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Frequency of Viral Replication Markers in Chronic HBV Carriers in N'Djamena, Chad

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Abstract

Introduction: According to the WHO, Chad is located in an area of high endemicity for hepatitis B virus (HBV). The aim of this study was to analyze the virological profiles of chronic HBV carriers. **Materials and Method:** This was a retrospective and analytical study including outpatients with chronic HBV of any age received in Department of Internal Medicine and Gastroenterology of National General Reference Hospital of N'Djamena from 2013 to 2017. **Results:** During the study period, 401 chronic hepatitis B virus carriers (mean age was 35 years ± 11 years with sex ratio of 3.26) were seen in outpatient clinic with a frequency of 3.34% (401/11,988). HBeAg (+) patients were 12.8% and HBeAg negative 87.2%. HBeAg-negative patients were significantly older (p = 0.000) than those with HBeAg (+). The mean HBV-DNA level was higher in HBeAg (+) patients. The HBV-DNA level in HBeAg-positive patients was higher than in HBeAg-negative patients with a significant difference (p = 0.043). The mean ALT level was 45 IU/L in HBeAg (−) patients. It was 49 in HBeAg (+) patients. **Conclusion:** HBeAg (−) chronic hepatitis B is the most predominant form in our study. This observation is important because it can help to adapt the management strategies.

Keywords

Chronic Hepatitis B, Epidemiology, HBeAg, Viral Replication, Ndjamena, Chad

1. Introduction

Hepatitis B virus infection is a major public health problem. In 2019, it is estimated that more than 296 million people are chronic carriers of hepatitis B, and

nearly 1.5 million registered in 2019 alone, of which more than 60% are in sub-Saharan Africa, with more than 820,000 deaths in the same year [1]. In these patients, the presence of viral replication and the necrotic and inflammatory action of the virus on the liver increases the risk of developing cirrhosis and hepatocellular carcinoma [2]. Since 2010, viral hepatitis is considered the fourth public health priority worldwide by the World Health Organization (WHO) after HIV/AIDS, malaria and tuberculosis [3]. Africa is one of the regions of high endemicity with Asia and Latin America [4]. Despite the existence of an effective vaccine recommended by the WHO since 1991, the number of patients chronically affected by the disease remains high. For these patients, two types of treatment are available, based either on the use of interferon to stimulate the host's antiviral defenses, or on the use of viral polymerase inhibitors that block the multiplication of the virus [5]. In Africa, the most frequent modes of contamination are vertical transmission from mother to child at birth and horizontal transmission in early childhood, with a very high risk of chronicity, respectively between 90% and 30% [3] [6]. The epidemiological aspect of the disease differs according to geographical areas and the biological expression varies from one patient to another.

Chad is a highly endemic area for HBV and the majority of the population does not know its serological status. Most patients with the virus are diagnosed at the stage of complications. However, the disease evolves in a chronic way and the hepatic lesions such as cirrhosis or liver cancer.

At a time when medicine has made great therapeutic advances, knowledge of the epidemiological and virological aspects of HBV in our country could help improve the management and follow-up of patients, hence the interest in carrying out this study whose aim is to analyze the virological profiles of chronic HBsAg carriers.

2. Patients and Method

This was a retrospective, and analytical study including all patients with HBsAg received in the department of internal medicine and gastroenterology from 2013 to 2017. All patients with HBsAg for more than six months documented, regardless of age, and with a certain number of follow-up tests among HBe status, anti-HBe antibodies, hepatitis B viral load (HBV-DNA) and transaminases (ALT and AST) were included in this study. The variables considered were epidemiological data (age and sex), biological data (HBsAg, HBeAg, anti-HBeAb, HBV-DNA), liver cytolysis activities (ALT, AST, Gamma GT). Data were analyzed using SPSS 18.0 software. Quantitative variables are presented as mean or median values with their dispersion indices. Results are presented in tables (**Tables 1-3**). The chi^2 test was used to investigate possible associations between HBeAg and patient characteristics including epidemiological (age, sex) and biological (HBV-DNA, ALT, AST, Gamma GT) data. A cut off value of $p \leq 0.05$ was statistically considered significant.

3. Results

During the study period, 401/11,988 cases consulted were HBsAg positive,

Table 1. Epidemiological profiles of chronic HBsAg carriers.

Paramètres	
Frequency of AgHbs (+)	3.34%
Sex-ratio (M:F)	3.26
Median (year)	35 ± 11 years
Age range (year)	
	Number **Perrcentage**
0 - 14	17 4.2
15 - 18	13 3.2
19 - 34	162 40.4
35 - 49	171 42.6
50 and over	38 9.5

Table 2. Biological profiles of HBsAg carriers.

Parameters	**Number**	**Percentage (%)**
AgHbe (+)	51	12.8
AgHbe (−)	350	87.2
HBV-DNA ≤ 2000 UI/L	282	70.4
HBV-DNA > 2000 UI/L	119	29.6
ALT level ≤ 40 UI/mL	269	67.0
ALT level >40 UI/mL	132	33.0
AST level ≤ 40 UI/L	316	78.9
AST level > 40 UI/L	85	21.1
Gamma GT level ≤ 40 UI/L	301	75.0
Gamma GT level > 40 UI/L	100	25.0

Table 3. Epidemiological and virological profiles of HBsAg carriers by HBeAg status.

Biological parameters	**AgHbe (+)**	**AgHbe (−)**	***p***
Mean age (years)	30	35	0.0001
Sex-ratio (M:F)	4.66	3.11	ns
ALT level (UI/L)	49	45	ns
AST level (UI/L)	43	42	ns
Gamma GT level (UI/L)	41	42	ns
HBV-DNA (UI/mL)	30,479,017	1,959,739	0.043

representing a frequency of HBV infection of 3.34%. The mean age of chronic HBsAg positive patients was 35 ± 11 years with a sex ratio of 3.26. The age group 19 - 49 years represented 83% of the study population.

Biologically, 87.2% of the patients had an AgHbe (−) profile and 12.8% AgHbe (+). Analysis of the HBV DNA profile showed that the mean level was 5,262,493 IU/mL (extremes ranging from 0 to 1,700,000,000). From all patients who were able to perform the B viral load, 70.4% had HBV-DNA values below 2000 IU/mL and those with HBV-DNA values above 2000 IU/mL represented 29.6%. The threshold of 2000 IU/mL is the one at which an antiviral therapeutic decision can be taken or not independently of the other variables according to the WHO recommendations. Regarding liver cytolysis, 67% of patients had normal ALT levels and 33% had abnormal ALT (>40 IU/mL); ASAT was normal in 78.9% of patients, 21.1% had an abnormality; GGT was normal in 75% of patients and 25% had Gamma GT levels above normal. In chronic carriers with positive and negative HBeAg, male sex predominated with a sex-ratio of 4.6 and 3.08 respectively in favor of male sex but there was no relationship between HBeAg and sex ($Chi^2 = 1.156$, $p = 0.282$). The mean age for HBeAg-negative patients was 35 years and for HBeAg-positive patients it was 30 years with a significant difference ($p = 0.000$). There was therefore a relationship between HBeAg status and age. The HBV-DNA level in HBeAg-positive patients was higher than in HBeAg-negative patients with a significant difference ($p = 0.043$). In our series, there was no relationship between biochemical variables and HBeAg (p up to 0.05).

4. Discussion

This is a first study in Chad which made it possible to know the profile of the patients carrying the HBV in Chad. But as any retrospective study it has limits because it is based on the exploitation of patient files.

The knowledge of the HBeAg status and the viral load of the chronic HBV carrier patient is an essential step for the treatment. Also, the knowledge of the proportion of chronic HBV carriers in a given cohort will allow a good programming for the management in a country with limited resources like Chad. It is for this last reason that some patients were not able to perform HBV DNA testing, limiting themselves to the HBeAg test, which is also considered a marker of viral replication. In this study the rate of chronic HBsAg carriers in outpatient clinics during the study period was 3.34%. This result is lower than those of several authors according to whom the prevalence of HBV infection in countries with high endemicity is higher than 8% [7]. Because this is a cohort study and not a study of the entire population. The average age of our patients was 35 years ± 11. Amidu *et al.* in Ghana found an age of 37.93 ± 0.93 years [8]. On the other hand Diallo *et al.* in Senegal found a mean age of 33 years [9].

In France, the Institut de Veille Sanitaire (InVS) and the Caisse Nationale d'Assurance Maladie et des Travailleurs Salariés in their 2003-2004 prevalence survey also found a predominance of adult and young patients [10].

Regarding gender, the number of male patients was much higher than female patients with a sex ratio of 3.2. This same observation was made by Agbenu *et al.*

in Togo [11]. Diallo *et al.* in Senegal found a sex ratio of 2.2 [9].

In the West, data from the Institut de Veille Sanitaire (InVS) and the Caisse Nationale d'Assurance Maladie et des Travailleurs Salariés in France in their 2003-2004 survey found a high number of male patients among HBV carriers with a sex ratio of 4.88 [10]. Ankouane *et al.* in Cameroon also found a sex ratio of 2.93 in favor of men [12]. This confirms the data of Zarski *et al.* who found a predominance of infection in males [13]. We have not found a clear scientific explanation for this predominance of infection in males, but it seems that plasma clearance of HBsAg is slower in men than in women.

The analysis of the HBeAg profile showed that 87.2% of the patients included in our study had a negative HBeAg status and only 12.8% were HBeAg carriers. This result is in agreement with those of several studies including that of Zarski *et al.* who obtained a predominance of chronic HBeAg negative carriers (72.25%) [13]. In the same region of Central Africa like Cameroon, Ankouane *et al.* reported that 92.9% of the patients were HBeAg negative against 7.1% of chronic carriers with HBeAg positive. On the other hand in Greece, Raptopoulou *et al.* found that chronic hepatitis B with HBeAg negative was the most predominant form with 92.1% of cases [14]. A prevalence of 80% - 90% has been reported in Italy as well as in Asia [15] [16].

HBeAg-negative viral hepatitis B is therefore the most predominant form in Chad. Our data showed that the mean age for HBeAg negative patients was significantly higher than for HBeAg positive patients. The HBeAg-negative patients were therefore older than the HBeAg-positive ones. Zarski *et al.* performed a study on the characteristics of HBeAg according to age and region of origin and found that in patients coming from Africa, the mean age was 36.7 ± 11.1 for HBeAg-negative versus 30.5 ± 12.1 for HBeAg-positive. In patients coming from Asia, the mean age was 44.5 ± 13.9 for HBeAg-negative versus 35.3 ± 12.8 for HBeAg-positive; on the other hand, in France the mean age was 50.1 ± 14 for HBeAg-negative versus 46.3 ± 15.5 for HBeAg-positive [13].

This result could be explained by the fact that in most cases and especially in sub-Saharan Africa, infection occurs in early childhood, the immune system not being competent, the infection follows a phase of immune tolerance with viral replication. The HBeAg, which is a marker of replication, is then secreted in the blood of the carrier and persists for a more or less long period of time, hence its positivity in young people. With time, the immune system reacts with hepatocellular destruction and induction of mutation of the B virus which becomes HBeAg (−). Thus the virus with AgHbe called wild type virus mutates to become a virus with negative AgHbe called pre-C mutant virus.

Analyzing the data from this study, we found that in HBV with HBeAg (+) as well as HBeAg (−), the male sex predominated with 75.70% of patients male patients in HBeAg-negative and 82.35% of male patients in HBeAg-positive hepatitis. In China, Scoot *et al.* observed a predominance of male subjects in both groups (HBeAg positive and negative) [16]. The same observation was made by Fattovich *et al.* in Italy. The male sex was the most affected in all cases [17].

On the results obtained, we also found that the mean HBV-DNA level for HBeAg-positive patients was significantly higher than the mean HBV-DNA level for HBeAg-negative patients with a statistically significant difference confirming that HBeAg+ is an indirect marker of high HBV replication, so there was a relationship between the presence of HBeAg and HBV-DNA. In the paper of Scoot *et al.*, they also described a superiority of HBV-DNA level in HBeAg positive patients compared to HBeAg negative patients. This confirmed the result of Chan *et al.* that HBV-DNA levels were higher in HBeAg positive patients [18]. This result is logically explained by the fact that HBeAg is a marker of viral replication secreted, and its positivity indicates definite replication, hence an increase in HBV-DNA levels in most HBeAg positive patients. On the other hand, a negative HBeAg test alone does not mean that there is no viral replication, hence the importance of performing a viral load test.

Finally, this study allowed us to observe that in HBeAg-negative patients, the average ALT level was lower than that of HBeAg-positive patients (45 IU/L *versus* 49 IU/L) but without a significant difference ($p = 0.093$); therefore, there is no relation between ALT and HBeAg.

5. Conclusion

Chronic hepatitis B with negative HBeAg is the most predominant form in our context. In chronic hepatitis B with positive HBeAg, viral replication is certain, but the negativity of HBeAg does not exclude viral replication, hence the interest in carrying out the viral load and complementary virological and biochemical tests.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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