Association of primary sclerosing cholangitis with HLA-B8

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SUMMARY The frequency of HLA antigens was studied in 25 patients with primary sclerosing cholangitis and compared with a control group of 561 kidney donors. Fourteen patients also had ulcerative colitis. A significant increase in the frequency of HLA-B8 (60%) was found in the primary sclerosing cholangitis patients compared with controls (25%) ($p < 0.001$). HLA-B8 was found in eight patients with ulcerative colitis. The frequency of HLA-B12 was significantly decreased (8%) compared with controls (30%) ($p < 0.02$). Piecemeal necrosis was observed on liver histology in 66% of HLA-B8 positive and 50% of HLA-B8 negative patients. Low titres of serum autoantibodies were frequently found in the primary sclerosing cholangitis group but did not correspond to the presence of HLA-B8. Raised serum concentrations of IgM and IgG were not related to HLA-B8. This study has shown that in patients with primary sclerosing cholangitis there exists a disease susceptibility gene closely associated with the B locus of the major histocompatibility complex which may be modified by other factors such as ulcerative colitis. Patients with ulcerative colitis and HLA-B8 may be particularly liable to develop primary sclerosing cholangitis.

Primary sclerosing cholangitis is an uncommon disease characterised by an intense inflammatory fibrosis usually involving the whole biliary system.¹ The aetiology of this disorder is unknown, although it is closely associated with ulcerative colitis which coexists in approximately two-thirds of patients with primary sclerosing cholangitis.¹

The associations between certain human leucocyte histocompatibility (HLA) antigens and an increased risk of certain diseases have recently been identified. HLA-B8 and HLA-DRW3, for example, have been closely associated with diseases involving immunological dysfunction such as autoimmune chronic active hepatitis.² HLA-A3 has been closely associated with idiopathic haemochromatosis.³

The purpose of the present study was to investigate possible associations between the HLA system and patients with primary sclerosing cholangitis, with and without coexisting ulcerative colitis.

Methods

PATIENTS

Twenty-five consecutive patients (17 men and eight women) with primary sclerosing cholangitis who were admitted to the Royal Free Hospital for investigation were studied. The diagnosis was based on accepted criteria – namely, the demonstration of multiple strictures in the biliary system, the absence of previous biliary tract surgery, and the exclusion of bile duct cancer by at least two years' follow-up.¹

Fourteen patients (10 men and four women) were also suffering from ulcerative colitis; no patient had Crohn's disease. One non-colitic male patient also had chronic pancreatitis, diabetes, and angio-immunoblastic lymphadenopathy and another non-colitic had chronic glomerulonephritis. None of the patients had a family history of primary sclerosing cholangitis or ulcerative colitis.

Serum immunoglobulins and autoantibodies were estimated. All patients included in the primary sclerosing cholangitis group were mitochondrial antibody negative. In addition, percutaneous liver biopsies were performed in all the patients using

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Menghini needles. The presence or absence of piecemeal necrosis on liver histology was assessed by one experienced observer (RG) who was unaware of the HLA-status of the patients. If present, the degree of piecemeal necrosis was assessed as mild, moderate, or severe.⁴

Control data were obtained by HLA typing 561 unrelated cadaveric kidney donors from the London area.

Tissue typing for 14A and 16B locus antigens was performed on peripheral blood lymphocytes using a standardised microcytotoxicity assay⁵ and international workshop sera.

The chi-squared test was used to analyse the results. In order to correct for derived probabilities the p values were multiplied by 30 (the number of HLA alleles tested).

Results

The frequencies for particular HLA-A and B locus antigens in the patients with primary sclerosing cholangitis and controls are shown in Table 1. In primary sclerosing cholangitis patients there was a significant increase in the frequency of HLA-B8 (60% vs 25%; $\chi^2=15.1$; corrected $p<0.001$) compared with control patients. In addition, the frequency of HLA-B12 was significantly decreased in primary sclerosing cholangitis patients (8% vs 30%; $\chi^2=5.7$; corrected $p<0.02$) compared with controls. HLA-B12 was not found in any patient who possessed HLA-B8. Nine of 10 patients who were found to have HLA-A1 also possessed HLA-B8. HLA-B8 was found in 57% of the primary sclerosing cholangitis patients with ulcerative colitis and HLA-B12 in only 7%.

There were no significant differences between the groups in the frequency of the remaining A and B locus antigens.

The concentrations of serum immunoglobulins IgM and IgG were not significantly different in HLA-B8 positive and negative patients (Figure). Similarly, no differences were observed with regard to the presence of low titres of antinuclear factors and smooth muscle antibody (Table 2).

Two-thirds of the HLA-B8 positive patients showed some degree of piecemeal necrosis on liver biopsy (Table 3). Piecemeal necrosis was also seen, however, in half of the HLA-B8 negative group. The difference between the groups was not significant.

Discussion

This study has shown that in primary sclerosing cholangitis there is an increased frequency of HLA-

Table 1 HLA antigens in patients with primary sclerosing cholangitis and in controls

HLA locus	PSC patients (25)		Controls (561)	
	(no.)	(%)	(no.)	(%)
A1	10	40	184	33
A2	12	48	288	51
A3	4	16	163	29
AW23	1	4	7	1
AW24	3	12	83	15
A25	0	0	12	2
A26	2	8	26	5
A11	2	8	69	12
A28	4	16	56	10
A29	0	0	58	10
AW30	2	8	28	5
AW31	4	16	16	3
AW32	3	12	38	7
AW33	2	8	0	0
B5	3	12	44	8
B7	3	12	141	25
B8	15*	60	140	25
B12	2†	8	170	30
B13	0	0	18	3
B14	3	12	58	10
B15	2	8	83	15
BW16	1	4	39	7
B17	1	4	58	10
B18	3	12	30	5
BW21	0	0	22	4
BW22	2	8	26	5
B27	5	20	50	9
BW35	2	8	90	16
B37	0	0	20	4
B40	3	12	62	11

* Significantly increased in primary sclerosing cholangitis patients compared with controls.

† Significantly decreased in primary sclerosing cholangitis patients compared with controls ($p<0.02$).

B8. The presence of HLA-B8 has previously been shown to be associated with diseases involving immunological dysfunction³ including chronic active hepatitis, coeliac disease, myasthenia gravis, and sicca syndrome.³ HLA-B8 appears to be associated with factors which promote an increased immunological response to a variety of antigens.⁶ It has been suggested that HLA-B8 may be linked to genes controlling antigen non-specific suppressor cells, with subsequent failure of a normal suppressor cell response.^{3,7} Primary sclerosing cholangitis has not previously been considered to be an autoimmune disease, but it is interesting that the frequency of HLA-B8 (60%) observed in this study is comparable with the frequency found in a number of studies of autoimmune chronic active hepatitis.^{2,3,8-10} In this study the frequency of HLA-DRW3 was not determined. This antigen is closely associated with HLA-B8 through linkage disequilibrium¹¹ and it is

Figure Concentrations of IgM and IgG in the primary sclerosing cholangitis patients. Shaded area represents the normal range.

probable that there is an increased frequency of HLA-DRW3 in primary sclerosing cholangitis.

The explanation of the low frequency (8%) of 12 found in the primary sclerosing cholangitis patients is not clear, as the frequency of HLA-B12 has been observed to be normal in previous studies of patients with autoimmune chronic active hepatitis.^{2 3 8-10} HLA-B12, like HLA-B8, is associated with heightened immune responses.^{3 6} None of our

Table 2 Serum autoantibodies in primary sclerosing cholangitis

	HLA-B8 positive patients (n = 15)		HLA-B8 negative patients (n = 10)		All patients	
	(no.)	(%)	(no.)	(%)	(no.)	(%)
Presence of:						
Antinuclear factor (<1 in 40)	8	54	5	50	13	52
Smooth muscle antibody (<1 in 40)	4	27	2	20	6	24

Table 3 Piecemeal necrosis in primary sclerosing cholangitis

Degree of piecemeal necrosis	HLA-B8 positive patients (n = 15)		HLA-B8 negative patients (n = 10)		All patients (n = 25)	
	(no.)	(%)	(no.)	(%)	(no.)	(%)
None	5	33	5	50	10	40
Mild	5	33	4	40	9	36
Moderate	5	33	0		5	20
Severe	0		1	10	1	4

patients with primary sclerosing cholangitis possessed both antigens, which have been shown to act synergistically in stimulating serum autoantibody production.⁶

We were unable to show any association between the presence in the serum of low titres of smooth muscle antibody and antinuclear factor and HLA-B8. In contrast with patients with autoimmune chronic active hepatitis the presence and titre of these circulating autoantibodies has been shown to correlate closely with HLA-B8.^{3 6}

It has been suggested that primary sclerosing cholangitis and primary biliary cirrhosis represent variations of the same disease spectrum.^{12 13} An increased frequency of HLA-B8 has not been observed, however, in a study of patients from our unit with primary biliary cirrhosis.¹⁴ From the results of this study it seems likely that primary sclerosing cholangitis and primary biliary cirrhosis are aetiologically distinct diseases.

The increased frequency of HLA-B8 was similar in the primary sclerosing cholangitis patients with and without coexisting ulcerative colitis. A number of studies have shown that the frequency of HLA-B8 is not increased in patients with ulcerative colitis alone.^{15 16} The factors which lead to patients with ulcerative colitis developing chronic liver and biliary disease are unknown. The presence of HLA-B8 may render an individual suffering from ulcerative colitis more susceptible to the development of chronic liver disease. It is also possible that the presence of HLA-B8 determines that the liver disease pursues a more aggressive course. This mechanism is thought to be of importance in patients with alcoholic liver disease who are also HLA-B8 positive.¹⁷ Some evidence for the latter possibility is the trend seen in this study for piecemeal necrosis to be more severe and more frequently seen in the HLA-B8 positive group. HLA-B8 may prove to be a useful marker of those patients with ulcerative colitis who are liable to develop chronic liver disease.

It appears that in primary sclerosing cholangitis,

as in autoimmune chronic active hepatitis, there is a disease susceptibility gene associated with the HLA-B8 locus of the major histocompatibility system which may be modified by other factors such as ulcerative colitis.

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