



Original Research

Current Condition of Chronic Hepatitis B Virus Infection in Cuban Adults



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ABSTRACT

Background: The reduction of the incidence of hepatitis B virus (HBV) infection in Cuba can be attributed to the effectiveness of the national immunization program. However, the number of patients with chronic HBV observed in clinical practice is not negligible.

Objective: A cross-sectional study was conducted to describe the main clinical characteristics of patients with chronic hepatitis B virus infection.

Methods: A total of 146 patients who had at least a 6-month history of hepatitis B surface antigen positivity were recruited between 2013 and 2015. Descriptive statistical analysis of the epidemiologic, clinical, biochemical, and virologic variables was performed.

Results: Men accounted for 67.8% of patients, and the median age was 43 years. The median time since diagnosis of infection was 9 years. Among the patients, 59% had chronic hepatitis, 34% had liver cirrhosis, and 7% were inactive carriers. Concomitant diagnoses demonstrated that 16.4% of patients had malignancies, predominantly lymphoma. Only 64.4% of patients had received antiviral treatment, and lamivudine was the most commonly used (61.6%) drug. Moreover, 70% of patients were identified during an inactive phase.

Conclusions: Patients with chronic HBV infection are still a health problem in the adult Cuban population, especially in patients with concomitant malignancies.

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Introduction

The hepatitis B virus (HBV) is a major cause of morbidity and mortality. Approximately one-third of the world's population has serologic evidence of past or present HBV infection, and 350 to 400 million people are chronic HBV surface antigen (HBsAg) carriers.¹ In the most recent global epidemiologic reports on HBV, European guidelines have confirmed that there is a decreasing prevalence of this infection in most regions of the world. The slight decrease in its incidence and prevalence, particularly evident in central sub-Saharan Africa, tropical Latin America, central Latin America, Southeast Asia, and central Europe, may be the result of expanded immunization in the latest decades. However, the absolute number

of HBsAg-positive persons increased from 223 million in 1990 to 240 million in 2005. This increasing overall number of individuals chronically infected with HBV and the widespread global differences in HBV prevalence is shocking. HBV infection prevalence data are needed at country and subnational levels to estimate disease burden to update the vaccination policy.²

In Cuba, HBV was an important health problem during the 1980s. The reporting of cases between the years 1989 and 2007 was variable, but the highest (20.3/100,000 habitants) was reported in 1992. The national immunization program against this virus in the population up to age 25 years and in high risk groups has resulted in a decline in the incidence and prevalence of this disease over the past 15 years.³ Despite the significant reduction in the incidence of new infections, there are still important numbers of chronic cases observed in clinical practice. However, there is not enough epidemiologic data to accurately estimate the number of HBsAg-positive people in the country. It is known that this infection is among the causes of liver cirrhosis, a disease that ranks

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10th among the leading causes of death in Cuba.⁴ This study was performed to identify the main epidemiologic and clinical characteristics of adult Cuban patients chronically infected with HBV.

Material and Methods

A prospective study was conducted at the National Institute of Gastroenterology, Havana, Cuba, between November 2013 and April 2015. The study was approved by the institution's ethics committee. Written informed consent was obtained from patients before enrollment in the study. A total of 1978 patients were admitted to the outpatient clinic during the period of the study. Of 150 patients recruited, 146 satisfied the inclusion criteria. The study included men and women who had had a positive serum surface antigen (ie, HBsAg) for more than 6 months. Exclusion criteria were other known chronic liver diseases, including autoimmune, metabolic, or hereditary diseases, as well as positivity for serological markers of human immunodeficiency virus or hepatitis C infection.

Variables collected in the study

Epidemiologic characteristics

Sex, age, origin (rural or urban), occupation, date of diagnosis of infection, smoking history, previous vaccination for HBV, concomitant diseases, and exposure to known risk factors were identified.

Virology

Reverse transcription polymerase chain reaction was used for the quantitative determination of viral load using commercially available kits (cobas AmpliPrep/cobas TaqMan/cobas TaqMan 48, Roche Diagnostics, Switzerland/U.S.). The lower limit of detection of HBV DNA was 20 IU/mL (2.0 E + 1 IU/mL), and the maximum was 1.70 E + 8 IU/mL. The HBsAg, HBV E antigen (HBeAg), and HBV E antibody (HBeAb) were measured with ELISAs.

Clinical

Definitive diagnosis of chronic hepatitis was determined by liver biopsy, liver cirrhosis (by a complete medical history), inactive carrier (normal transaminases, HBV DNA < 20,000 IU/mL, and normal or minimal inflammation histology), and the prior or concurrent use of antiviral treatments.

Liver biopsy

Histologic evaluation was performed using the METAVIR (Algorithm for Evaluation of Histological Activity) scale. Measurements of hepatic hardness in kilopascals (kPa) were made with the FibroScan Echosens 402, Paris, France (M probe; ultrasonic frequency 3.5 MHz) and expressed as degree of fibrosis (F) (reference values: F0–F1, < 7 kPa; F2, 7–8 kPa; F3 and F4, 8–10 kPa, and F5 > 10.5 kPa).

Phases of chronic HBV infection

- Immune phase: Immune tolerant (HBeAg-positive, normal transaminases, and HBV DNA > 20,000 IU/mL, mild or no liver necroinflammation, and mild or no fibrosis).
- Immunoreactive: Increased or fluctuating levels of transaminases and HBeAg-positive, HBV DNA < 20,000 IU/mL, moderate to severe activity of liver necroinflammation, and fibrosis.
- Nonreplicative or inactive carrier: At the 1-year follow-up visit (checked every 4 months), normal serum aminotransferases, normal histology, or minimal inflammation, HBeAg-negative, and HBeAb-positive. Serum HBV DNA levels undetectable or below 20,000 IU/mL.

Biochemical determinations were performed in the clinical laboratory of the Gastroenterology Institute using routine validated methods (Roche Hitachi 902 Chemistry Analyzer, Switzerland).

Statistical analysis

The variables were recorded and processed in a database created in the Statistical Package for Social Sciences for Windows version 21.0 (IBM-SPSS Inc, Armonk, New York). The medians, means, SDs, and frequencies were defined. The χ^2 test was used to assess the relationships between categorical variables. A *P* value of 0.05 was used to determine statistical significance. The estimated prevalence rate of each specific disease was determined as the number of patients with HBV/clinic population during the period \times 100.

Results

HBV represented 8.5% among all liver diseases observed during the period of study. Men were more affected, and the median age was younger than 45 years. The HBV patients mostly lived in urban areas of the western region of Cuba. More than 80% of patients were professionals, and 6 of them (4.1%) were health workers, mainly nurses. Seven new patients were diagnosed during the study period, whereas 89 patients (61%) were diagnosed with chronic infection during the prior 10 years. There were 40 patients (27.3%) younger than age 35 years who were not immunized, and 10 of these patients were between ages 23 and 31 years who had a previous history of malignancies diagnosed during childhood or adolescence.

Malignancy was the most common concomitant disease: 9 patients had non-Hodgkin lymphoma, 5 had Hodgkin lymphoma, 3 patients had leukemia (2 had acute lymphoblastic leukemia and 1 patient had acute promyelocytic leukemia), and 2 patients had nervous system neoplasms (neuroblastoma and medulloblastoma). Other malignancies (adenocarcinomas) were reported, each them in a different patient: uterus, laryngeal, thyroid, prostate, colon, and malignant histiocytosis. Two patients with non-Hodgkin lymphoma also had other malignancies (Table I).

HBV infection was first detected in 74 patients (50.7%). Of these patients, 64 had chronic liver diseases, and 10 had acute hepatitis. Fifty-nine patients (40.4%) were identified by routine medical checkups for other comorbidities. In addition, 6 (4.1%) patients were infected perinatally and 4 (2.7%) were blood donors. Three patients (2.1%) were diagnosed during pregnancy. Ninety-four patients (64.4%) had received previous treatment, with lamivudine being the most common drug used in 90 patients (61.6%) followed by interferon in 31 patients (21.2%). Other treatments included adefovir in 15 patients (10.3%) and tenofovir in 11 patients (7.5%). Most patients had undergone more than 1 treatment since being diagnosed. The definitive diagnoses, differences in age, biochemical indicators, and virologic indicators are shown in Table II.

Most patients (71.2%) had low viral loads (< 20,000 IU/mL). Liver necroinflammation was observed in 85% of patients, whereas fibrosis was reported in 53% of patients. Coinciding with histology, the highest proportion of patients had mild or no fibrosis on liver elastography (Table III).

The majority of patients were in the nonreplicative phase (70%) with HBV DNA levels below 20,000 IU/mL, and 10 patients were inactive carriers with normal histology. Fifty-four patients had chronic hepatitis and 37 patients had liver cirrhosis. An additional 19.2% of patients (5 with cirrhosis and 23 with chronic hepatitis) were in an immune-tolerant phase, and 11.6% of patients (8 with cirrhosis and 9 with chronic hepatitis) were in an immunoreactive phase. Of the patients in an immunoreactive phase, 70% had received antiviral treatment.

Table I

Main epidemiologic characteristics of 146 patients with chronic hepatitis B virus infection. Institute of Gastroenterology, Havana, Cuba, 2013–2015.

Characteristic	Result
Sex	
Male	99 (67.8)
Female	47 (32.2)
Age, y	43 (20–83)
Origin	
Urban	122 (83.6)
Rural	24 (16.4)
Occupation	
Professional	26 (17.8)
Others	120 (82.2)
Tabacco use	20 (13.7)
Time since diagnosis, y	9 (1–49)
Hepatitis B vaccination	9 (6.2)
Concomitant diseases	
Malignancies	24 (16.4)
Diabetes	4 (2.7)
Hypothyroidism	2 (1.4)
Down syndrome	2 (1.4)
Asthma	1 (0.7)
Chronic kidney disease	1 (0.7)
Ulcerative colitis	1 (0.7)
Exposure to known risk factors	
Surgical or dental surgery history	56 (38.4)
Blood transfusions	32 (21.9)
Multiple sexual partners	5 (3.4)
Needle punctures	2 (1.4)

* Values are presented as n (%), except age and time since diagnosis, which are presented as median (range).

Discussion

The incidence of chronic HBV infection detected in this study was higher than expected, particularly in patients with median age younger than 45 years. These results originated from a tertiary care center and may not be representative of the actual prevalence of this infection in Cuba. However, the study results draw attention to this diagnosis and suggest the need for further multicenter seroprevalence studies. There may be an underreporting of chronic HBV infections, and it would be of a great interest to re-examine this issue several years after implementation of the national immunization program.⁵

Men were the most affected. The global difference in the prevalence of the infection among men and women is small. The incidence has been reported to be 3.9% in men and 3.5% in women.² In Iran, the highest prevalence of chronic infection is reported in patients aged 30 to 40 years and is 25% higher in men.⁶ In Chile, 76% of the infected population is between ages 20 and

Table III

Elastography results of patients with chronic hepatitis B virus infection. Institute of Gastroenterology, Havana, Cuba, 2013–2015.

Degree of fibrosis	Patients	%	Hardness*
F0–F1	28	63.6	5.3 (1.2)
F2	6	13.6	7.9 (0.4)
F3	6	13.6	11.5 (2.0)
F4	4	9.1	21.1 (6.4)

* Values for hardness are presented as mean kilopascals (SD).

49 years, and men account for 86% of all cases.^{7,8} Similarly, Zhang et al⁹ in China reported that HBV infection occurs mostly in men, with a ratio of 3.28 to 1 compared with women and in patients with a mean age of 41.6 years.

With regard to sexual behavior, which is considered among the main routes of transmission for this hepatitis, our study did not suggest that it is the most important route of transmission. The possibility of underreporting was not ruled out because most of the patients were at the age of a sexually active life. However, a multicenter case-controlled study of the risk factors for hepatitis B and C conducted in blood donors in China failed to identify a specific risk factor associated with HBV infection.^{10,11} The biological risks in health workers are known. Similar to our results, Caciari et al¹² reported the seroprevalence of HBV is approximately 4% of health workers exposed to higher risks.

Several patients were not immunized on a vaccination schedule according to ages, or they did not complete all doses of the vaccination scheme. It is possible that some of these patients left the vaccination program or did not achieve an adequate level of seroprotection. Although the Cuban vaccine has shown high levels of seroprotection (between 75% and 94%), this possibility was not ruled out.⁵ The vaccine has shown seroprotection efficacy from a second dose when administered after an interval of 2 to 6 months. However, when the interval is extended to 8 months, it does not reach 90% seroprotection.¹³

The number of patients with a history of malignancies was striking. Many reasons could explain this phenomenon, including chemotherapy-induced hepatitis B reactivation in patients with resolved HBV infection or a hidden infection that was not properly diagnosed.^{14,15} The association between hepatitis and Hodgkin lymphoma is not known.¹⁶ The association of non-Hodgkin lymphoma with HBV has been studied much less intensively than the association with hepatitis C virus. However, an interesting meta-analysis of 12 studies showed a significant association between the 2 entities (odds ratio = 2.56; 95% CI, 2.24–2.92).¹⁷ The data available may underestimate the true association between these diseases if people with occult hepatitis are taken into account.

Table II

Definitive diagnoses of patients with chronic hepatitis B virus (HBV) infection. Institute of Gastroenterology, Havana, Cuba, 2013–2015.*

Indicator	Chronic hepatitis (n = 86)	Liver cirrhosis (n = 50)	Inactive carrier (n = 10)	P value
Age, y	40.7 (13.8)	54.6 (14.9)	38.9 (14.5)	< 0.001
Sex				0.149
Male	60	35	4	
Female	26	15	6	
Time since diagnosis, y	11.4 (9.2)	11.7 (7.1)	7.6 (14.6)	0.413
Alanine aminotransferase, UI/L	58.4 (69.0)	55.0 (54.2)	16.5 (6.4)	0.030
Aspartate aminotransferase, UI/L	60.3 (111.4)	41.4 (23.4)	17.3 (3.0)	0.052
HBV DNA (viral load), UI/mL	2400 (0–1.7 E+8)	20 (0–1.7 E+8)	81 (0–15,800)	0.003†
Antiviral treatment	64 (74)	30 (60)	–	0.079

* Values are presented as mean (SD) for age, time since diagnosis, alanine aminotransferase, and aspartate aminotransferase; as n for sex; as median (range) for HBV DNA; or as n (%) for antiviral treatment.

† Based on independent samples median test.

Recent reports examining HBV DNA in serum have shown that occult HBV infection is associated with non-Hodgkin lymphoma and chronic lymphocytic leukemia.^{18–20}

A substantial proportion of patients were diagnosed with liver cirrhosis. Leluzzi et al²¹ showed the incidence of cirrhosis of 1.56 out of 100 people/year, and it is has been associated with advancing age and sustained viral replication. The results of elastography correspond to those obtained in histology because most patients showed mild or no fibrosis. Marcellin et al²² placed cutoffs to assess liver fibrosis as 7.2 kPa to 18.2 kPa for F0 to F2 and up to F4, which were similar to values detected in our sample. These results support the utility of elastography for detecting fibrosis or cirrhosis in patients with HBV. Chan et al²³ found variations in elastography measurements depending on alanine aminotransferase (ALT) values and showed high diagnostic accuracy for cirrhosis with cutoff values of 13.4 kPa. However, patients with the same degree of fibrosis and greater ALT have higher hardness values on elastography. Based on algorithms that establish the optimal cutoff points based on ALT values, it is possible to avoid liver biopsy in 62% of patients.

The majority of patients showed viral inactivity, and we were unable to determine with certainty the factors associated with the inactivity because this study was not designed for that purpose. The annual incidence of reactivation (approximately 1.2%) is associated with the male gender, an HBV DNA viral load > 1000 IU/mL, and the presence of genotype B²⁴. It is worth mentioning that the most common genotype in Cuba is A and is present in 67% to 92.4% of all HBV-infected individuals.^{25,26} More than 50% of patients had HBV viral load < 2000 IU/mL, which may be related to receiving antiviral treatment.

Patients with compensated cirrhosis without antiviral treatment were those with normal liver function, without cytolysis, and undetectable HBV DNA. Regarding the treatment of immune-tolerant patients, there are more studies supporting the utility with oral antiviral agents. Chan et al²⁷ showed a 76% reduction in viral load to < 69 IU/mL with little HBeAg seroconversion at 192 weeks of treatment. However, the literature still reports little chance of HBeAg seroconversion (< 5% at 4 years of treatment) and minimal risk of disease progression in immune-tolerant patients, prompting current guidelines to suggest no treatment for this type of patient.²⁸ The emergence of new therapeutic agents for highly resistant diseases opens the way for future trials aimed at treating patients with high viral loads to achieve the best chance of seroconversion.

Conclusions

Chronic HBV remains a health problem in the adult Cuban population, especially in patients with concomitant malignancies. Actions should focus on the proper implementation of the vaccination program and long-term monitoring of the results of its application.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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