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Full Length Research Paper

Chronic carriage of hepatitis B virus with HBeAg+ at the university teaching hospital YalgadoOuedraogo: epidemiological and clinical features

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Abstract

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Introduction: The prevalence of the hepatitis B infection is estimated at 9.1% in Burkina Faso. We aimed at describing the epidemiological and clinical features of the disease. Materials and methods: we implemented a cross-sectional study from January 1st, 2004 to December 31st, 2015. Patients aged more than 15 years with positive HBsAg for over six months and positive HbeAg were included. Results: We analyzed the data of 148 participants. The sex ratio was three; 69% of the participants were ≤34 years old. The mean duration of HBsAg carriage was 6.4 ± 5.6 years. The hepatic fibrosis blood test showed an activity ≥ 2 in 25 (83.3%) patients and fibrosis ≥ 2 in 23 (76.7%) patients. The liver biopsy found no inflammatory (A0) and a minimal activity (A1) in 25% and 62.5% of the patients, respectively. Portal fibrosis without (F1) and with some septa (F2) was found in three patients, respectively. Conclusion: Viral hepatitis B is a silent disease with a small proportion of patients experiencing viral replication activity. The control of this disease of public health interest is based mainly on programs of large immunization of the populations and a close monitoring of the infected people.

Key words: Viral hepatitis B, HBe antigen, HBs antigen, Sub Saharan Africa, Burkina Faso.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALAT	alanine amino transferase
CHU-YO	Centre Hospitalo-UniversitaireYalgado Ouédraogo (University Teaching Hospital Yalgado Ouédraogo)
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	Hepato-cellular carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human-Immuno-deficiency Virus
IU	International Unit
VHB	viral hepatitis B
WHO	World Health Organization

INTRODUCTION

Chronic viral hepatitis B refers to an inflammatory disease of the liver caused by the hepatitis B virus (HBV) which has been active for more than six months. It is a major public health problem. Actually, the prevalence of

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chronic HBV carriage, which is less than 2% in developed countries, is more than 7% in sub-Saharan Africa (Schweitzer A, Horn J, Mikolajczyk RT, Krause G, & Ott JJ, 2015; Spearman et al., 2017). According to the World Health Organization (WHO) in 2015, around 257 million people suffered from chronic hepatitis B worldwide with higher frequency in African countries and more than 800,000 people died from it (World Health Organization, 2017a, 2017b).

Despite the existence of an effective vaccine recommended by WHO against hepatitis B since 1991 and introduced in the Expanded Program of Immunization in Burkina Faso since 2006, the number of patients infected with HBV still remains high. Burkina Faso is ranked as a highly endemic area (World Health Organization, 2017b) with a prevalence of the hepatitis B surface antigen (HBsAg) estimated at 9.1% (Meda N et al., 2018). This is probably because in sub-Saharan Africa, the HBV infection, most often acquired at birth, promotes chronic carriage through the immunotolerance reaction of the body (Lee HA et al., 2020).

HBV replication may be due to the wild virus excreting the hepatits B e-antigen (HBeAg) or the preC / C mutant preventing the excretion of HBeAg. The e antigen, which is also produced from the region in and near the core gene, is a marker of active viral replication. It serves as an immune decoy and directly manipulates the immune system; it is thus involved in maintaining viral persistence. HBeAg can be detected in patients with circulating serum HBV DNA who have “wild type” infection. As the virus evolves over time under immune pressure, core promotor and precore mutations emerge, and HBeAg levels fall until the level is not measurable by standard assays. Although HBeAg is associated with a high contagiousness, the detection and quantification of HBV-DNA remains the best test for viral replication. The viral replication phase, when uncontrolled by the body, could progress to cirrhosis or primary liver cancer; it should prompt doctors to discuss the indication of an antiviral treatment. In the management of the disease in patients with HbeAg+, whether or not under medication, the objective is to obtain the HBe seroconversion which most often allows the control of the infection, especially by the immune system. HBV DNA level, HBeAg status, degree of hepatic histological activity and fibrosis, and serum transaminases are the most important parameters in determining indication, regimen, and duration of HBV treatment. The aim of our study was to describe the epidemiological and clinical features of chronic VHB in patients with HbeAg+ in the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo.

MATERIALS AND METHODS

Our study took place in the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo. It was a cross-sectional descriptive study with a retrospective data collection from January 1st, 2004 to December 31st, 2015. The study population consisted of i) positive HBsAg patients screened by the National Blood Transfusion Center and referred to the hepato-gastroenterology department for treatment;ii) and chronic VHB patients with positive HBeAg who were followed-up as outpatients in the same department. Patients aged more than 15 years with positive HBsAg for over six months and positive HbeAg were included. Patients who had a decompensated cirrhosis or a primary liver cancer were excluded. Data were collected using a paper data collection form, entered in computer directly using the epi-data software. Data were then cleaned before the analysis. The statistical analysis was descriptive and carried out using Epi Info software.

Study overview

Once recruited, the patients’ paper medical files were used to extract information on socio-demographic characteristics, lifestyle, risk factors and clinical, biological, radiological and histological data. Monthly, then quarterly and bi-annually check of the transaminases were carried out. Serum creatinine and phosphorus were performed every six months in patients on treatment. Tests for HBsAg, HBeAg and HBV-DNA were performed every six months or every year depending on the patient ability to afford the costs. HBsAg was detected using the rapid diagnostic test (the Determine TM Abbott) or the Elisa method (Vidas®). The quantification of HBsAg was carried out by the HBs Ag II quant II Cobas method: 0.05 IU / mL to 52,000 IU / mL (log10: 2.11) and the quantification of HBV-DNA by a real-time PCR (Roche CobasTaq Man, sensitivity threshold 20 IU / mL). An abdominal ultrasound and / or an 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®).

Operational definitions, biochemical and virological profiles

- HBV Chronic carrier: a subject whose HBsAg test is positive for more than 6 months and the anti-HBc (total IgG) antibody test is positive.
- Chronic active hepatitis: a chronic hepatitis B carrier whose alanine amino transferase (ALT) quantificationis twice above the superior threshold of the normal range of values, continuously or in a fluctuating manner and the HBV-DNA is detectable.
- Chronic inactive carrier: a chronic hepatitis B carrier whose ALT quantification is still within the normal range and the HBV-DNA is less than 2000 IU / ml.

Duration of HBsAg carriage: this is the time interval between the date of HbsAg detection and the end of our

study.

- Immunotolerance: a patient whose HBV-DNA > 20,000 IU / ml with its ALT still within the normal range
- HBs seroconversion: it is the loss of the HBs antigen with or without the detection of the Anti-HBs antibody (Ab) and the Anti-HBc Ab is negative.
- HBe seroconversion: it is the loss of theHBeAg with or without the detection of the anti-HBe Ab.

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 immunotolerance phase with an HBV-DNA > 20,000 IU / ml and ALT consistently within the normal range.

RESULTS

From January 1st, 2004 to December 31st, 2015, we recruited a total of 1,264 patients with chronic VHB and included 148 (11.7%) carriers of HBeAg.

Sociodemographic characteristics

The sample included 111 men for a sex ratio of three; 69% were ≤34 years of age. There were 66/148 students, and 63/148 workers in the formal public or private sectors. Singles or widows represented 93/148 participants. Blood donation (44.6%) and routine check-up (29%) were the most frequent circumstances for diagnosing HBV infection.

Medical history of the participants

The duration of HBsAg carriage was between 1 and 12 years with a mean duration of 6.4 ± 5.6 years. A family history of HBsAg carriage and cirrhosis or HCC was found in nine (6.1%) and ten (6.8%) cases, respectively. Physical examination was normal in 99.3% of cases, with a body mass index <18.4 in 10.8% or ≥25 in 25% of the participants.

Biological characteristics

Transaminases were above normal range in 43 (29%) untreated patients and viral load was detectable in 95 /98 cases with a mean viral loadof 15 084 810 IU / mL (7.18 log 10) and a range from 11 to110 000 000 IU / mL.

The five biochemical and virological profiles were found. The profiles 5 and 4 were the most frequent with 19 (46.3%) and 14 (34.1%) patients, respectively. Figure 1 shows the patients' biochemical and virological profiles.

The quantification of the HBsAg was performed in 14 patients of whom 12 were treated with tenofovir and two untreated. The viral loads were >20 000 IU/ml and the HBsAg> 1000 IU/ml for the two untreated patients. The duration of treatment for patients who performed the HBsAg quantification varied between 1 and 4 years. All treated patients were on tenofovir. The HBsAg decrease rate was 0.18 log/year. At two and four years of treatment, the means HBsAg were 14 122 UI/ml and 10,052 IU/ml, respectively. Six of 14 patients lost the HBeAg (4 treated and 2 untreated). The likelihood of losing HBeAg was correlated with the loss of HBsAg. With an HBsAg concentration <1500IU/ml or > 20 000 IU/ml, the HBe seroconversion rates were obtained in 75% and zero cases, respectively. Figure 2 represents the distribution of the HBsAg concentration as a function of HBe seroconversion.

Anti-HBeAb was performed in 93 patients; 33 patients were positive for both anti-HBeAb and HBeAg. A loss of HBeAg was observed in 16/33 patients including 14 treated and 2 untreated. All these patients were inactive carriers (undetectable viral load and normal ALT). Fifteen of 85 untreated patients had a negative HBeAg. A spontaneous negativation of the HBsAg was observed in 8 (9.4%) patients. The human immune-deficiency virus (HIV), the hepatitis C virus (HCV) and the hepatitis D virus (HDV) statuses were positive at 1/148, 4/146 and 1/55 patients, respectively.

Other paraclinical investigations

Abdominal ultrasound was normal in 126 (85.1%) patients. A fatty or dysmorphic liver was observed in 9 (6.1%) and 7 (4.7%) cases, respectively. The hepatic fibrosis blood test showed an activity A ≥ 2 in 25 (83.3%) patients and fibrosis F ≥ 2 in 23 (76.7%) patients (Table II). The liver biopsy was performed in 8 (5.4%) patients; 2 patients showed no inflammatory activity (A0); 5 had a minimal activity (A1). Portal fibrosis without septa (F1) was found in three patients and three others had portal fibrosis with some septa (F2) (TableII).

DISCUSSION

Study Limits

A significant number of patients participating at the study, lacked laboratory and ultrasound 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 does not present the whole reality of our cohort. However, what is observed in this work gives us a fairly objective picture of the evolution of a regularly monitored VHB patient.

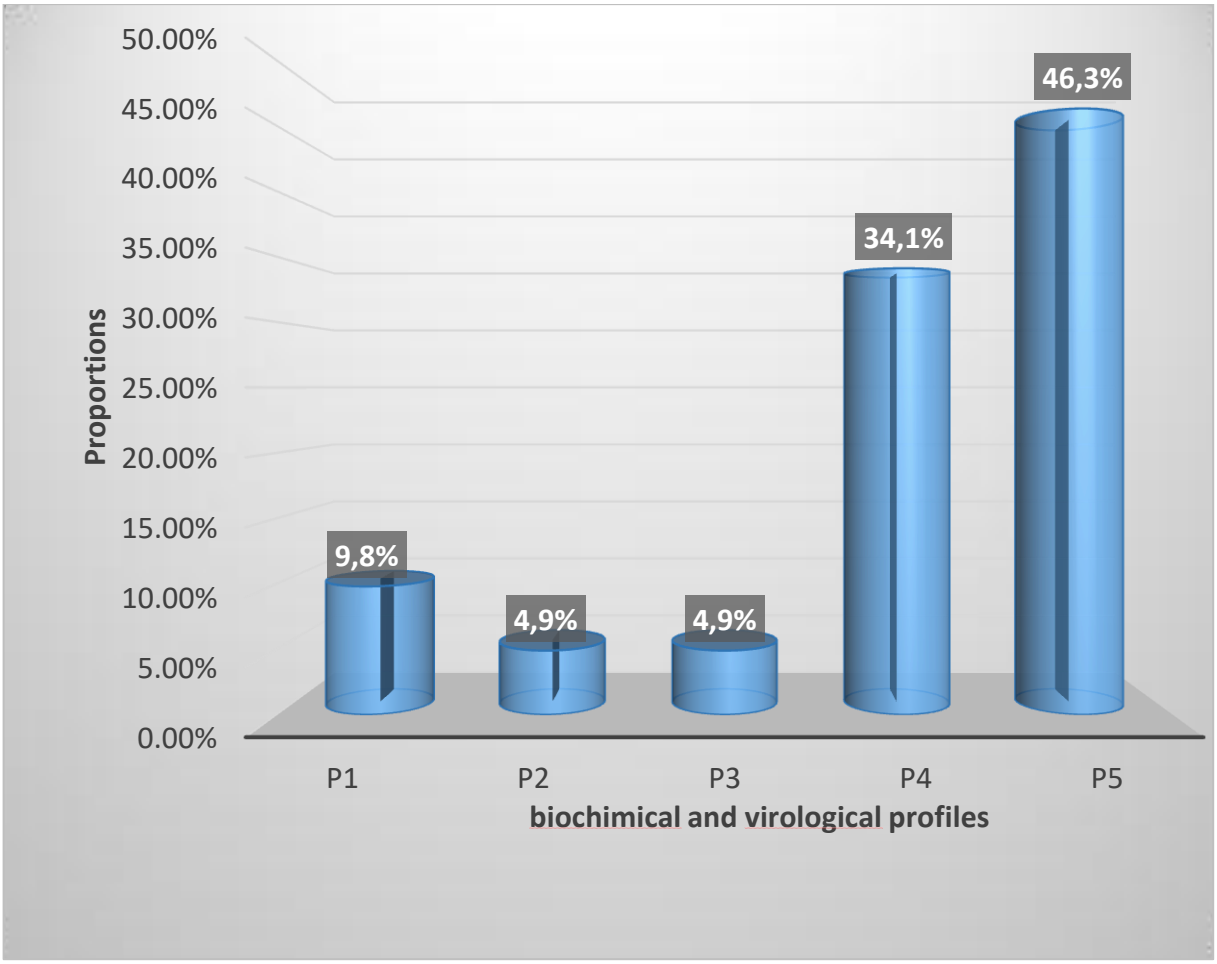

Figure 1. Distribution of the biochemical and virological profiles.

Sociodemographic characteristics

With a sex ratio=3, our results were comparable to those of other studies on the topic (Bermingham SL et al., 2015; Kpossou et al., 2020; Wongjarupong et al., 2020) and clearly indicated that VHB became chronic more often in men than in women. The mean age was 33; Bougouma and Khelifafound a mean age of 37.5 and 35 years among patients with positive HBeAg, respectively. Other studies found a mean age as low as 33 years (Bermingham SL et al., 2015; Kpossou et al., 2020; Wongjarupong et al., 2020). According to the literature (Nnakenyi, Uchechukwu, & Nto-Ezimah, 2020), patients with HBeAg are generally less than 40 years. Pupils and students represented 45% of our sample, followed by civil servants and private sector employees. These groups used to be the target of blood collection campaigns and / or the yearly health check-ups as part of occupational medical visits. The level of education of these groups was undoubtedly also a contributing factor to the high rate of representativeness. Consumers of alcohol represented 14.9% of the sample. This result was lower than those of Ganesan (Ganesan, Eikenberry, Poluektova, Kharbanda, & NA, 2020) in the United States and even Kabore (unpublished thesis) in Burkina Faso, who found respectively about 50% and 34% of alcohol consumption in their study populations. The fibrosis observed in HBV infection is thought to be accelerated by alcohol consumption (Askgaard G, Gronbaek M, Kjaer MS, Tjonneland A, & JS, 2015; Jaquet A et al., 2018; Jaquet A et al., 2017). In Europe, alcohol is the main cause of liver disease. In our context, it comes after viral aetiologies (Pimpin et al., 2018; Vento S, Dzudzor B, Cainelli F, & Tachi K, 2018). Our study population being younger, mainly constituted of pupils and students, was not socially and financially ready to consume alcohol regularly. A family history of HBsAg carriage, cirrhosis or primary liver cancer was found in 12.8% of the cases; a high rate that would probably be the result of a weak detection of HBV in the general population.

Clinical and paraclinical features

The most frequent circumstances of diagnosis in our study

Table I. Basic characteristics.

Characteristic	Frequency	Percent (%)
Gender :male	111	75
Age group		
15-24	17	11
25-34	86	58
35-44	33	22
45-54	9	6
≥ 55	3	2
Occupation		
Pupils / Students	66	44.6
Civil servants	39	26.4
Employees of the private	24	16.2
Farmers and housewives	11	7.4
Tradespeople	6	4
Religiouspeople	2	1.4
Maritalstatus		
Singles/widows	93	62.84
Married/ cohabiting	55	37.16
Alcoholdrinking	22	14.9
Family history of positive HBsAg or HCC*	9	6.1
Circumstances of diagnosis		
Blood donation	66	44.6
Routine check-up	43	29.0
Disease investigation/diagnosis	37	25.0
Prenatalvisits	2	1.3

*Hepato-cellular carcinoma.

Table II. Distribution of patients having performed an anatomo-pathology examination of the biopsy and / or the hepatic fibrosis blood test according to the activity and fibrosis grading of the METAVIR score.

Results	Frequency	Percent (%)
Fibrometer(n = 30)		
Activity grading		
A1	**5**	16.7
A2	**21**	70
A3	**4**	13.3
Fibrosis stage		
F1	**7**	23.3
F2	**15**	50
F3	**5**	16.7
F4	**3**	10
Histology(n = 8)		
Activity grading		
A0	2	25
A1	5	62.5
A3	1	12.5
Fibrosis stage		
F1	3	37.5
F2	3	37.5
F3	1	12.5
F4	1	12.5

was the blood donation with a frequency of 45%, followed by the routine health check-ups (18%). The physical examination of the participants was normal in 99.3%. As the HBV infection is generally silent, these results call for a generalized practice of systematic screening in order to prevent serious complications such as cirrhosis or hepatocellular carcinoma. Screening strategies such as the “optout” option (Cunningham CO et al., 2009; JC, WH,

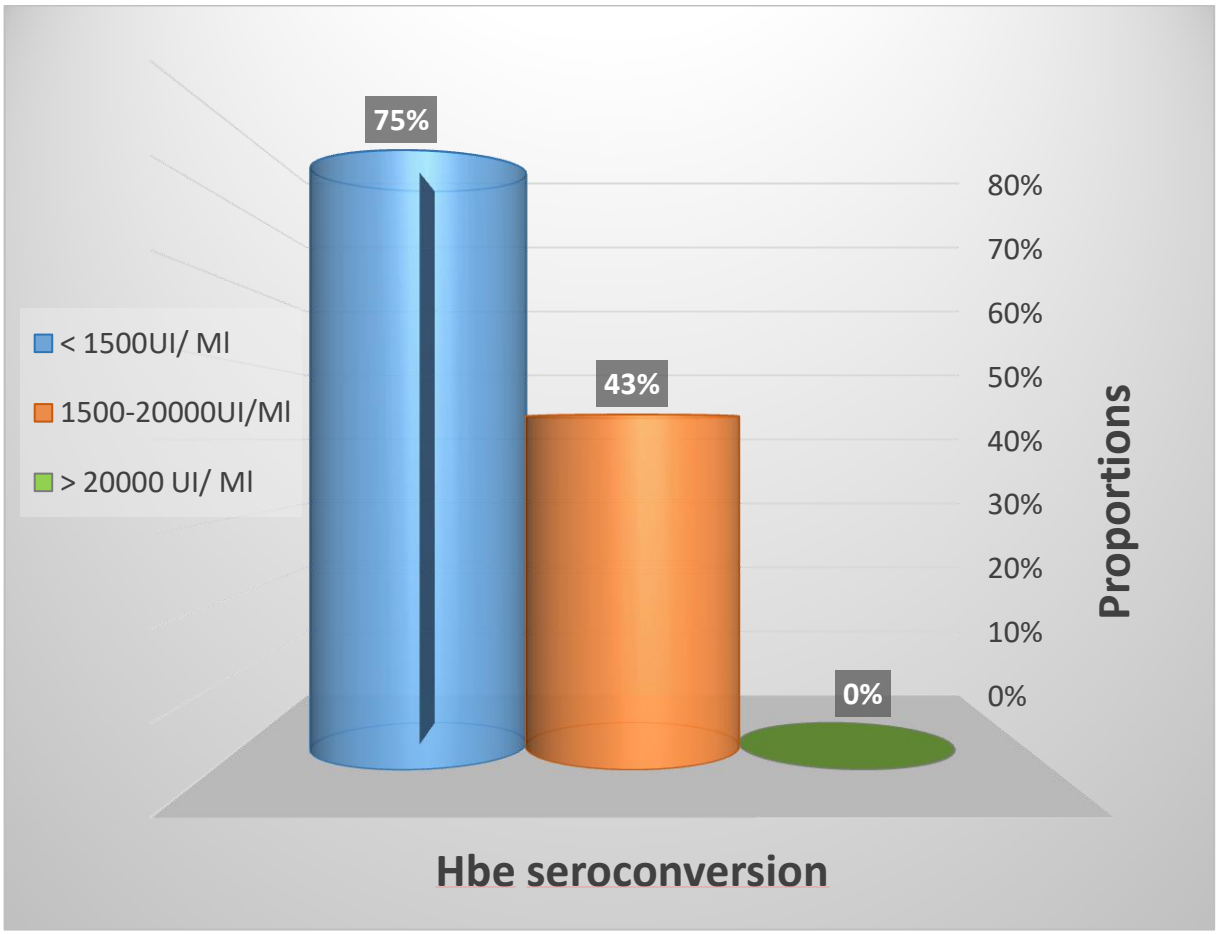

Figure 2.HBsAg concentration as a function of HBe seroconversion.

& BC, 2016) successfully practiced in the fight against the HIV infection should be considered with great attention in the response against the HBV infection in Burkina Faso, both in the prevention of mother-to-child transmission of HBV and in the prevention of the horizontal transmission.

We also found 11.7% of chronic HBV carriers with positive HBeAg. This result is also comparable to Khelifa's (Khelifa F & Thibault V, 2009) in Algeria and Sia's (Sia R, 2009) in Burkina Faso, which were respectively 13% and 12.2%.Zarski (Zarski JP et al., 2006) and Ayed (Ayed K et al., 2007) in 2006 found higher prevalences of 24.7% and 23.2% respectively. This decrease in HBeAg levels over years is thought to be due to the progressive decrease in the prevalence of chronic VHB caused by the wild strain of the virus because of the hepatitis B immunization programs (Wu et al., 2017).

The mean concentrations of HBsAg in untreated subjects were comparable to the results of Asian studies (Zeng LY et al., 2014). High concentrations of HBsAg with normal ALT in patients without treatment, described a situation of immune tolerance (Lee HA et al., 2020). At the contrary, the decrease in the level of HBsAg in treated patients is a good indicator of the effectiveness of the treatment, in particular when using tenofovir. This observation suggests that the kinetics of the decrease of the HBsAg concentration during treatment could be used as a Predictive test of recovery from HBV infection. Therefore, the quantification of HBsAg level could be a new hepatitis B follow-up test, completing or even substituting the viral load in constraint economic contexts (Cornberg et al., 2017; Martinot-Peignoux, Lapalus, Asselah, & Marcellin, 2014).

The duration of treatment varied between 1 and 4 years and the decrease rate of HBsAg levels was 0.18 log / year. This rate was lower than the one observed in treatments using interferon (0.7 log / year) but greater than the treatment using the lamivudine (0.02 log / year) (Dusheiko, 2013; Leung N, 2011; Xu et al., 2021). Studies found that the decrease in HBsAg levels in patients under nucleoside analogues treatment, was usually slower. The decrease in HBsAg concentrations could also predict HBe seroconversion (Cornberg et al., 2017).

Profiles 5 (patients in immunotolerance phase) and 4 were

the most represented with 19 (46.34%) and 14 (34%) patients, respectively. The first profile (inactive carrier) represented 9.8% of the cases. This profile generally remains stable with a low risk of occurrence of cirrhosis or hepato-cellular carcinoma. In this case there is no indication to treat but the patient's follow-up must be rigorous and prolonged (European Association For The Study Of The Liver, 2009). The profile 5 is characterized by a rapid viral replication with normal transaminase activity; there is no indication for treatment but it must be monitored by regular transaminase quantification every 3 to 6 months, except after the age of 30 or in a family history of cirrhosis or hepato-cellular carcinoma (26). The other profiles (P2, P3, P4) are treated immediately or after performing a liver biopsy with pathology analysis, because of the high risk of serious hepatic complications.

CONCLUSION

Viral hepatitis B is a silent infection with a small proportion of patients experiencing viral replication activity. The management of this disease of public health interest is based mainly on the primary prevention through vaccination of the healthy population and the secondary prevention by closely monitoring the infected people. To achieve a good population coverage by the prevention, particular emphasis should be put on systematic screening through specific health policy enabling coverage of vulnerable groups as well as the whole population, and not only targeting the students and workers in the formal sector who are the traditional focus of most screening activities.

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