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Searching for chronic hepatitis B patients in a low prevalence area – role of racial origin

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Abstract

Background: Clinical studies for testing new drugs against hepatitis B ought to be carried out in low prevalence areas despite difficulties on patient recruitment. In such areas, relatives of chronic hepatitis B patients are considered to be at risk of acquiring the hepatitis B virus (HBV). The aim of this study was to evaluate the prevalence of HBV markers (anti-HBc, HBsAg and anti-HBs) in familial members of chronic hepatitis B (CHB) patients according to their origin (Asian or Western) in a low prevalence area, the city of São Paulo, Brazil.

Methods: Twenty three Asian CHB probands and their 313 relatives plus 31 CHB probands of Western origin and their 211 relatives were screened for HBV serological markers; the study was carried out in the outpatient clinic of the University of São Paulo School of Medicine.

Results: Mother to child transmission was greater in the Asian group whereas sexual transmission was more frequent in the Western group ($p < 0.0001$). Anti-HBc was positive in 90% and 57% of the Asian and Western parents ($p = 0.0432$) and in 97% and 33% of the Asian and Western brothers ($p = 0.0001$), respectively. HBsAg was more frequent among the Asian (66%) than the Western (15%) mothers ($p = 0.0260$) as well as among the Asian (81%) than the Western (19%) brothers ($p = 0.0001$). We could detect 110 new HBsAg-positive subjects related to the 54 index patients, being the majority (81%) of Asian origin.

Conclusion: In low prevalence area of hepatitis B, family members and household contacts of chronic HBV carriers are at high risk for acquiring hepatitis B.

Background

Hepatitis B virus (HBV) infection is a major health problem. Of the 2 billion people who have been infected with the hepatitis B virus (HBV), more than 350 million have chronic (lifelong) infections. These chronically infected persons are at high risk of death from cirrhosis of the liver and liver cancer, diseases that kill about one million persons each year. Treatment with antiviral drugs can slow the progression of the liver disease to cirrhosis and thus avoid or delay the necessity of liver transplantation. Therefore, early hepatitis B diagnosis could benefit many asymptomatic patients.

In the last decade new antiviral drugs for hepatitis B have emerged and revolutionized the treatment of its chronic from. Lamivudine is a nucleoside reverse transcriptase

inhibitor and is currently used in many countries for the hepatitis B treatment. Despite the potent action of this drug, the development of viral resistance prompted the search for new therapeutic agents and new strategies to treat hepatitis B [1]. Adefovir is a new nucleoside analogue that has shown to be effective in cases of lamivudine-resistant virus [2-4]. Even considering these data, the report of an HBV variant resistant to adefovir [5] adds weight to the need for developing new therapies to treat CHB. To this end, several clinical trials with monotherapy and drug-combination regimens are in progress worldwide [6].

A critical step of the drug approval process is patient recruitment, comprising 25% of the time of clinical trials. To expedite the approval process of anti-HBV drugs, there is a growing interest in clinical trials in Latin America and other HBV emerging regions. In Brazil, the prevalence of HBsAg varies greatly through out its large territory – being high at the Amazon basin, medium at the northeast and low at the southeast and south regions of the country [7]. Although the prevalence of HBsAg is low in blood donors (0.36%) of the low prevalence area of São Paulo, among risk groups for HBV infection in the same city, HBsAg prevalence can be very high.

The aim of the present study was to evaluate the prevalence of HBV markers (anti-HBc, HBsAg and anti-HBs) in family members of patients with chronic hepatitis B – in a low prevalence area – according to their origin, Western or Asian.

Methods

All study procedures were approved by the institutional review board of the Department of Gastroenterology of the University of SãoPaulo School of Medicine, São Paulo.

Patients

The prospective surveillance program in relatives of patients with chronic hepatitis B (CHB) comprised clinical assessment and serological screening. The criterion for proband (index case) inclusion in the cohort was being a chronic hepatitis B carrier, defined by HBsAg positivity for longer than 6 months. The exclusion criteria were: hepatitis C infection, hepatitits D infection or history of alcoholism. Using these criteria, a total of 54 out of 59 consecutive patients with chronic hepatitis seen in our Department could be included. Of these CHB index cases, 23 were identified as Asian descendent (Japanese or Chinese) and 31 as Westerns. All family members of the probands were tested for HBV serological markers: 211 and 313 relatives of the oriental and occidental origin, respectively.

Mode of HBV transmission

The mode of HBV transmission was classified by the following clinical and serologic criteria:

a) Probably mother to child: (i) when mother presented anti-HBc and anti-HBs positive and familial history of hepatitis B-related diseases or (ii) in the absence of serologic history of hepatitis B-related diseases in the family;

b) Mother to child: when the mother was (i) HBsAg positive or (ii) deceased due to HBV-related hepatitis, liver cirrhosis or hepatocellular carcinoma or (iii) the mother presented history of acute hepatitis B near partum;

c) Sexual (horizontal): (i) when mother presented anti-HBc and anti-HBs negative or anti-HBs positive due to vaccination or (ii) absence of familial history of HBV-related liver diseases and the subject presented risk factors for contamination (e.g.: drug user, promiscuity, blood transfusion) or (iii) spouse positive for HBsAg or (iv) absence of familial HBV-related diseases;

d) Intrafamilial: father or brother or sister were chronic HBV carriers;

e) Unknown: not in the above classifications or absence of data.

Serology assays

The presence of the antibodies, anti-HBc and anti-HBs, and the antigen HBsAg in serum was determined by enzyme-immunoassays from ABBOTT LABORATORIES (U.S.A).

Statistical analysis

All data are expressed as means ± standard deviation (SD). The Student *t* test was used to analyze the significance of age. The Pearson x^2 was used to test significance of proportions between the ethnic groups when the expected frequencies exceeded 5, otherwise Fisher Exact test was used. A p value of <0.05 was considered significant. Data analysis was performed with the Epi Info statiscal package [8].

Results

Demographic characteristics

The demographic characteristics of the probands are shown in Table 1. Sex and age parameters were comparable in the Asian and Western study groups. Both groups presented a higher proportion of the male gender, although among the Asian patients the fraction of women was slightly higher than among the Western counterparts. Among the Asian probands, all except one were Japanese descendent. Table 2 shows the demographic characteristics of the family members; sex and age parameters were comparable in the Asian and Western groups.

Table 1: Demographic characteristics of probands

Variable	Probands		
	Asian	Western	p
n	23	31	
Male	15 (65.2%)	25 (80.6%)	0.3344
Age (mean ± SD)	42.8 ± 10.5	42.9 ± 16.8	0.9120

[probands are HBsAg-positive chronic hepatitis B index cases]

Table 2: Demographic characteristics and consanguinity of relatives

Variable	Relatives		
	Asian	Western	p
n	313	211	
Male	164 (52%)	97 (46%)	0.8120
Age (mean ± SD)	29.9 ± 18.2	31.3 ± 19.6	0.5833
Consanguinity	237 (76%)	157 (74%)	0.1737

Table 3: Prevalence of anti-HBc, HBsAg and anti-HBs in relatives of CHB probands

Markers	Asian	(%)	Western	(%)	p
Anti-HBc+	181/305*	59.3%	77/209**	36.8%	<0.0001
HBsAg+	89/313	28.4%	21/211	9.9%	<0.0001
Anti-HBc+/ Anti-HBs+	80/305*	26.2%	54/209**	25.8%	0.9977
Isolated anti-HBc+	12/305*	3.9%	2/209**	0.9%	0.0782

* anti-HBc was not done in 8 relatives; ** anti-HBc was not done in 2 relatives.

Ethnic influence on prevalence of HBV infection among relatives of chronic HBV carriers

Table 3 summarizes data collected from the patients; notable differences exist in the prevalence of anti-HBc and HBsAg among Asian and Western relatives from chronic hepatitis B patients. Positivity for anti-HBc was higher among Asian (59.3%) than among Western (36.8%) relatives ($p < 0.0001$). Also, HBsAg-positive serum was found in 28.4% and 9.9% of the Asian and Western relatives, respectively ($p < 0.0001$).

Comparing Asian and Western family members that entered in contact with hepatitis B virus, more Asians presented HBsAg positive. On the other hand, more Western relatives seroconverted to anti-HBs positive (Table 4).

Familial relation and prevalence of HBsAg

Concerning the degree of familial relation, anti-HBc was positive in 90% and 57% of the Asian and Western parents ($p = 0.0432$) and in 97% and 33% of the Asian and Western brothers ($p = 0.0001$), respectively. HBsAg was more frequent among the Asian (66%) than among the Western (15%) mothers ($p = 0.0260$) and, even more so, among the Asian (81%) than the Western (19%) brothers ($p = 0.0001$). Likewise, the progeny of the Asians (28%) presented more HBsAg than of the Westerns (7%; $p = 0.0467$).

Mode of HBV transmission to probands

The "mother to child" mode of HBV transmission was the most important one in the Asian probands; whereas the "sexual" mode was the predominant known way of transmission in the Western group ($p < 0.0001$); see Table 6.

Table 4: Prevalence of anti-HBs and HBsAg among relatives with anti-HBc positive

Markers	Asian	(%)	Western	(%)	p
HBsAg+	89/181	49%	21/77	27.2%	0.0018
Anti-HBc+/ Anti-HBs+	80/181	44%	54/77	70.1%	0.0018
Isolated anti-HBc+	12/181	6.6%	2/77	2.5%	0.2416

Table 5: Prevalence of anti-HBc, HBsAg and anti-HBs in different familial category

	Anti-HBc+			HBsAg+			Anti-HBs+ plus anti-HBc +		
	Asian n (%)	Western n (%)	p	Asian n (%)	Western n (%)	p	Asian n (%)	Western n (%)	p
Parents	18/20 (90%)	12/21 (57%)	0.0432	8/20 (40%)	3/21 (14%)	0.1323	10/20 (50%)	9/21 (43%)	0.8845
Mothers	9/9 (100%)	7/13 (54%)	0.0941	6/9 (66%)	2/13 (15%)	0.0260	3/9 (33%)	5/13 (38%)	1.0000
Fathers	9/11 (82%)	5/8 (62%)	0.6026	2/11 (18%)	1/8 (12%)	1.0000	7/11 (64%)	4/8 (50%)	0.6576
Brothers/ Sisters	58/60 (97%)	14/42 (33%)	<0.0001	49/60 (81%)	8/42 (19%)	<0.0001	5/60 (8.3%)	6/42 (14%)	0.3534
Sons/ Daughters	10/29* (31%)	12/52*** (23%)	0.3975	9/32 (28%)	5/54 (7%)	0.0467	0/29* (0%)	7/52*** (13%)	0.0460
Spouses	15/17 (88%)	18/30 (60%)	0.0888	0/17 (0%)	1/30 (3%)	1.0000	14/17 (82%)	16/30 (53%)	0.0942
Others	80/179** (45%)	21/64 (33%)	0.1317	23/184 (12%)	4/64 (6%)	0.2502	51/179** (28%)	16/64 (25%)	0.787

*anti-HBc was not done in 3 relatives, ** anti-HBc was not done in 5 relatives, ***anti-HBc was not done in 2 relatives.

Table 6: Transmission mode of HBV among the probands

Mode	Asian	Western	*p* =
Probably mother to child	03	03	
Mother to child *	**12**	**02**	***0.0001**
Sexual (horizontal)*	**0**	**11**	
Intrafamiliar	02	03	
Unknown	06	12	
Total	23	31	

Discussion

The Japanese oversea immigrants have a history exceeding more than 100 years. Today, there is an estimate of 2.5 million Japanese-descendent people living outside Japan, of whom 1.3 million are in Brazil and one million in the United States [9].

Overall, the US population has approximately 0.2% of HBsAg positive individuals, but figures are different within ethnic groups. African Americans presented higher prevalence than Caucasians and Asian Americans even higher, especially the immigrants from China and Southeast Asia [10]. In Brazil, data on prevalence of hepatitis B among Asian descendents as a comparative study between different ethnic groups are scarce and not precise. In the present study, Asian relatives from patients with chronic hepatitis B (CHB) have shown higher anti-HBc and HBsAg prevalence than that observed in family members of patients from Western origin (Table 3). These results are very similar to the presented by others and to the predicted and observed prevalence from the mathematical model developed by Carrilho in 1987 [11-14].

At the "Hospital das Clínicas", research on familial HBV carriers began in 1971, when Carrilho and collaborators studied 19 Asian and 26 Western CHB patients and 165 and 186 respective relatives [14]. The latter study found that, altogether, the prevalence of HBsAg and anti-HBs was 135/165 (81.8%) in the Japanese and 68/186 (36.5%) in the occidental relatives ($p < 0.0001$). These

data are similar with those of the present study which, in turn, may also be confirmed by the mathematical model described by Carrilho [14].

It is noticeable in the present surveillance that 110 cases of HBsAg-positive individuals – the majority of Asian origin (Table 3) – were identified, whom otherwise would not have been diagnosed. Further study comparing the natural course of chronic hepatitis B in these populations is needed to assess the benefit of early detection of the disease.

The findings of a greater prevalence of HBsAg among the Asian families and, for the Western equivalents, a higher prevalence of anti-HBs suggest the longer state as chronic carriers for the Asians (Table 4). This may be due to the age of acquisition of the disease, which may influence the prognosis [15]. Children infected by vertical route (mother to child) may have greater tolerance to HBV with less hepatic damage, but greater prevalence of the chronic stage [16]. In fact, when we analyzed the mode of transmission of HBV in the proband groups (Table 6), it was observed that "mother to child" transmission was greater among the Asian patients and "sexual" transmission among the Western ones. Yet, it is important to mention that notable differences exist in the prevalence of acute flares of hepatitis in Asian and Western patients [17]. Studies in patients with CHB have shown more serological fluctuation in Asians than in patients in the United States [17]. In a study with 224 HBeAg positive Asian patients, flares of disease activity occurred in 40% but, unlike observed for the Western counterparts, this seldom led to seroconversion or to a sustained virologic response [17], what is in agreement with our results. The differences in the natural history of the infection in Asian and Western patients get particularly relevant when deciding on the need of antiviral treatment.

The marker anti-HBc was more frequent among Asian parents and brothers and the HBsAg, in turn, was more so in Asian mothers, brothers and sons (Table 5). These differences are significant and suggest, specially for the Asian subjects, that vertical or peri-natal transmission from mothers are the most significant way of acquiring HBV infection. The importance of familial screening for hepatitis B among the brothers and sisters of the Asian probands is highly endorsed by the finding of 81% HBsAg positive among their brotherhood.

While anti-HBc is the principal marker for HBV prevalence study in any population, anti-HBs is the hallmark of immunity conferred by vaccination or recovery from HBV infection. In the present study, for economical reasons, anti-HBs was checked only in those who were anti-HBc positive, thus investigating only the recovery cases. Since extended hepatitis B vaccine program was introduced in low prevalence areas in Brazil only in 1998 and vaccine was available for risk groups only, it remains important to evaluate the vaccine coverage in those areas.

In conclusion, Asian relatives from chronic HBV carriers have presented a greater prevalence of HBV markers when compared to Western equivalents. More Asian family members were HBsAg positive while more Western relatives presented anti-HBc and anti-HBs positive. Considering that hepatitis B can be asymptomatic, the present results emphasize the importance of screening the families of the CHB carriers, increasing the chances of a better treatment outcome and helping to halt the spread of this infectious disease.

Competing interests
None declared.

Authors' contributions
SKON conceived, designed, carried out the entire study in addition to the standardization of the protocol and preparation of the manuscript. FJC, RAC, MEN and LCS participated in the design of the study, preparation of the manuscript and performed the statistical analysis. All authors read and approved the final manuscript.

List of abbreviations
Anti-HBs, Hepatitis B surface antibody

Anti-HBc, Hepatitis B core IgG antibody

HBV, Hepatitis B Virus

HBsAg, Hepatitis B surface antigen

CHB, chronic hepatitis B

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