Health Programme Office, Centres for Disease Control, Atlanta, Georgia 30333 USA.

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Are HLA antigens important in the development of alcohol-induced liver disease?

R FAIZALLAH, J C WOODROW, N K KRASNER, R J WALKER, A I MORRIS

Abstract

The prevalences of 10 HLA-A and 16 HLA-B antigens were determined in 50 patients with alcoholic cirrhosis and 120 alcoholic patients without cirrhosis and compared with those in a control group of 550 healthy subjects from the same geographical area. B40 was absent in the patients with cirrhosis but was found in 18 (15%) of the patients without cirrhosis ($p = 0.0087$). No other association was noted.

It is concluded that there is no good evidence to date of an association between HLA antigen state and susceptibility to alcohol-induced cirrhosis.

Introduction

While the quantity of alcohol consumed and duration of consumption probably play a major part in the pathogenesis of alcohol-induced cirrhosis, other as yet poorly identified factors exist since most alcoholics do not develop cirrhosis despite very heavy drinking.[1] One possible factor—genetic predisposition—has been studied in some detail by investigation of the HLA polymorphism among alcoholics. The results have so far been conflicting, some workers showing no evidence of any association between a particular HLA antigen and alcohol-induced cirrhosis[2] while others have shown possible linkage with A28, B8, B13, and B40,[3-5] all in fairly small groups. In the present study we investigated a larger number of patients to assess their antigen state and determine whether there was any association with alcohol-induced cirrhosis.

Gastrointestinal Unit, Walton Hospital, Liverpool L9 1AE
R FAIZALLAH, MB, MRCP, medical registrar
N K KRASNER, MD, FRCP, consultant physician and gastroenterologist
R J WALKER, BSC, FRCP, consultant physician
A I MORRIS, MD, MRCP, consultant physician and senior lecturer
Department of Medicine, University of Liverpool, Liverpool L69 3BX
J C WOODROW, MD, FRCP, professor

Subjects and method

Over two years we studied 170 consecutive alcoholics, all of whom had been admitted for detoxification or treatment of alcoholism. Fifty patients showed signs of chronic liver disease, and histology of liver biopsy specimens in 39 showed cirrhosis; in the remaining 11 liver biopsy was contraindicated and cirrhosis was diagnosed on clinical and biochemical grounds—for example, evidence of portal hypertension or hepatic encephalopathy. The group with cirrhosis comprised 15 women (mean age 58·1 ± SD 10·5 years) and 35 men (mean age 54·9 ± 9·4 years). The mean alcohol intake in this group was 194 ± 96 g/day for a mean duration of 15·3 ± 8·3 years. Of the remaining 120 patients, 26 had no biochemical evidence of liver injury or any clinical evidence of liver disease; liver biopsy was unjustified in these and they were included in the group without cirrhosis. In the remaining 94 there was biochemical evidence of liver injury and liver biopsy yielded either normal findings or evidence of liver injury short of cirrhosis, the commonest being steatosis. Of these patients, 51 were women (mean age 48·1 ± 12·8 years) and 69 men (mean age 48·4 ± 12·9 years.) The mean alcohol intake in this group without cirrhosis was 186·8 ± 115 g pure alcohol daily for a mean of 8·5 ± 7·4 years. Lymphocytes from venous blood samples were typed by a modified cytotoxicity technique[6] for specificity to 10 HLA-A and 16 HLA-B antigens. ABO blood groups were determined on the blood samples and compared with those of a large control series from the same geographical area.

Serum samples were tested for the presence of antinuclear, smooth-muscle, mitochondrial, parietal cell, and reticulin antibody by fluorescence antibody methods. Tests for the presence of hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) were carried out in most cases. Relative risks were calculated according to the method of Haldane.[7]

Results

Table I gives the prevalences of the HLA-A and B series antigens in alcoholic patients with and without cirrhosis and the controls together with the significances of the differences between the three groups. B40 was absent in the patients with cirrhosis but present in 18 (15%) of those without cirrhosis and in 64 (11·6%) of the normal controls. No other noticeable differences were apparent, in particular with regard to A28, B8, and B13.

Table II gives the prevalences of the ABO blood groups in patients and controls; there was no significant difference between the three groups. Four patients showed very low titres of antinuclear antibodies; two had antibodies to smooth-muscle, one to reticulin, and six to

parietal cell antibodies; and none had antimitochondrial antibodies. HBsAg was absent in all the patients tested, and only four were positive for HBcAg, which is a lower prevalence than has been cited in recent reports.[8 9]

Discussion

In an earlier study A28 was noted to be absent in all the patients with cirrhosis in the series.[3] Although in our series the prevalence of A28 was lower in the group with cirrhosis, the difference was not significant (table I). In the same series B8 was claimed to be increased in the group with cirrhosis; this too was not supported in our study, the relative risk being 1·1 (p=0·93). Likewise, other studies have failed to show this association—if the results from the present study and those from seven other centres are combined[2-5 10-12] the relative risk of developing cirrhosis in people with B8 is 1·28 (p=0·78), with evidence of heterogeneity between the various centres. No significant difference could be found when men and women with cirrhosis were analysed separately in our series: five women (33%) and 10 men (28·6%) had B8 antigen.

A more recent series from Chile showed a significantly higher prevalence of B13 in patients with cirrhosis[4]; this again was not supported by our series (p=1; table I). In a small series from Oslo B40 was more common among patients with cirrhosis,[5] yet we found it to be absent in all 50 patients (p=0·0082); this is probably not statistically significant since a probability value of less than 0·0019 would have to be observed before any difference is considered to be significant when 26 specificities are being compared.[13] When results from five previous series are combined with ours with regard to B40[2 4 5 10 11] the combined relative risk of developing cirrhosis is 1·8 (p=0·017), with evidence of appreciable heterogeneity between the various centres (p=0·018).

This heterogeneity and lack of consistency in the results from various centres can only reinforce our conclusion that there is no true association between a particular HLA antigen and alcohol-induced cirrhosis. This in turn would suggest that other perhaps more important factors might be responsible for the development of alcoholic cirrhosis. Possibilities include autoimmune reactions that occur in alcoholism[14-18] and the metabolic derangements in the liver induced by alcohol.[19-21] More recently racial variation in aldehyde dehydrogenase isoenzymes has been shown between Japanese and Europeans.[22 23] It may be argued that these factors may be genetically controlled. If such control does exist there is no consistent evidence that it is in the HLA chromosome region.

TABLE I—*Prevalences of 26 HLA antigens in patients and controls (figures are numbers (%) of subjects positive for each antigen)*

Antigen	Alcoholic patients		Controls (n=550)
	With cirrhosis (n=50)	Without cirrhosis (n=120)	
A1	16 (32)	48 (40·0)	193 (35·1)
A2	22 (44)	62 (51·7)	245 (44·6)
A3	14 (28)	33 (27·5)	154 (28·0)
A9	10 (20)	19 (15·8)	101 (18·4)
A10	5 (10)	12 (10·0)	51 (9·3)
A11	6 (12)	17 (14·2)	74 (13·5)
A28	1 (2)	11 (9·2) p=0·18	32 (5·9) p=0·4
A29	5 (10)	4 (3·3)	40 (7·2)
AW30/31	1 (2)	4 (3·3)	28 (5·0)
AW32	4 (8)	5 (4·5)	36 (6·6)
B5	5 (10)	7 (5·8)	49 (8·9)
B7	20 (40)	38 (31·7)	161 (29·3)
B8	15 (30)	28 (23·3) p=0·47	156 (28·4) p=0·93
B12	17 (34)	32 (26·7)	166 (30·2)
B13	2 (4)	2 (1·7) p=0·72	26 (4·7) p=1·00
B14	4 (8)	14 (11·7)	40 (7·3)
B15	7 (14)	12 (10·0)	64 (11·6)
BW16	3 (6)	3 (2·5)	25 (4·6)
B17	3 (6)	13 (10·8)	48 (8·7)
B18	4 (8)	8 (6·8)	30 (5·5)
BW21	1 (2)	2 (1·7)	26 (4·8)
BW22	5 (10)	4 (3·3)	30 (5·5)
B27	2 (4)	18 (15·0)	50 (9·1)
BW35	9 (18)	19 (15·8)	65 (11·8)
B37	3 (6)	4 (3·3)	16 (2·9)
B40	0	18 (15·0) p=0·0087	64 (11·6) p=0·02

TABLE II—*Prevalence of ABO blood groups in patients and controls (figures are numbers (%) of subjects)*

Blood group	Alcoholic patients		Control[11] (n=15 377)
	With cirrhosis (n=50)	Without cirrhosis (n=120)	
A	18 (36)	36 (29·9)	6012 (39·1)
B	5 (10)	16 (13·4)	1445 (9·4)
AB	1 (2)	5 (3·9)	384 (2·5)
O	26 (52)	63 (52·8)	7519 (48·9)

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