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HLA-A, B, C and DR in Hepatitis B Virus (HBV)-Related Liver Cirrhosis: A Study of 851 Elderly Subjects

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ABSTRACT

The possible correlation between HLA system and liver cirrhosis secondary to HBV infection has been studied in 102 hospitalized elderly patients affected by liver cirrhosis (histologically proven) and 749 elderly health controls. Increased frequencies of HLA-A2, Cw4, Cw5, DR4, DR5 and DR7 have been observed in patients with liver cirrhosis and previous HBV infection, while a lower frequency of HLA-A2 and higher frequencies of HLA-A3, B35, Cw4, DR3 have been observed in patients without previous HBV infection when compared with controls.

INTRODUCTION

Chronic hepatitis (CH) is a pathological condition with increasing frequency and is characterised by a wide range of causative factors, including hepatitis B virus (HBV) and alcohol abuse, and these two factors can interact with each other, representing in turn either the promoting or the exacerbating element or being the only etiological cause of liver disease (4, 9, 13). The complexity of the anatomical and clinical picture as well as the different individual response to the very same exogenous factor (HBV, alcohol) have led to the hypothesis of a genetic background capable to influence the host-virus reaction (3, 5, 10-12).

The purpose of this study was to verify a possible correlation between the HLA system and HBV related liver cirrhosis, because only few studies so far have been carried out with clashing and indefinite results (5, 7, 8, 13).

PATIENTS

Between 1987 and 1989, 102 hospitalized patients affected by histologically proven liver

cirrhosis (LC) (average age 74y), and 749 healthy elderly controls (average age 73.5y) were studied. Patients and controls were tested for hepatitis B markers (*i.e* HBsAg, anti HBsAg, anti HBcAg, HBeAg and anti HBeAg) to define the possible viral etiology of liver cirrhosis or a possible previous HBV infection (5). 434 controls (58%) and 33 patients (32.4%) were negative for every HBV marker; 315 controls (42%) and 58 patients were HBsAb and/or HBcAb positive. 11 patients with LC were surface HB Antigen (HBsAg) positive. All patients and controls were HBeAg negative. None of the patients and controls was an alcohol abuser.

METHODS

Patients and controls were typed for HLA antigens of Class I and II. The peripheral lymphocytes were separated through spinning on a gradient according to Boyum (2). B-lymphocytes were identified by means of sheep AET pretreated red blood cells (7). Typing of A, B, C and DR loci was accomplished by a microdroplet cytotoxicity test (8). Class I antigen determination was performed by using a set of 180 sera defining 17 antigens for locus A, 29 for locus B, 7 for locus C. DR locus typing was possible by the use of Pel-Freeze plates (Wisconsin, USA) defining 14 specificities.

Statistics. For comparisons the Chi-squared test, with Yates' correction or Fisher exact was used.

RESULTS

The correlation between HLA antigens in the group of patients with LC HBV negative (n = 33) and controls (n = 749) underlines higher frequency of HLA-A2, Cw4, Cw5, DR4, DR5 and DR7 in patients with liver cirrhosis (table 1).

Table 1. HLA and liver cirrhosis: comparison between 33 patients with liver cirrhosis (LC) HBV negative, and 749 controls (C).

HLA	LC	%	C	%	p-value
A2	20	60.6	318	42.5	0.04
Cw4	13	39.4	165	22.0	0.02
Cw5	6	18.2	42	5.6	0.003
DR4	13	39.4	67	8.9	0.0001
DR5	13	39.4	159	21.2	0.01
DR7	10	30.3	120	16.0	0.03

When comparing HLA antigens between patients with LC with positive HBV markers and controls we observed a higher frequency of HLA-A3, B35, Cw4, DR3 in patients with LC (table 2).

Table 2. Comparison between 69 patients affected by liver cirrhosis (LC) with positive HBV markers and 749 controls (C).

HLA	LC	%	C	%	p-value
A2	20	29.0	318	42.5	0.03
A3	22	31.9	124	17.1	0.002
Cw4	24	34.7	165	22.0	0.01
B35	23	33.3	152	20.3	0.01

A comparison between patients with LC HBV negative and patients with LC and previous HBV infection (HBsAg+ or HBsAb and/or HBcAb+) yields a statistically significant difference for HLA-A2 and DR4, which are more frequent in HBV negative patients, even if the frequency of DR4 in two groups shows a weak, statistically significant difference (table 3).

Table 3. Comparison between 33 patients with LC without (HBV-), and 69 patients with LC and previous HBV infection (HBV+).

HLA	LC-HBV	%	LC-HBV+	%	p-value
A2	20	60.6	20	29.o	0.002
DR4	7	21.3	5	7.2	0.04

DISCUSSION

Previous studies aimed at demonstrating a correlation between clinical evolution of HBV and/or alcohol related liver hepatitis, but none of them showed statistically significant differences between the groups of patients studied. Moreover, we are not aware of any study in elderly people. The results obtained in our study confirm the unclear correlation between HLA and LC in the elderly, too. Only Cw4 antigen was regularly related to LC and was more frequent in patients (HBV positive and negative) than in controls. On the other hand, the different frequencies of HLA antigens we found in the patients with LC (HBV positive and HBV negative) when compared to controls and between the two groups compared with each other, could be explained by a multifactorial pathogenesis of LC.

The increased frequency of DR4 and of HLA-A2 (table 3), in patients being HBV negative but affected by LC, may point to a possible role played by the above - mentioned antigens in the susceptibility to HBV infection. The higher frequency of DR4 was in agreement with Watanabe (14) who found an increased frequency of the HLA-Bw4, DR4, DRw53, DQw4 in non-responders to antihepatitis B vaccine. Our data underline the importance of HBV infection as an etiological factor of LC, although, nowadays, attention has been drawn to hepatitis C virus infection or the association of both B and C viruses. Further studies are needed to elucidate the possible correlation between HBV and HCV infections, and their importance as etiological factors of CLD.

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