ALAT) changes.

Transaminases (ALT)	Frequency	Percent (%)
Normal	188	78
Abnormal with fluctuation	42	17.4
Consistently abnormal	11	4.6
TOTAL	241	100

Fig. 1. Distribution of patients according to ultrasound results.

Fig. 2. Distribution of untreated patients according to virological and biochemical profile.

Table 3

Distribution of patients according to the grade of inflammatory activity and the stage of fibrosis of the METAVIR score (n = 25) assessed by the histology and the fibrometer.

Results	Frequency	Percent (%)
Histology (n = 25)		
Activity grade		
A0	3	12
A1	11	44
A2	6	24
A3	5	20
Fibrosis stage		
F0	4	16
F1	8	32
F2	8	32
F3	4	16
F4	1	4
Fibrometer® (n = 132)		
Activity grade		
A0	13	9.8
A1	58	43.9
A2	55	41.6
A3	6	4.5
Fibrosis stage		
F0	10	7.6
F1	78	59.1
F2	27	20.4
F3	12	9.1
F4	5	3.8

Our study population consisted mainly of employees of the formal sector (public or private). This category of population generally benefits from an annual occupational health check-up and also constitutes a target audience for blood collection operations. It is also more educated,

therefore better informed and has more financial capacity to meet the demands of regular monitoring.

Occasional alcohol consumption was noted in 41.2% of patients. This result was comparable to Ganesan's¹² in the United States and even Kabore (unpublished thesis) in Burkina Faso, who found respectively 50% and 34% of alcohol consumption in their study populations. Alcohol is a risk factor in the progression of the fibrosis when consumption topped at more than 50 g per day. The fibrosis observed in HBV infection is worsened by the alcohol consumption.^{13,14} Alcohol is the 1st cause of the hepatocellular carcinoma in Western countries, before the HBV infection. In Sub Saharan Africa, alcohol is less involved in hepatitis, even if it is recognized as an accelerating factor in the liver degeneration by viral infection aetiologies.^{15,16} In our study, HBV testing was performed by the majority during a health check-up. The increasing awareness raised by WHO, in relation to the objectives to control hepatitis by 2030³ might explain this preventive screening.

Clinical and paraclinical characteristics

Hepatitis B screening and viral load

Overall, 121 (37.2%) partners and 109 (33.5%) children of the HBsAg-positive patients were also screened for HBV. This finding showed that the family screening is not common in Burkina Faso and raised the issue of the efficacy of the HBsAg-positive patients' follow-up to prevent other horizontal transmission within the family. The very low proportion of immunized people among HBsAg-negative family members put a particular emphasis on this issue.

The HBV viral load was detectable in 79.4% of patients. This result indicated an ongoing viral replication in patients carrying anti-HBeAb despite the absence of HBeAg. In the literature authors showed that most HBeAg negative patients who had an ongoing viral replication while carrying anti-HBeAb were infected with a viral strain with a G1896A-mutation in the pre-core region.^{7,17} This mutation leads to the generation of a stopping codon preventing the HBeAg synthesis while viral replication remains possible. A detectable viral load means an ongoing viral replication which will result in the onset of the hepatic activity and then hepatic fibrosis. This activity and fibrosis could in turn progress to cirrhosis and then hepatocellular carcinoma.

Co-infection

The prevalence of HBV-HIV co-infection was 0.9% in our study. This prevalence is lower than the findings elsewhere which were from 10% to up to 25%.^{18,19} The HBV-HIV co-infection rate in Burkina Faso was similar to the national HIV prevalence which was 0.92% according to the UNAIDS 2015 report. Therefore, HBV infected people has similar risk than the general population to acquire HIV infection. In the literature, the HBV-HIV co-infection rate fluctuates between 5 and 7% in low-endemicity countries for hepatitis B and 10–20% in intermediate to high endemicity countries. The modes of transmission of HIV and HBV are common and 50–80% of patients infected with HIV have at least one serological marker for HBV.²⁰

The hepatitis D test was positive in one patient. The HDV and HBV transmission modes are comparable and HDV can only infect HBsAg positive subjects. The HDV infection can occur in two ways: an HBV-HDV co-infection (simultaneous infection with both viruses) or a superinfection of an HBV chronic infection by the HDV. The HBV-HDV coinfection induces a high risk of fulminant hepatitis. Actually, the superinfection by the delta virus of a chronic hepatitis B patient or an HBsAg carrier is characterized by more severe liver damages, a more rapid progression to cirrhosis and a high risk of developing a hepatocellular carcinoma.²¹; therefore, the HDV screening should be systematically performed in any patient infected with hepatitis B.

Four (1.2%) patients had a positive result for anti-HCVAb testing. The presence of anti-HCVAb does not necessarily imply chronic hepatitis C; the analysis of viral RNA is necessary to confirm the diagnosis. In the literature, HBV-HCV co-infection is associated with more severe

histological lesions (high risk of malignant degeneration), and an inhibition of the HBV replication. The majority of HBV-HCV co-infected patients have a detectable level of HCV RNA and an undetectable or low level of HBV DNA, which means that the hepatitis C virus is predominant and it is responsible for liver damage in these patients.^{22,23}

Virological and biochemical profile

In our study, inactive HBV carriers represented 67.2% of untreated patients. Bennajma in Morocco and Sia²⁴ reported a rate of 59% and 22.98% respectively of inactive HBV carriers. No case of reactivation was diagnosed. The prognosis for this profile is usually very good and long-term follow-up studies demonstrated that the disease most often remains inactive. The risk of HCC is seldom.²⁵ In other studies, a low risk of viral reactivation (annual incidence of less than 1.1%) has been observed in inactive HBV carriers who had an HBsAg concentration <1000 IU/mL.²⁵ The quantifications of HBsAg and the viral load are essential monitoring tools for HBV patients.²⁶ Liver biopsy is seldom implemented because it is scary for the patients. The blood test using the FibroMeter is preferred, although it remains very expensive for the economic context (\$125/analysis). The liver biopsy was performed for 25 (7.7%) patients. Although invasive the liver biopsy remains the "gold standard" for assessing the degree of the liver activity and fibrosis. There is a poor correlation between serum transaminase activity and the degree of liver damage, especially in patients with chronic HBeAg negative hepatitis. The liver biopsy is therefore recommended before starting antiviral B treatment. However, the FibroMeter® is in practice a better alternative for safety reasons and it can be used in follow-up to assess the stage of the fibrosis.²⁷

Limitations of the study

A significant number of patients lacked biological and ultrasound monitoring data. Financial reason seemed to be behind this, as the study was designed to analyse routine data. We therefore believe that the description given in this work did not present the whole reality of our cohort. However, what was observed in this work gave us a fairly objective picture of the evolution of an HBsAg-positive HBeAg-negative patient regularly monitored.

Conclusion

The proportions of negative HBeAg in chronic hepatitis B patients are increasing sharply in Burkina Faso. Most of the patients have a high viral load, a low to moderate inflammatory activity or fibrosis stage. Sensitizing the population about the modes of transmission and generalizing the HBV screening and vaccination still remain the strongest weapons to control the HBV infection. A particular emphasis should be placed in Burkina Faso on family screening when a case is diagnosed in the family.

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CRedit authorship contribution statement

Eric Nagaonlé Somé: Data curation, Writing – original draft, Writing – review & editing. **Alice Nanelin Guingané:** Writing – original draft, Writing – review & editing. **Issaka Zongo:** Writing – review & editing. **Daouda Sané:** Methodology, Investigation, Investigation, Formal analysis, Data curation, Data Curation. **Koiné Maxime Drabo:** Writing – review & editing. **Roger Sombié:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

None.

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