HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Original article

Hepatitis B virus infection among oncohematologic disease patients in Central Brazil: prevalence, risk factors and immunization

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ARTICLE INFO

Article history:
Received 18 August 2018
Accepted 21 November 2018
Available online 28 March 2019

Keywords:
Epidemiology
Hepatitis B
Leukemia
Lymphoma
Oncology

ABSTRACT

Introduction: Carriers of oncohematological diseases are at high risk for hepatitis B virus (HBV) infection.
Objective and method: To investigate the epidemiology of HBV infection in Goiânia, Central Brazil, 322 individuals with oncohematological diseases (leukemias, Hodgkin lymphoma and non-Hodgkin lymphoma) were interviewed and blood samples were collected for the detection of serological markers of HBV-DNA by polymerase chain reaction (PCR). Medical records of participants were also reviewed.
Results: Non-Hodgkin's lymphomas ($n = 99$) and chronic myeloid leukemia ($n = 108$) were the most frequent oncohematological diseases. The overall prevalence of HBV was 13.97% (45/322). Of the total participants, 8.69% (28/322) presented isolated positivity for anti-HBs, suggesting low vaccine coverage. HBV-DNA was detected in 25% (1/4) of HBsAg positive samples and in 25% (3/12) of anti-HBc isolated, suggesting HBV occult infection. All samples were identified as subgenotype A1. Entries in patient records and the findings of this investigation suggest anti-HBc seroconversion during oncologic treatment. Age 50 years or over and use of a central catheter during therapy were associated with HBV exposure.

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https://doi.org/10.1016/j.htct.2018.11.008

Conclusion: The low frequency of hepatitis B immunized individuals, detection of HBV DNA in HBsAg negative samples, and the suggestion of HBV exposure during treatment evidenced the potential for health-related viral dissemination in people with oncohematological diseases in our region, reinforcing the importance of serological monitoring, vaccination against hepatitis B, and adoption of strict infection control measures in these individuals.

Introduction

Globally there are 257 million chronic carriers of the hepatitis B virus (HBV) who are at risk of developing cirrhosis and hepatocellular carcinoma.[1] HBV is classified into the *Hepadnaviridae* family.[2] By definition, HBV is a hepatotropic virus because it replicates within hepatocytes.[3] However, it can also infect and replicate in hematopoietic and lymphoid cells.[4]

HBV has been a concern among patients with hematologic malignancies, due to their multiple opportunities for infection.[5] HBV reactivation can occur due to immunosuppressive therapy, or those undergoing its immunocompromised state.[6] Because most of them are subjected to invasive procedures and blood transfusion, new infections can occur due to breaches in infection control practices during treatment[7] and/or unsafe blood[8] (AND HEWIT). Furthermore, HBV has been related to the pathogenesis of non-Hodgkin lymphoma (NHL).[9–11] Therefore, hepatitis B screening and vaccination have been recommended for these patients.[12,13]

Some investigations have shown a high prevalence of hepatitis B virus among carriers of hematologic malignancies.[13–15] In Brazil there is no data on the hepatitis B virus infection in this population. The objective of this investigation was to evaluate the epidemiology of HBV among carriers of hematologic malignancies in Goiás, Central Brazil.

Material and methods

This study was carried out between July 2010 and August 2012 among 322 carriers of Hodgkin or non-Hodgkin lymphomas and leukemia treated at two referral hospitals in Goiás, Central Brazil. These hospitals attend to 65% of patients with oncohematologic diseases in the State of Goiás.

The inclusion criteria were: being diagnosed with an oncohematologic disease (Hodgkin Lymphoma, Non-Hodgkin Lymphoma and Leukemia), aged 18 years or older and being in outpatient treatment. Patients infected with HIV were excluded.

All eligible individuals in outpatient treatment for oncohematologic diseases were invited to participate in the study. Those who agreed to participate were interviewed about sociodemographic characteristics and risk factors for HBV infection. Data on medical diagnostics, invasive procedures and previous HBV serology were obtained through medical records of participants.

After the interview, blood samples (10 mL) were collected to detect HBV serology as follows: HBsAg (Hepanostika HBsAg Ultra, Biomerieux, France), anti-HBs (Bioelisa anti-HBs, Biokit, Spain) and anti-HBc total (Hepanostika anti-HBc, Uni-Form, Biomerieux, France).

All positive samples of HBV DNA were also re-tested for HBeAg (ETI-EBK PLUS, Diasorin, Italy) and anti-HBe (ETI-AB-EBK PLU, Diasorin, Italy).

All HBsAg and/or anti-HBc positive samples were submitted for nucleic acid extraction, according to Niel et al.[16] HBV DNA detection was performed by the semi-nested PCR for pre-s/s region amplification, as previously described by Motta-Castro et al.[17] Nucleotide sequences of the pre-s/s region were obtained by direct sequencing with the BigDye Terminator 3.1 cycle sequencing kit (applied Biosystems, Foster City, Ca) and a set of specific primers. Sequencing reactions were analyzed on an ABI 3130 automated sequencer (Applied Biosystems). HBV sequence alignment was performed using the Clustal W program with 54 HBV sequences representing all HBV genotypes. Phylogenetic analysis was performed by the maximum likelihood method (bootstrap resampling test with 2000 replicates) in the MEGA v.6.0 software. The nucleotide sequences obtained in this study were deposited in GenBank under accession numbers MH268242 to MH268245.

Descriptive analyses and calculated population estimates and their confidence intervals were used for all the variables studied. The univariate and Poisson regression with robust variance were used to estimate predictors of HBV exposure. Variables with p value <0.20, sex, in addition to central catheter use and previous blood transfusion, were included in the model. The significance level used in the tests was 5%.

Results

Sociodemographic data revealed that most of the participants were male (55%), with white skin (50%), married (62.4%) and reported a low education level: 28.3% less than five years of schooling, 32.3% between 5 and 9 and the rest (39.4%) more than 9 years. The mean age was 49 years old (range 18–89 years; standard deviation: 16.64).

Among the 322 patients studied, 45 (13.97%) had been exposed to HBV. Of these, one (0.31%) was only HBsAg-positive, three (0.93%) were anti-HBc/HBsAg positive, 29 (9%) were positive for anti-HBc/anti-HBs and 12 (3.73%%) were only positive for anti-HBc. In addition, 28 (8.69%) were only positive for anti-HBs, suggesting previous HBV vaccination. A total of 249 participants were susceptible to HBV infection (Table 1).

According to oncohematologic disease, the HBV prevalence ranged from 3.70% among carriers of Hodgkin Lymphoma to 42.86% among those with acute myeloid leukemia (Table 2).

Table 1 – Prevalence of Hepatitis B virus markers among 322 carriers of hematologic malignancies in Goiania, Central Brazil.

Markers	Positive		CI 95%
	n	%	
HBsAg only	1	0.31	0.05–1.74
HBsAg and anti-HBc	3	0.93	0.32–2.70
Anti-HBc and anti-HBs	29	9.00	6.34–12.63
Anti-HBc only	12	3.73	2.14–6.40
Any HBV marker	45	13.97	10.61–18.19
Anti-HBs only	28	8.69	6.08–12.28

CI: confidence interval.

Only the carriers of acute lymphoid leukemia were not exposed to HBV.

All HBsAg and/or anti-HBc positive ($n=45$) samples were submitted for nucleic acid extraction for HBV DNA detection, that was found to be positive in 4 samples: one HBsAg/anti-HBc (carrier of acute myeloid leukemia), and three anti-HBc isolated (2 carriers of chronic lymphoid leukemia, and 1 carrier of chronic myeloid leukemia). The HBV DNA was successfully sequenced, and all samples were identified as genotype A1. All of them were retested for HBeAg and anti-HBe markers. The HBsAg reagent sample was also reagent for the HBeAg marker (sample 216). The anti-HBe marker was detected in one anti-HBc isolated sample (sample 48) (Table 3).

Patients who were only positive for anti-HBs were excluded from the analysis. Table 4 shows the bivariate analysis of potential factors associated with HBV exposure. Age 50 years or older, previous treatment with practical dentistry, previous sexually transmitted infection (STI), and non-condom use in the last sexual intercourse showed a p value <0.20, and were included in the Poisson regression model. In addition, central catheter use was included in the model. According to this model, age 50 years or older (adjusted PR: 2.64; 95% CI: 1.31–5.34); and use of central catheter (adjusted PR: 2.12; 95% CI: 1.07–4.19) during therapy were associated with HBV exposure (Table 5).

In 223/322 (69.25%) medical records, there was information on previous testing for HBV serological markers. However, in 8 out of 223 patients there was a disagreement between the results of this investigation and those which were reported in the medical records. According to the medical records, these eight patients were negative for HBV markers, but they were found to be anti-HBc positive in the screening for this study.

Discussion

The overall prevalence for hepatitis B virus infection in study participants [(13.97%, 95% CI: 10.61–18.19)] was similar to that estimated for the adult population in Brazil [11.6% (95% CI: 10.7–12.4)].[18] On the other hand, when comparing the prevalence of HBV due to oncohematologic disease, with studies conducted in countries with similar endemicity to Brazil, the frequency found in patients with chronic lymphoid leukemia [29.17% (95% CI: 14.92%–49.17%)] was almost five times greater than that found in patients with the same disease in Canada [6.3% (IC 95%: 3.79–10.31)].[19] For patients with non-Hodgkin lymphoma, the prevalence estimated in this study [17.17% (95% CI: 11.01–25.79)] was higher than that found in 554 cases in eight Western European countries [9.9% (95% CI: 7.71–12.7)],[20] however, lower than that found in Italy in 570 NHL carriers (24%).[21] Nevertheless, studies with more complex designs are necessary to understand the real significance of these differences.

All four HBV DNA positive samples were identified as A1 subgenotype. This genotype is common in sub-Saharan Africa, Northern Europe, West Africa, and India,[22] and studies show the circulation and predominance of this genotype in Brazil.[23]

HBV infection may decrease the efficacy of chemotherapy in patients with oncohematologic diseases and compromise liver function levels, as well as adversely affect the prognosis of these patients. On the other hand, chemotherapy may increase viral replication and induce hepatitis B reactivation, and serologic evaluation of HBV markers is recommended prior to initiation of immunosuppressive therapy.[24] Despite this, in 99 medical records there were no reports of previous HBV serological testing.

These findings are troubling because chemotherapy patients are immunosuppressed, in frequent contact with the hospital environment and at risk of acquiring healthcare-related infections. In cases of patients with inactive HBV infection, their disease may be reactivated, making them potential sources of viral dissemination.[25] In fact, outbreaks in oncological units are not uncommon when infection control measures are neglected.[7,26] Analysis of patient records reinforces this concern. In eight patients whose medical records revealed anti-HBc negativity during the cancer treatment period, the results of this study suggested seroconversion to anti-HBc. Therefore, although the study design does not allow us to infer causality, the association between the central venous catheter use and positive HBV markers suggests

Table 2 – Prevalence of HBV markers according to the oncohematologic disease in Goiás, Central Brazil.

Oncohematologic disease	Total	HBV+	%	CI 95%
Acute myeloid leukemia	12	03	25.0	8.90–53.23
Chronic myeloid leukemia	113	16	14.2	8.91–21.77
Acute lymphoid leukemia	2	0	–	
Chronic lymphoid leukemia	24	7	29.2	14.92–49.17
Hodgkin lymphoma (LH)	64	02	3.1	0.86–10.7
Non-Hodgkin's lymphoma	107	16	15.0	9.42–22.92

CI: confidence interval.

Table 3 – Characteristics of the four HBV-DNA positive patients with oncohematologic diseases.

Characteristics	Patient (sample)			
	48	77	216	326
HBsAg	NR	NR	R	NR
Anti-HBc	R	R	R	R
HBeAg	NR	NR	R	NR
Anti-HBe	R	NR	NR	NR
Genotype	A1	A1	A1	A1
Sex	Male	Male	Male	Male
Age	77	63	34	60
Disease	CLL	CLL	AML	CML

NR: non-reagent; R: reagent; CLL: chronic lymphoid leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia.

Table 4 – Analysis of potential variables associated with HBV exposure among carriers of oncohematologic diseases in Goiânia, Central Brazil.

Variable	Total	Pos.	HBV		%	x	p
			%	Neg			
Age							
<50	146	11	7.5	135	92.47		
≥50	148	34	23.0	113	76.87	13.51	<0.0001
Sex							
Female	130	16	12.3	114	87.7		
Male	164	29	17.7	135	82.3	1.62	0.204
Formal education (Years)							
≤4	86	12	14.0	74	86.0		
5–9	99	16	16.2	83	83.8	0.184	0.912
>9	109	17	15.6	92	84.4		
History of hepatitis in family							
No	218	30	13.8	188	86.2		
Yes	64	12	18.8	52	81.3	0.97	0.324
Central catheter for therapy							
No	248	37	14.9	211	85.1		
Yes	46	8	17.4	38	82.6	0.183	0.669
Previous blood transfusion							
No	190	28	14.7	172	84.3		
Yes	104	17	16.3	87	83.7	0.134	0.714
Previous surgery							
No	65	09	13.8	56	86.2		
Yes	229	36	15.7	193	84.3	0.137	0.711
Tatooing/piercing							
No	273	44	16.1	229	83.9		
Yes	01	4.8	20	95.2	95.2	1.940	0.164
Practical dentistry							
No	196	22	11.2	174	88.8		
Yes	98	23	23.5	75	76.5	7.56	0.006
Previous time in prison							
No	274	40	14.6	234	85.4		
Yes	20	05	25.0	15	75.0	1.55	0.212
Condom use in the last sexual intercourse							
No	69	05	7.2	64	92.8		
Yes	225	40	17.8	185	82.2	4.52	0.034
Previous STI							
No	223	29	13.0	194	87.0		
Yes	71	16	22.5	55	77.5	3.77	0.052

Table 5 – Multivariate analysis of risk factors associated with exposure to HBV (HBsAg and/or anti-HBc) in carriers of oncohematologic diseases in Goiânia, Goiás, Brazil, 2012–2014.

Variable	PR adjusted (CI 95%)[a]
Age ≥50 years	2.64 (1.31–5.34)
Practical dentistry	1.50 (0.85–2.64)
Non-condom use in the last sexual intercourse	2.22 (0.93–5.31)
Previous STI	1.29 (0.75–2.20)
Central cateter use	2.12 (1.07–4.19)

[a] Adjusted by age, sex, previous practical dentistry, condom use in last sexual intercourse and previous sexually transmitted infection, and central catheter use.

that the chemotherapy environment could have played a role in viral dissemination in these patients.

In this study, three patients were HBsAg positive and one presented a serological profile of acute infection and elevated viremia (HBsAg+/HBeAg+/anti-HBc-/HBVDNA+). Moreover, 25% (3/12) of the anti-HBc isolated samples detected HBV-DNA. This serological profile suggests occult HBV infection, defined by the persistence of viral DNA in HBsAg negative individuals.[27] Koo et al.,[28] reported a 5.2% HBV-DNA positivity in 58 anti-HBc samples isolated from lymphoma patients, a frequency lower than that found in the patients in this study (25%). Otherwise, this investigation did not detect HBV-DNA in anti-HBs+/anti-HBc+.[27] These results, therefore, confirm that the monitoring of these patients should not be restricted to the serological detection of HBsAg,[29] and highlight the importance of detection of HBV-DNA in anti-HBc samples. In fact, Yang et al.,[6] recently investigated 197 lymphoma patients and reported a higher frequency of HBV reactivation among patients anti-HBs−/anti-HBc+ at baseline, compared to the anti-HBs/anti-HBc−.

Only 28 (8.69%) participants presented a serological profile of previous vaccination, which was not indicated in any patient records. For immunocompromised individuals, as carriers of oncohematologic diseases, vaccination against HBV is highly recommended and should be performed, whenever possible, up to 14 days prior to the start of immunosuppressive therapy. Preferably, vaccination should not occur during the maximum immunodepression period, in order to obtain a better immune response.[24]

Considering the change in the epidemiological profile of HBV infection as a result of the implementation of universal vaccination against hepatitis B; the disease burden is gradually shifting to older age groups,[18] who in turn are at increased risk of oncohematologic diseases.[30] Indeed, in this study there was a gradient of HBV positivity for older individuals. Furthermore, of the four HBsAg positive patients, only one was younger than 49 years old.

History of STIs and non-use of condoms during last sexual intercourse were associated with exposure to HBV in the univariate analysis. Therefore, caregivers should take advantage of the treatment opportunity to undertake health promotion actions, including information on HBV transmission and safe sex practices.

Some limitations of the study should be considered in interpreting the results. The cross-sectional nature of the study precludes inferring causality. Therefore, the association identified in this study suggests, but does not necessarily confirm, cause and effect. Behavioral variables may suffer response bias due to the cultural and moral characteristics of the investigated group, which may be under- or overestimated. However, the results of this study show epidemiological plausibility, indicating accurate answers to these questions. Furthermore, the positivity of anti-HBc registered in medical records should be interpreted with caution, since patients were tested at different laboratories and information on the sensibility and specificity of the assays was not available.

The present investigation showed the potential for HBV nosocomial dissemination and hepatitis B reactivation among carriers of oncohematological diseases in our region, supporting the importance of hepatitis B vaccination, as well as adoption of infection control precautions and monitoring of patients at oncohematology services.

Conflicts of interest

The authors declare no conflicts of interest.

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