HLA antigens in systemic lupus erythematosus

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SUMMARY Forty-five patients suffering from systemic lupus erythematosus were studied in respect of their serologically defined HLA antigens. HLA-B8 antigen was found in 37.8% of patients as compared to 22% of controls. Individuals carrying the HLA-B8 antigen have a 2.15 times greater risk of developing systemic lupus erythematosus than those not carrying this antigen.

Associations between the antigens of the major histocompatibility system in man (HLA) and some diseases have been studied by several workers. In diseases where the involvement of autoantibodies in the pathogenesis was assumed or proved, an increased frequency of HLA-B8 was found, e.g. in chronic aggressive autoimmune hepatitis, myasthenia gravis, coeliac disease, thyrotoxicosis, insulin-dependent diabetes, idiopathic Addison's disease, and Sjögren's syndrome.

The distribution of HLA antigens in systemic lupus erythematosus (SLE) has been studied by several authors (Table 1). However, the results were not conclusive: generally only weak associations between SLE and HLA antigens were found by some and questionable results or lack of any association were found by others (Table 1).

The proved association between HLA-B8 and some autoimmune diseases together with the possible association of this antigen with SLE (Grumet *et al.*, 1971; Goldberg *et al.*, 1973; Stenszky *et al.*, 1973) attracted our attention. We therefore investigated the frequency of individual HLA antigens, with special reference to HLA-B8, in SLE patients in the Research Institute of Rheumatic Diseases and Clinical Ward of the Medical Faculty, Charles University, Prague.

Material and methods

A total of 45 Czech patients with SLE (38 females, 7 males) were investigated. Their ages ranged from 15 to 75 years, mean 44 years. The diagnosis of SLE was established by the presence of at least four

of the preliminary criteria for the classification of SLE proposed by the American Rheumatism Association and by the presence of antinuclear serum antibodies as determined by immunofluorescence (Coons and Kaplan, 1950). The controls consisted of 350 unrelated Caucasians whose HLA antigens had been typed in the same laboratory (Ivašková *et al.*, 1974).

HLA typing was performed by the lymphocytotoxic microtechnique using peripheral lymphocytes. 21 antigens were typed (Table 2). Three to six mono- or oligospecific antisera were used for the definition of each specificity. Differences in prevalence of HLA antigens between patients and controls were determined by the χ^2 test. The corrected P value was calculated by multiplying P by the number of antigens tested. The relative risk for a given antigen, indicating how many times more frequent it is in individuals carrying this antigen than in those lacking it, was calculated according to Svejgaard *et al.* (1974).

Results

The distribution of HLA antigens in patients with SLE and in controls is given in Table 2. HLA-B8 was found in 37.8% of the patients as compared with 22% of the controls ($P < 0.025$). Despite this difference, the corrected P value is not significant. The distribution of other HLA antigens compares well with that in the control group. The relative risk of SLE for HLA-B8 is 2.15 (the 95% confidence interval is 1.14-4.06).

The percentage of patients meeting the individual criteria for classification of SLE is given in Table 3. A multifactorial analysis of these and many other clinical and laboratory parameters and their possible relation to HLA-B8 antigen is in progress.

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Table 1 HLA antigen in SLE: survey of literature

Author	No. of patients	No. of controls	Race	Antigens	% positive		No. of antigens tested	P corrected	Relative risk
					Patients	Controls			
Grumet <i>et al.</i> (1971)	25†	82	Caucasian	HLA-B8 HLA-Bw15	36 36	16 10	21	>0.05 >0.05	2.95 5.20
Bitter <i>et al.</i> (1972)	28	280	Black	HLA-B7 HLA-Bw35	50 50	<10 <10	?		
Stastny (1972)	40	40	Black	HLA-Aw19§ HLA-B5	52.5** <7.5	<7.5	22	<0.01	13.6
Goldberg <i>et al.</i> (1973)*	120	120	{ Caucasian Mexican Black	HLA-A1	22	9	23	>0.05	2.85
				HLA-B8	19	8		>0.05	2.69
Suciu-Foca <i>et al.</i> (1974)	53	80	?	HLA-A11 4C (W5, W18)	21 47	11 24	26	>0.05 >0.05	2.15 2.81
Nies <i>et al.</i> (1974)	42	886	Caucasian	HLA-A10 HLA-B5	24 24	11 11	25	>0.05 >0.05	2.55 2.55
	40	283	Mexican	HLA-B5 HLA-Bw40	28 28	17 12		>0.05 >0.05	1.90 2.85
	40	120	Black	HLA-B5	23	5		>0.05	5.66
Stenzky <i>et al.</i> (1973)	90	450‡	Caucasian	HLA-A2 HLA-B5 HLA-B8 HLA-Bw40	64.4 33.3 32.2 3.3	48.1 19.4 19.1 16.1	20	>0.05 >0.05 >0.05 >0.05	1.95 2.07 2.01 0.18
Kissmeyer-Nielsen <i>et al.</i> (1975)	65	562	Caucasian	No significant (after correction) deviation found			28		
Watters <i>et al.</i> (1971)				In 15 patients a questionable frequency increase of Bw15-related antigen Patients were not matched for race (mixed) with controls					

P corrected and relative risks were calculated from data in each paper.

* Results from Arnett *et al.* (1972) are included in this paper.

† Out of 40 SLE patients tested only 25 were matched for race with controls.

‡ Personal communication.

§ Defined by serum TH-Li.

** Twofold increase in comparison with controls; frequency in controls not given.

Table 2 HLA antigen frequency in 45 SLE patients compared with 350 controls

HLA	Controls		Patients	
	No.	%	No.	%
<i>First locus</i>				
A1	112	32.0	17	37.8
A2	168	48.0	16	35.5
A3	106	30.0	15	33.3
A9	51	14.5	8	17.8
A10	67	19.1	7	15.5
A11	31	8.9	8	17.8
A28	35	10.0	0	0.0
<i>Second locus</i>				
B5	44	12.6	5	11.1
B7	77	22.0	14	31.1
B8	77	22.0	14	37.8*
B12	67	19.1	7	15.5
B13	25	7.1	5	11.1
B14	9	2.5	1	2.2
B18	50	14.4	3	6.7
B27	28	8.0	5	11.1
Bw15	45	12.8	2	4.4
Bw17	26	7.4	3	4.4
Bw21	23	6.5	0	0.0
Bw22	15	4.3	3	6.7
Bw35	68	19.4	9	20.0
Bw40	34	9.7	2	4.4

* P < 0.025, P corrected > 0.05.

The relative risk of SLE for HLA-B8 is 2.15 (95% confident limits 1.14-4.06).

Table 3 Percentage of 45 patients meeting the preliminary criteria for the classification of SLE

Criterion	%
Facial erythema	71.11
Discoid lupus	13.33
Raynaud's phenomenon	35.55
Alopecia	42.85
Photosensitivity	26.66
Oral or nasal ulcers	0
Arthritis without deformity	93.33
LE-cells	84.44
Chronic false-positive STS	0
Profuse proteinuria	26.65
Cellular casts	55.33
Pleuritis	40.00
Pericarditis	13.33
Psychosis	4.44
Convulsions	17.77
Haemolytic anaemia	4.44
Leucopenia	60.00
Thrombocytopenia	20.00

STS = serological tests for syphilis.

Discussion

The increased frequency of HLA-B8 antigen found in our group of patients agrees with data previously published (Grumet *et al.*, 1971; Goldberg *et al.*, 1973; Stenzky *et al.*, 1973) concerning an association between this antigen and SLE. This association was not found to be significant in any of the above

reports nor in our study after P values had been corrected for the number of antigens tested. However, the combined relative risk for HLA-B8 calculated from all these data (467 SLE patients) is highly significant (Iványi *et al.*, 1976).

In addition to HLA-B8, three cross-reacting antigens, HLA-Bw35, HLA-B5, and HLA-Bw15, have most frequently been mentioned in the literature in association with SLE (Table 1). It is interesting that while an increased frequency of HLA-B8 antigen has been described in several autoimmune diseases, an association of one of these, namely Graves's disease, with HLA-Bw35 was found recently in Japanese patients (Grumet *et al.*, 1975). Accordingly, the occurrence of different HLA antigens in association with the same disease in different ethnic groups may be expected for other HLA-B8-associated diseases as well. The association of SLE with HLA-Bw35 (Bitter *et al.*, 1972), HLA-B5 (Nies *et al.*, 1974; Stastny, 1972), and HLA-Bw15 antigens (Grumet *et al.*, 1971), seen mainly in non-Caucasian patients (see Table 1), agrees with this assumption.

Further data are needed to permit calculation of the combined relative risk for the above-mentioned group of antigens in SLE. Nevertheless, the available data may indicate that Ir genes which control the ability to mount an autoimmune reaction occur in linkage disequilibrium with HLA-B8 in Caucasians and with antigens of the cross-reacting group HLA-Bw35, HLA-B5, and HLA-Bw15 in non-Caucasians. Interestingly, insulin-dependent juvenile diabetes mellitus is associated with both HLA-B8 and HLA-Bw15 antigens (Nerup *et al.*, 1974). The associations between HLA antigens and some diseases are most frequently interpreted as the result of HLA-linked gene action controlling the immune response to various antigens and the susceptibility to certain viruses. This interpretation is based on the analogy of the HLA system with the mouse H-2 system, where these genes have already been precisely located. However, the mouse H-2 system is also associated with a genetic factor that regulates the level of complement and influences the metabolism of androgen hormones and cAMP (for review see Iványi, 1975). The possible analogies in man offer alternative interpretations of HLA and disease associations.

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