

The Role of HLA Antigens in Chronic Hepatitis B Virus Infection

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Abstract

Objective: To investigate the mechanism underlying the development of chronic hepatitis B virus infection (HBV) in Turkish population using HLA tissue typing.

Methods: The study group I consisted of 20 patients with HBV- related chronic liver disease (cirrhosis, chronic active hepatitis or chronic persistent hepatitis). The study group II included 30 HBV chronic carriers. The control group consisted of 50 healthy subjects with negative serologic markers for HBV. HLA typing was performed by Terasaki's microlymphocytotoxicity method.

Results: The frequencies of HLA-DR13 and DQ3 were significantly higher in the patients with HBV-related chronic liver disease compared to those of control group. The absence of HLA-A24 and CW1 was also significant in group I. The frequencies of HLA A2, B8, B13, CW3, DR13 were significantly higher in group II compared to the control group. There were increased frequencies of HLA- B8, B13, DR7, DRI 3, and DQ3 in both group I and group II.

Conclusion: HLA-A24 and Cw1 were associated with low risk for HBV-related chronic liver disease and HLAB13, B8, DR7, DR13 and DQ3 were associated with high risk for chronic HBV infection in the Turkish population (JPMA 52:253; 2002).

Introduction

Hepatitis B virus (HBV) infection may result in a number of conditions from asymptomatic carriage to acute or chronic liver failure. About 20-60 percent of the Turkish population is infected with HBV likewise South-Eastern Europe, Middle East, Mediterranean Region, Central Asia, Japan and Southern America. In 2-7 percent of the infected people, virus is not cleared^{1,2}.

The outcome of HBV infection can be determined by several factors like virulence of the viral strains and the host immune response. Variation in immune response is often associated with polymorphism of the major histocompatibility complex (MHC). Class I molecules of MHC include antigens encoded by genes in the HLA A, B and C loci, whereas class II molecules include those encoded by genes in the HLA D regions.

An efficient T-cell response to viral component is critical for protective immunity. The HBV is not a cytopathic agent. Inflammation and hepatic necrosis in HBV infection are assumed to result from the T lymphocyte response of host to viral antigens³. Antigen-specific T-cell receptors recognize peptides bound to HLA molecules and the repertoire of peptides bound, depends on the HLA type of the individual. HLA tissue typing has become a useful system for studying the role of genetic factors in various diseases. The role of the HLA types in the outcome of HBV infection has been previously investigated, but they were unable to reach a definite conclusion^{4,5}. Different HLA types related to chronicity has been reported from different countries. It has been assumed that this difference could be due to racial characteristics.

The purpose of this study was to determine HLA tissue typing of the patients with chronic hepatitis B virus infection, to show the possible role of HLA tissue types on the chronicity of HBV infection and to assess which HLA types were protective against chronicity in Turkish population.

Patients and Methods

This study was conducted between June 1995 and December 1996. The subjects were divided into three groups: Group I included 20 patients with HBV-related chronic liver disease (cirrhosis, chronic active hepatitis, chronic persistent hepatitis) diagnosed on by liver biopsy or laparoscopy. Their mean age was 40 years with a range of 28 to 60 years. Group II consisted of 30 HBV chronic carriers (defined as a person who is HBsAg positive for 6 months or who is IgM anti HBe negative and HBsAg positive) (18 males and 12 females). They were all asymptomatic. Their physical examination as well as the biochemical findings were normal. Their ages ranged from 20 to 48 years with a mean of 28. Groups I and II together formed chronic hepatitis B infection group. Group III was the control group and included 50 healthy subjects with negative serology for HBV. Their mean age was 30 years with a range of 16 to 38 years (28 male and 22 female).

HBV markers were analysed by micro-ELISA method. Heparinised venous blood was drawn from all subjects and HLA tissue typing was accomplished by Terasaki's microlymphocytotoxicity test⁶. HLA antigens studied were A1, A2, A3, A11, A23 (9), A25 (10), A26 (10), A28, A29 (19), A30 (19), A31 (19), A32 (19), A33 (19), A66 (10), A74 (19), B7, B8, B13, B14, B18, B27, B35, B37, B38 (16), B39 (16), B40, B41, B42, B44 (12), B45 (12), B49 (21), B50 (21), B51 (5), B52 (5), B55(22), B57 (17), B62 (15), B63 (15), B70, Bw4, Bw6, Cw1, Cw2, Cw3, Cw4, Cw5, Cw6, Cw7, DR1, DR2, DR4, DR7, DR8, DR9, DR10, DR11 (5), DR13 (6), DR14 (16), DR17 (3), DR 52, DR 53, DQ1, DQ2, DQ3.

Relative risk for any HLA antigen was calculated. For comparisons, the chi-square test with Yate's correction and if the value is under 5, Fischer exact test was used.

Results

The frequencies of HLA A24, DR13 and DQ3 antigens were higher and of HLA CW1 antigen was lower in group I compared to control group (table 1).

Table 1. The Phenotype frequencies of HLA antigens to be found statistically significant between normal subjects and patients with HBV-related chronic liver disease.

HLA antigen	Chronic liver disease (n = 20)		Controls (n = 50)	Relative risk
	n	%	%	
DR13	3	15	-	- (increased risk)
DQ3	3	15	2	8.6 (increased risk)
A24(9)	3	15	42	0.2 (decreased risk)
Cw1	0	0	16	0 (decreased risk)

The frequencies of HLA A2, B8, B13, Cw3 and DR13 antigens were higher in group 11 than in the cControl group (table 2).

Table 2. The Phenotype frequencies of HLA antigens to be found statistically significant between normal subjects and asymptomatic HBV carriers.

HLA antigen	Asymptomatic carriers (n = 30)		Controls (n = 50)	Relative risk
	n	%	%	
A2	17	56	32	2.7 (increased risk)
B8	7	23	8	3.5 (increased risk)
B13	5	16	2	9.8 (increased risk)
Cw3	9	30	8	4.9 (increased risk)
DR13	3	10	0	- (increased risk)

The frequencies of HLA B8, B13, DR7, DR13 and DQ3 antigens were higher in both group I and 11 compared to the control group (table 3).

Table 3. The Phenotype frequencies of HLA antigens to be found statistically significant between normal subjects and the persons with chronic HBV infection.

HLA antigen	Chronic HBV infection (n = 30)		Controls (n = 50)	Relative risk
	n	%	%	
B8	11	22	8	3.2 (increased risk)
B13	7	14	2	8 (increased risk)
DR7	10	20	6	3.9 (increased risk)
DR13	6	12	0	- (increased risk)
DQ3	6	12	2	6.6 (increased risk)

Other HLA antigens tested in the study groups showed statistically insignificant differences when compared to controls.

Discussion

In this study, the association between HLA antigens and chronic HBV infection were noted. HLA B8, B13, DR7, DR13 and DQ3 appeared significantly more frequently in the patients with chronic HBV infection. DR13 and DQ3, both MHC class II antigens, are found significantly more frequently in the patients with HBV-related chronic liver disease. It is observed that HLA DR13 marginally increased the risks of HBV-related chronic liver disease and chronic carriage of HBV. There were 8 antigens in association with DR13 which were not detected in the control group, but none of these except DR13 were significantly increased in the study group. HLA A24 and Cw1 antigens were associated with decreased risk of HBV-related chronic liver disease.

Cellular immunity is very important to eliminate HBV from hepatocytes and some specific HLA molecules play a role in presenting viral antigens to T lymphocytes. In healthy carriers, cellular immune response is inadequate and there is no significant liver damage. Cellular immune response is effective in the development of hepatocellular necrosis⁷.

Several recent studies have shown that hepatic expression of HLA class 1 antigens were increased in chronic HBV infection. Interferon therapy has a similar effect⁸.

Protective HLA types against viral persistence have been studied. It has been reported that HLA B35 frequency increased in chronic HBV carriers. HLA A2, A26, DR2, DR4, DR5, DR8 and DQ1 prevented viral persistence^{5,9,10}. Our results suggest that HLA A2, B8, B13, Cw3 and DR 13 are protective for chronic carriage of HBV. HLA A2 increased risk of chronic HBV carriage by 2.7 times and HLA A2 antigens showed linkage disequilibrium with B25, B46, CW1 10. The risk of chronic carriage in the presence of HLA B8 antigen was 3.5 times higher. HLA B8 antigen was frequently found together with A1 and Cw7. In western population, HLA B8 antigen was higher in frequency in HBV carriers and chronic HBV infection¹¹. Paterson reported that HLA B8 was found frequently in the patients with hepatocellular carcinoma¹².

HLA B8 antigen was found in 22% patients with chronic hepatitis B infection and in 8% in the controls. These results correlate well with Sung's and Paterson's studies^{12,13}.

Pol showed that frequency of HLA B8 antigen was higher in individuals who failed to develop antibody response after HBV vaccination¹⁴.

We observed that most risky antigen for chronic carrier state was HLA B13. HLA DR7 also increased the risk of chronicity by 3.9 times. Similar results were reported previously^{12,15,16}.

Weissman reported that frequency of HLA DR7 was higher in the individuals who were unresponsive to the hepatitis B vaccine¹⁷. In this study, we observed that HLA B13, DR13 and DQ3 were the antigens associated with increased risk for chronic HBV infection¹⁵.

We found that HLA A24 and HLA Cw1 were protective for HBV related chronic liver disease. HLA DR13 frequency was 15% in chronic liver disease, but none of the controls had the same antigen. DR13 is a split of DR6 and it shows linkage disequilibrium with B44 in Japanese population, it is also related with DQ6 as well. Thursz and colleagues found that DRB1*1302 allele had significantly higher frequency in the patients who recovered I-IBV infection compared to those who had chronic HBV infection. They suggested that this allele was protective against chronicity. However, they also observed that presence of HLA DR13 which included DRB1* 1302 allele was associated with higher risk for chronicity¹⁸.

HLA DQ3 antigen was found to be associated with increased relative risk for HBV-related chronic liver disease in this study. DQ3 antigen has been found more frequently with DR 4, 5, 6, 7, 8, 9 and 10. It has been reported that DR 3, 4 and 5 frequency was higher in chronic HBV infection^{19,20}. We found no significant difference in the frequencies of HLA DR3 and DR4 antigens between study and control groups.

HLA B35 frequency was high in chronic active hepatitis¹⁰. In this study HLA B35 frequency was higher in group I and II compared to controls, but this was not statistically significant.

Our findings suggest that the genes encoding the immune response of the host affect the clearance of hepatitis B virus and the outcome of hepatitis B infection.

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