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ORIGINAL ARTICLE

FAMILIAL DISTRIBUTION OF HEPATITIS B VIRUS INFECTION IN ESPIRITO SANTO STATE, BRAZIL

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ABSTRACT

To evaluate the familial distribution of hepatitis B virus (HBV), a retrospective analysis of medical records of patients treated in Vitória, Espírito Santo, Brazil, was performed. Patients with markers of HBV infection who had a family member with evidence of HBV infection were index cases of each family. Of the 65 index cases, 26 (40%) had chronic hepatitis (CH), 13 (20%) liver cirrhosis (LC), 4 (6.1%) hepatocellular carcinoma (HCC), 20 (30.8%) were inactive carriers and two (3.1%) had immunity after contact with HBV. Among 275 family members, 226 had evidence of HBV infection, 171 of which were HBsAg positive and 55 had previous contact and immunity. HBsAg was significantly higher in consanguineous than non-consanguineous relatives (170/244 and 1/31, respectively, $p < 0.0001$) and among siblings of index cases. There were 2 to 12 affected individuals per family, involving one, two, or three generations. In 14/65 families, two or more cases of LC, CH, or HCC were observed, compromising up to three generations. Results demonstrate familial clustering of HBV in Espírito Santo in up to three generations and familial aggregation of severe forms of the infection. Family investigation of HBV is important, allowing early diagnosis and treatment before progression to advanced forms of the disease.

KEY WORDS: Chronic hepatitis; liver cirrhosis; hepatocellular carcinoma; viral transmission; familial aggregation.

INTRODUCTION

The familial distribution of hepatitis B virus (HBV) infection has been described worldwide since 1972 (Ohbayashi et al., 1972; Szmuness et al., 1973; Bruguera et al., 1974; Tong et al., 2013), including Brazil in Amazonian region (Brasil et al., 2003) and São Paulo (Carrilho et al., 2005).

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In the State of Espirito Santo, Brazil, familial clustering of HBV infection has been reported since the 1980s. Gonçalves et al (1984) described a case of HBsAg positive hepatocellular carcinoma (HCC) diagnosed during pregnancy with an unfavorable evolution to maternal and fetal death. HBsAg was positive in the blood of the fetus and in five of the eight children of the patient. Clustering of cases of HBsAg positive hepatocellular carcinoma also was reported in two families. In the first, two brothers were diagnosed with HBsAg positive hepatocellular carcinoma within a three-month interval. In the same family, two brothers were HBsAg positive, one with liver cirrhosis and the other with chronic hepatitis. In the second family, the first case of HBsAg positive hepatocellular carcinoma was diagnosed in a 31-year-old man, and the second case was diagnosed five years later in a 55-year-old sister. Among three other siblings, two were carriers of the hepatitis B virus (Gonçalves et al.,1986).

As serology for HBV is routinely performed on family members of patients treated at the University Hospital in the City of Vitoria, a review of records of these patients was carried out to expand information on familial transmission of hepatitis B in Espirito Santo State, which has areas of high prevalence of HBV.

MATERIAL AND METHODS

A retrospective analysis of the medical records of patients treated at the outpatient unit for hepatitis B at the Gastroenterology and Hepatology Department of the University Hospital of the Federal University of Espirito Santo, in Vitoria, the capital of the State, was carried out in the period between January 2018 and December 2020. In all patients diagnosed with hepatitis B, family investigation in husbands, wives, sexual partners, parents, siblings, and offspring is routinely performed, with a request for HBV serology. Medical records of 343 hepatitis B cases diagnosed in the period were reviewed and 65 patients had at least one communicant with evidence of HBV exposure. Each case in this group was included as an index case for each family. Data on gender, age, stage of chronic infection by the HBV, and clinical form of the disease (chronic hepatitis, liver cirrhosis, hepatocellular carcinoma) from index cases and family members investigated were annotated, including the degree of kinship with the index case.

Family members were classified as consanguineous (father, mother, grandparents, siblings, offspring, uncles, nephews, cousins) and non-consanguineous (husband, wife, brother-in-law, sister-in-law, son-in-law, daughter-in-law). To keep individual identity confidential, families were identified by numbers.

When necessary, frequencies were compared by the Chi-square test. All variables are presented with a 95% confidence interval, and a p value less than 0.05 was considered significant.

The study was approved by the Research Ethics Committee of the University Hospital (protocol 4.344.09; CAAE: 37202020.0.0000.5071).

RESULTS

Members of 65 families were investigated. Data on the index cases in each family are summarized in Table 1. The results of the search for serological markers for HBV infection and the clinical forms of infection in 275 family members are summarized in Table 2. Of these, 171 (75.6%) were chronic HBsAg carriers, and 55 (24.3%) had previous contact and immunity to HBV (HBsAg negative, anti HBc positive, and anti-HBs positive). Prevalence of HBsAg was significantly higher in consanguineous relatives than in non-consanguineous (respectively 170/244 and 1/31; p <0.0001) with a greater proportion among siblings than other relatives. The only HBsAg positive non-consanguineous relative had chronic hepatitis B and was the husband of a patient with chronic hepatitis B.

Table 1. Gender, age, and clinical presentation of 65 index cases of HBV infection identified at the University Hospital, Vitória, Espírito Santo State, Brazil.

Gender (N; %; 95% CI*)	
Male	32 (49.2; 37.5 – 61.2)
Female	33 (50.7; 38.9 – 62.5)
Age (Mean ± SD**;95%CI)	
Male	56.4 ± 11.0 (51.2-59.7)
Female	55.7 ± 11.7 (51.7-59.7)
Clinical presentation N (%;95% CI)	
Inactive Carrier	20 (30.8; 20.9 - 42.9)
Chronic Hepatitis	26 (40.0; 29.0 - 52.1)
Liver cirrhosis	13 (20,0; 20.9-42.9)
Hepatocellular Carcinoma	4 (6.1; 2.4-14.8)
Functional cure	2 (3.1; 0.8-10.5)

*CI= Confidence Intervals. **SD= Standard Deviation

Table 2. Markers of hepatitis B virus (HBV) and clinical presentation in 275 family members of 65 index cases diagnosed at University Hospital in Vitoria, Espírito Santo State, Brazil.

HBV markers	N (%; 95% CI*)
Negative for all markers	49 (17.8; 12.7-22.9)
HBV infection	226 (82.1; 77.2-86.2)
HBsAg positive	171 (75.6; 69.7-80.8)
HBsAg (-), anti-HBc (+), and anti-HBs (+) **	55 (24.3; 19.2-30.3)
Clinical presentation in 171 HBsAg (+) members	
Inactive carrier	92 (53.8; 46.3-62.1)
Chronic Hepatitis	50 (29.2; 22.9-36.4)
Liver Cirrhosis	21 (12.3; 8.2-18.4)
Hepatocellular Carcinoma	8 (4.6; 2.4-9.3)

*CI= Confidence Interval. **functional cure

Among the 65 index cases, 13 were HBeAg positive and 52 HBeAg negative. The frequency of HBV contact markers in family members in both groups was similar (in the positive HBe group: 34 had positive HBsAg and 10 had a functional cure; in the negative HBe group: 137 had positive HBsAg and 45 had a functional cure; p=0.7816).

The number of individuals with hepatitis B infection per family, including index cases, ranged from two to 12 (an average of 3.4 cases), with one generation involved in 25 families (38.46%), two generations involved in 32 families (49.2%), and three generations involved in eight families (12.3%).

In 14 out of the 65 families evaluated, a clustering of cases with advanced disease with two or more cases of hepatocellular carcinoma and/or cirrhosis affecting one, two, or three generations was observed (Table 3). In family six, the index case was a woman with chronic hepatitis B, whose mother died of hepatocellular carcinoma and who had an uncle with liver cirrhosis, four aunts with chronic hepatitis B, and one aunt inactive carrier. In family 12, there was a diagnosis of two cases of hepatocellular carcinoma, in two male brothers. In family 30, the index case was a woman with HBsAg positive cirrhosis, who had two brothers with HBsAg positive cirrhosis and three offspring and one sister inactive carriers of the virus (HBeAg negative chronic infection). In family 34, the index case was a woman with cirrhosis who had six HBsAg positive sisters (one with cirrhosis, two with chronic hepatitis, and three inactive carriers), a daughter with chronic hepatitis, and two sons with inactive HBV infection. In family 46, we observed a cluster of severe cases in three generations. The index case was a man with chronic hepatitis B whose father had died of liver cirrhosis, the sister underwent liver

transplantation for HBV associated cirrhosis and hepatocellular carcinoma, a daughter, a son, and a nephew had chronic hepatitis B and another nephew was a carrier of the hepatitis B virus.

Table 3. Occurrence of advanced liver disease in two or more members of the same family among relatives of 65 index cases with hepatitis B virus infection diagnosed at University Hospital in Vitoria, Espírito Santo State, Brazil

Family identification	Number of relatives with advanced disease				Generations affected
	HCC	LC	CH	Total	
1	1	2	1	4	1
6	1	1	5	7	2
7	1	1	2	4	2
12	2	0	0	2	1
14	0	2	0	2	2
20	1	1	0	2	1
22	0	2	0	2	2
30	0	3	0	3	2
34	0	2	3	5	2
43	0	2	0	2	2
45	0	2	2	4	1
46	1	1	4	6	3
54	1	1	0	2	2
62	0	2	0	2	2

HCC= hepatocellular carcinoma; LC= liver cirrhosis; CH= chronic hepatitis

In five families, there were six HBsAg positive fathers, who had HBsAg positive offspring. The investigation revealed that in two cases, the wives had evidence of previous contact and immunity to the B virus; in three, the wife's serological status was unknown, and one had vaccination immunity. In one of the families, the HBsAg positive father (generation 1) died of cirrhosis and had eight children, two HBsAg positive. One HBsAg positive son (generation 2) with chronic hepatitis, has two children both with chronic hepatitis B.

DISCUSSION

Results demonstrated that there is a high rate of familial clustering of HBV infection in Espirito Santo, confirming studies from different parts of the world, including Brazil. Family clustering of HBV infection in two or three generations, observed in 40 families (61.5%) reinforces the hypothesis

of family transmission, as suggested by Yang et al. (2018). The presence of clinically significant liver disease (chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma) in 34.9% of family members reinforces the importance of family investigation for early diagnosis and treatment of hepatitis B among relatives of patients with HBV infection. The occurrence of advanced cases of the disease among relatives in 14 families confirms what had already been observed in Espírito Santo (Gonçalves et al., 1986) and reported in the literature (Ohbayashi et al., 1972; Tong et al., 2013; Yang et al., 2018). In fact, a case-control study in Taiwan demonstrated that HBsAg-positive patients with a family history of hepatocellular carcinoma in a first-degree relative are at significantly increased risk for HCC when compared to HBsAg-positive patients without a family history of HCC (Yu et al., 2000). Genetic factors may be involved in susceptibility to cirrhosis and familial HCC (Chan et al., 2004). More recently, a family history of cirrhosis or HCC has been recognized as a determining factor in the natural history of HBV infection and used as an independent criterion for the indication of treatment for chronic hepatitis B, even in the absence of classic criteria, according to various treatment protocols such as Brazilian Clinical Protocol and Therapeutic Guidelines for Hepatitis B and Co-infections (Brasil, 2017) and guidelines published by the American Association for the Study of the Liver (Terrault et al., 2018) and the European Association for the Study of the Liver (EASD, 2017).

Transmission of the B virus among family contacts appears to be important in high-endemic regions. The demonstration that HBsAg positivity was significantly higher among consanguineous relatives, especially siblings, offspring, and mothers, confirms several studies demonstrating the importance of vertical transmission in the intrafamilial spread of HBV (Gonçalves et al., 1984; Gonçalves et al., 1986; Chakravarti et al., 2005).

Although maternal-fetal transmission is the most frequent form of vertical transmission of HBV infection, father-to-child transmission may also play a role in transmission. In five families studied here, six cases of HBsAg positive fathers with HBsAg positive offspring were observed. In three of these studied families, mothers were HBsAg negative, suggesting transmission of the B virus from the father to the children. Integration of HBV DNA into the Y chromosome (Huang et al.,2003) was reported, which was not confirmed in a Chinese study that did not demonstrate the integration of HBV DNA into any tissue of 164 fetuses born to HBsAg positive fathers and HBsAg negative mothers (Cai et al., 2013). However, some studies demonstrate that HBsAg-positive children with HBsAg-negative mothers may acquire the infection from HBsAg-positive fathers (Yang et al., 2018) demonstrated by the identical genotype between fathers and children (Takegoshi & Zhang, 2006). Horizontal transmission through contact with skin lesions, sharing contaminated toothbrushes or razor blades may be the main route of transmission of infection from father to offspring (Lobato et al., 2006).

It is possible that horizontal transmission in childhood may also be responsible for intrafamilial transmission. Childhood transmission could occur due to close contact with HBsAg-positive family members. In fact, HBsAg negative children under one year of age become progressively positive, reaching a peak in ages from five through nine years (Yao, 1996). In Brazil, Lobato et al (2006) studying household contacts of HBsAg positive and negative pregnant women found that the prevalence of HBsAg positive is significantly higher in contacts of HBsAg positive women, with a higher prevalence among siblings. They also observed a higher frequency of the habit of sharing toothbrushes among the contacts of HBsAg positive pregnant women and considered this to be one of the factors associated with intrafamilial transmission of the HBV in areas with a high prevalence of infection.

In conclusion, the results show familial clustering of hepatitis B in Espírito Santo State, with the infection observed in up to three generations, reinforcing the hypothesis of vertical transmission of the disease. In addition, familial aggregation of advanced forms of the disease was observed, suggesting the possible existence of genetic factors in the susceptibility and evolution of the infection. Therefore, family investigation of every diagnosed case of hepatitis B is extremely important, allowing the diagnosis and treatment of cases in the family before progression to more advanced forms of the disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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