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Original Article

Role of HLA-B7, B8, B27, and B51 in Protection against Hepatitis B Virus Infection

M. Najafizadeh, N. Farhadi[1], B. Sarkari[2]

Department of Microbiology and Immunology,
Azerbaijan Medical University,
Baku, Azerbaijan.
[1]Department of Physiology,
School of Medicine,
Yasuj University of Medical Sciences,
Yasuj, Iran.
[2]Department of Parasitology and Mycology,
School of Medicine,
Shiraz University of Medical Sciences,
Shiraz, Iran.

Correspondence:
Bahador Sarkari PhD,
Department of Parasitology and Mycology,
School of Medicine,
Shiraz University of Medical Sciences,
Shiraz, Iran.
Tel\Fax: +98 711 2305291
Email: sarkarib@sums.ac.ir
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Abstract

Background: It has been argued that unprecedented degree of human leukocyte antigen (HLA) loci polymorphism within a population is required to avoid the devastating effects of infectious diseases. The present study was conducted to determine the associations between some of HLA class I genes and the outcome of hepatitis B virus (HBV) infection.

Methods: Using sequential sampling method, 64 individuals were selected and categorized into two groups according to their clinical and serological profiles. The patients in the case group were 27 patients with chronic HBV infection and the controls were 37 individuals considered as HBV natural convalescent who recovered from HBV infection. Antibodies against HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) were assessed to exclude primary HBV infection. Individuals with viral clearance were positive for anti-HBs and anti-HBc without the presence of HBsAg at two time points. HLA typing was performed by serological method. Collected data were analyzed by SPSS software version 13.

Results: The most frequent HLA antigens among the studied subjects were B51 (40. 1%), B27 (14.1%), B8 (12.5%), and B7 (10.9%). A significant correlation was found between HBV persistence and HLA-B27 ($P<0.05$). The association between other HLAs (HLA 7, 8, 57) with HBV clearance was not significant. The two studied groups were statistically different in sex but not in age.

Conclusion: Findings of the present study demonstrated an association between HLA class I and outcome of HBV infection where HLA B27 was linked to an increase in HBV persistence. These findings support the hypothesis that HLA class I-restricted cytotoxic T cells play an important role in HBV chronicity.
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Keywords ● HLA ● hepatitis B ● genetic protection

Introduction

Chronic hepatitis B affects an estimated 350 million of world population and is the leading cause of cirrhosis and hepatocellular carcinoma.[1,2] Infection with hepatitis B virus (HBV) in adulthood results in viral persistence and development of chronic hepatitis in 5-10% of cases, but factors that determine viral persistence or clearance are not

well understood.[3] Outcome after acute hepatitis B virus (HBV) infection and its course may be influenced by the host immune response.[4,5,6] Host genetic factors and environmental factors including hepatitis B virus genotype are widely viewed as common basis of the different outcomes of HBV infection.[7,8] The variable pattern and clinical outcome of the infection were mainly determined by virologic, host immunological, genetic, and experimental factors.[9]

The immune response genes are human leukocyte antigen (HLA)-linked and encode structures that allow immune functions.[10] HLA molecules play a key role in the selection and establishment of the antigen-specific T cell repertoire and play a major role in the subsequent activation of those T cells during the initiation of an immune response.[11] The immune response is coordinated by the HLA class I and class II molecules, which present foreign antigens to $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, respectively.[3,10,12]

HLA may be involved in the chronicity of hepatitis B virus infection and plays an important role in immunological reaction to it.[1,7] Most of the reports of human genes associated with HBV infection have currently focused on HLA associations.[9] The genes encoding these molecules are the most polymorphic in the human genome and are ideal candidates for the investigation of association with HBV outcomes.[3]

It has been argued that unprecedented degree of HLA loci polymorphism within a population is required to avoid the devastating effects of infectious diseases, which have been the major causes of mortality during mammalian evolution and remain the most serious threat to health in developing countries.[13] The opening questions include which human genes are important in infection and how to find them.[6] Clinical utility will only arise when genetic-based disease markers are available to predict which patients will get progressive liver disease or which patients will respond to a given treatment.[13] Thus, this study was conducted to determine associations between some of HLA class I genes with the outcome of HBV infection. We studied the distribution of HLA B7, B8, B27, and B51 in patients who developed natural immunity against HBV and those with chronic hepatitis B.

Subjects and Methods

Participants of this study were the people referred to Iran Red Crescent Society clinic in Baku, Azerbaijan Republic. Using sequential sampling method, 64 individuals were selected and divided into two groups according to their clinical and serologic profiles. Case group consisted of 27 patients with chronic HBV infection and controls were 37 subjects considered as HBV natural convalescent who recovered from an HBV infection. The patients in the case group were considered infected with HBV if they tested positive for hepatitis B surface antigen (HBsAg) twice. The controls were eligible to be tested for viral clearance if they had (i) a baseline negative HBsAg test, (ii) no history of HBV vaccination (iii) not received any treatment for HBV infection. Antibodies against hepatitis B core antigen (anti-HBc) and HBsAg (anti-HBs) were assessed to exclude primary HBV infection. Individuals with viral clearance were positive for anti-HBc and anti-HBs without the presence of HBsAg at twice evaluations. All serum specimens were stored at -70 °C until testing for HBV serology using commercially available kits DIA-Pro, Italy and based on manufacturer's instruction. HLA typing was performed by serological method using Terasaki's microlymphocytotoxicity plates (Biologic Analyzer system GmbH Germany), based on manufacture's instruction. Collected data were analyzed by SPSS software version 13. ANOVA was used to compare means of more than two independent groups. Chi-square (χ^2) test was used to evaluate the HLA differences between the patients and control groups. Associations between the quantitative data were studied by correlation analysis. The level of significance in all cases was set at a two-tailed $P<0.05$.

Results

HBV clearance was found to be associated only with HLA-B27. Viral clearance has occurred in 5.5% of controls with HLA-B27 whereas 26% of patients with HBV infection had HLA-B27 ($P<0.05$; table 1). For HLA-B7, recovery from HBV was found in 13.5% of cases while virus persistence was seen in 7.5% of cases. Our findings showed that recovery from HBV infection happened in 13.5% of controls and 11% of patients with HBV infection who had HLA-B8. Also the results showed that 40.5% of controls and 40.7% of patients had HLA-B51. However, these differences in patients and control groups were not statistically significant for HLA-B7, B8, and B51 ($P>0.05$; table 1). The most frequent HLA antigens among the subjects were B51 (40.6%), B27 (14.1%), B8 (12.5%), and B7 (10.9%).

Table 1: HLA-typing features of patient and control groups.

HLA	Control			Patient			Total		
	Negative	Positive	Percent	Negative	Positive	Percent	Negative	Positive	Percent
HLA-B7	32	5	13.5	25	2	7.4	57	7	10.9
HLA-B8	32	5	13.5	24	3	11.1	56	8	12.5
HLA-B27	35	2	5.4	20	7	25.9	55	9	14.1
HLA-B51	22	15	40.54	16	11	40.74	38	26	40.6

Regarding the demographic characteristics of the participants, mean age of the patients and healthy controls were 32.26 ± 14.20 and 37.95±12.44 years respectively. The two studied groups were statistically different in sex ($P<0.05$) but not in age ($P>0.05$).

Disscussion

In this comprehensive study of HLA class I genetic effects on the outcome of HBV infection in Azerbaijanis, B27 was associated with an increase in HBV persistence. Recovery from hepatitis B virus (HBV) infection depends on the cellular immune responses.[13] There is strong evidence in HBV infection that host genetic factors play a major role in determining the outcome of infection. The identification of inheritance of HLA genes is associated with increased risk of the disease.[14] It is notable that overall, the class I alleles have the strongest associations, suggesting that the $CD8^+$ cytotoxic T lymphocytes are important in determining viral clearance or persistence. These findings concur with the recent demonstration that chimpanzees acutely infected with HBV were unable to eliminate the virus.[3] There are several prominent disease associations with class I alleles including the spondyloarthropathies with HLA-B27.[11] In autoimmune diseases with an infectious etiology, it is likely that immune responses to peptides derived from the initiating pathogen are bound and presented by particular HLA molecules to activate T lymphocytes that play a triggering or contributory role in disease pathogenesis.[11] The key role of HLA class I and II-encoded molecules in antigen presentation has naturally generated the hypothesis that polymorphism at these loci may explain the variation in outcomes from infectious diseases and the development of autoimmune diseases.[13]

On the contrary, this study showed conflicted results for other HLA B7, B8, and B51 suggesting an increased effect in HBV clearance but without any significant association (table 1). A number of early studies reported strong associations between specific major histocompatibility complex (MHC) class I and chronic HBV infection. These associations were not reproducible, as illustrated by the study of Mota in Argentina reporting an association of Bw35, with persistence, and Van Hattum reporting that Bw35 was associated with self-limiting infection.[11,12] Hwang indicated that alleles of A33, and DR7, are associated with HBV chronicity among Koreans.[13] B*08 and its extended haplotype have been associated with other immune-mediated diseases, including autoimmune hepatitis.[3] Karan showed that HLA-A24 and Cw1 were associated with low risk for HBV-related chronic liver disease and HLA- B13, B8, DR7, DR13 and DQ3 were associated with high risk for chronic HBV infection in the Turkish population.[9] In other study in the chronic hepatitis group, CW6, DRB5, and DQB1*05 antigens were significantly more frequent than in the control group. And B8, CW7, DRB1*03 and DQB1*02 antigens were more frequent in the naturally immune group.[4]

Processing of antigenic peptides presented by HLA class I molecules involves the transport associated with antigen processing (TAP) molecules. A Japanese study suggested that polymorphisms in the TAP2 gene influenced the progression of liver disease.[14]

There are a number of reasons for studying the associations of MHC polymorphisms and the outcome of infection. Biologists are looking for an explanation why some patients recover from infection with no sequel while others develop chronic hepatitis, end-stage liver disease, and hepatocellular carcinoma. Immunologists are looking for mechanisms which confer protective immunity to the infection, and clinicians are looking for prognostic markers to guide the management of individual patients.[15]

Findings of this study support the hypothesis that human leukocyte antigen class I-restricted cytotoxic T cells play an important role in HBV chronicity. Further studies including the multi-cohort studies are needed to clarify these preliminary associations and to identify other potential candidate genes.

Conflict of Interest: None declared

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