Histocompatibility Antigens in Active Chronic Hepatitis and Primary Biliary Cirrhosis

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Summary

The frequency of antigens HL-A 1 (48%) and HL-A 8 (52%) in 54 patients with active chronic hepatitis from south-east England was significantly higher than in 89 control subjects from the same region (22% and 17% respectively). No correlation could be detected with the age and sex of the patients or with the presence of a particular immunological abnormality but the frequency of HL-A 1 and HL-A 8 was much lower in the nine patients who were positive for HBAG than in the 45 HBAG-negative cases. These results provide further evidence of the importance of genetic factors in active chronic hepatitis. In contrast the frequency of HL-A 1 and HL-A 8 in primary biliary cirrhosis, both in 45 patients from south-east England and in 28 patients from western Scotland, was not significantly different from that found in control groups from the same regions.

Introduction

There is a growing interest in the distribution of histocompatibility antigens in autoimmune disorders, and in one study of active chronic hepatitis from Australia an increased frequency of HL-A 1 and HL-A 8 was reported (MacKay and Morris, 1972). In this paper we describe the distribution of histocompatibility antigens among 54 patients with active chronic hepatitis seen in south-east England. Since primary biliary cirrhosis has clinical and immunological features in common with active chronic hepatitis we also studied 73 patients with this condition, 45 from south-east England and 28 from the west of Scotland. The findings are considered in relation to the pattern of immunological abnormalities and the occurrence of hepatitis-B-associated antigen (HBAG) in some of the patients with active chronic hepatitis.

Subjects and Methods

Tissue typing with a standard lymphocytotoxicity test (Batchelor, 1973) and blood grouping were performed on 54 patients with active chronic hepatitis and 45 with primary

biliary cirrhosis, all of whom were resident in the south-eastern region of England. The results were compared with those in a control group of 89 healthy subjects from the same area. A further 28 patients with primary biliary cirrhosis from the west of Scotland were also studied using a similar method of tissue typing (Dick *et al.*, 1972) and were compared with 597 controls from the same region. The diagnosis of active chronic hepatitis was established from a clinical history of more than three months' duration, serum aspartate aminotransferase and γ -globulin levels of greater than twice normal, and the histological features on liver biopsy of chronic aggressive hepatitis with or without cirrhosis. HBAG was persistently detected in the serum of nine of these patients, in eight by immunodiffusion and counter-immunoelectrophoresis and in one by radioimmunoassay only (Reed *et al.*, 1973). Diagnostic criteria for primary biliary cirrhosis included prolonged pruritus or jaundice, serum alkaline phosphatase levels greater than twice normal, anti-mitochondrial antibodies in the serum, and a compatible histological picture.

All control subjects and patients were British apart from five of the nine with HBAG-positive active chronic hepatitis, who were from Greece, Spain, Iran, and Jamaica (2) respectively. Statistical analysis was by the χ^2 test with Yates's correction. The P values given here are uncorrected for the number of antigens tested but as in other surveys of histocompatibility antigen distributions the differences were considered to be significant only if P remained less than 0.05 after multiplying by the number of antigens tested, in this case 23.

Results

The distribution of histocompatibility antigens in the patient groups was the same as in the corresponding control subjects with the exception of HL-A 1, HL-A 8, and W 28 (see table). In the 54 patients with active chronic hepatitis the frequency of HL-A 1 and HL-A 8 was higher ($P < 0.002$ and $P < 0.0005$ respectively) and that of W 28 lower ($P < 0.025$) than in the control group. After correction of the P value, however, the difference with respect to W 28 did not remain significant.

No correlation could be detected between the occurrence of HL-A 1 or HL-A 8 and the presence of antimitochondrial, antinuclear, smooth muscle, or microsomal antibodies, the L.E. cell phenomenon, or the age and sex of the patients. In contrast a marked negative correlation was apparent between both tissue types and the presence of HBAG in the serum. The frequency of HL-A 1 and HL-A 8 in the nine HBAG-positive cases was the same as that in controls, whereas in the 45 HBAG-negative cases these two antigens were much commoner than in the controls ($P < 0.001$ and $P < 0.0005$ respectively), the differences remaining significant after correction. In three of the HBAG-negative cases only two antigens, HL-A 1 and HL-A 8, were detected out of a possible four. To determine whether these patients were homozygous for these antigens will require a more detailed study of their families.

In primary biliary cirrhosis the frequencies of HL-A 1 and HL-A 8 were not significantly higher than in the control

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Percentage Frequency Distribution of Histocompatibility Antigens. (H = HL-A Antigens. W = Workshop Antigens)

								First-series Antigens								Second-series Antigens														
								H 1	H 2	H 3	H 9	H 10	H 11	W 28	W 19	H 5	H 7	H 8	H 12	H 13	W 5	W 10	W 14	W 15	W 16	W 17	W 18	W 21	W 22	W 27
South-east England																														
Controls	..	..	..	..	..	..	..	22	52	27	21	6	12	19	18	17	19	17	33	5	14	19	9	11	5	11	5	2	6	14
Primary biliary cirrhosis	..	..	..	..	..	..	..	44	61	17	24	2	2	7	15	12	29	33	29	0	10	12	10	12	7	7	7	0	0	5
Active chronic hepatitis	..	..	..	..	..	..	..	48	58	15	23	4	13	2	4	10	27	52	38	2	8	4	0	8	8	4	4	0	4	4
HBAg negative	..	..	..	..	..	..	..	53	61	17	24	0	12	0	5	10	29	62	37	0	5	5	0	7	10	5	2	0	0	5
HBAg positive	..	..	..	..	..	..	..	22	44	11	33	22	11	11	0	11	22	0	33	11	22	0	0	22	0	0	22	0	22	0
Western Scotland																														
Controls	..	..	..	..	..	..	..	31	48	23	18	7	9	7	14	5	30	31	33	4	8	10	8	8	4	6	5	2	4	9
Primary biliary cirrhosis	..	..	..	..	..	..	..	29	54	29	11	14	11	11	11	11	25	32	21	4	18	14	21	4	0	0	7	4	0	21

subjects, either in the south-East of England or in the west of Scotland (see table). Analysis of the patients with primary biliary cirrhosis in whom HL-A 1 or HL-A 8 was detected failed to show any correlation between their tissue type and the presence of smooth muscle or antinuclear antibodies or their age and sex.

The distribution of ABO and rhesus blood groups was not significantly altered from normal in any of the groups of patients examined.

Discussion

The results in our HBAG-negative patients with active chronic hepatitis are comparable with those found in the one previous study from Australia (Mackay and Morris, 1972). Though not stated it is likely that most of the cases in that study were negative for HBAG since this antigen is rarely found in Australia (Cooksley *et al.*, 1972). Recent evidence has shown that HBAG-positive and HBAG-negative types of active chronic hepatitis are similar with respect to both clinical and serological manifestations though the sex ratio and country of origin do differ (Reed *et al.*, 1973). In the present series there was a striking difference in tissue types between the two subgroups, which could indicate different mechanisms of pathogenesis, but the number of HBAG-positive cases tested was small and five of the nine were from other countries where the distribution of histocompatibility antigens in the normal population could be different.

We had expected to find an increased frequency of HL-A 1 and HL-A 8 in primary biliary cirrhosis patients, parallel to the findings in active chronic hepatitis, since there is, as already mentioned, some overlap between these two disorders. Furthermore, genetic factors are probably also involved in both conditions. A similar pattern of autoantibodies has been found in the relatives of both groups of patients (Galbraith *et al.*, 1974) and there are a number of reports describing two cases of primary biliary cirrhosis within a family, including one in which twin sisters were affected (Chohan, 1973).

An association between HL-A 1, HL-A 8, and the L.E. cell phenomenon was implied in the Australian study of active chronic hepatitis. In contrast, recent findings in myasthenia gravis suggest a negative correlation between HL-A 8 and autoantibodies (Feltkamp *et al.*, 1974), but in our study there was no correlation, either positive or negative, between the presence of various immunological abnormalities and the HL-A 1 and HL-A 8 tissue types.

An increased frequency of HL-A 1, HL-A 8, or both has also been reported in gluten-sensitive enteropathy (Stokes *et al.*, 1973), dermatitis herpetiformis (Gebhard *et al.*, 1973),

systemic lupus erythematosus (Grumet *et al.*, 1971), and childhood asthma (Thorsby *et al.*, 1971). These conditions, however, are not usually part of the pattern of multisystem involvement seen in active chronic hepatitis or primary biliary cirrhosis (Golding *et al.*, 1973). To our knowledge the commonest disorders in this multisystem involvement—namely, Sjögren's syndrome, renal tubular acidosis, and fibrosing alveolitis (Golding *et al.*, 1973)—have not been examined for HL-A 1 and HL-A 8 frequency but in ulcerative colitis and autoimmune thyroiditis, which also form part of the spectrum of multisystem involvement, no increase in frequency has been found (Asquith *et al.*, 1974; Doniach and Van Rood, 1974). Thus multisystem involvement in active chronic hepatitis and primary biliary cirrhosis may be related secondarily to the autoimmune liver disease rather than to the genetic background.

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Addendum

A further four patients with HBAG-positive active chronic hepatitis have now been studied (three Britons and one Spaniard), and none had HL-A 8. Thus the frequency of HL-A 8 in the HBAG-positive cases overall (0%) is now significantly lower ($P < 0.00003$) than the figure of 62% obtained in the HBAG-negative cases, of whom 55 have now been typed. This raises the intriguing question of whether the inability of HBAG-positive patients to eliminate the antigen may be related to absence of HL-A 8.

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