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HLA ANTIGENS IN PATIENTS WITH LICHEN PLANUS

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Abstract. HLA-ABC antigens were determined in 89 patients with biopsy-confirmed lichen planus, and the HLA antigen frequencies were compared with those in 1967 controls. The younger patients were predominantly male, the older patients predominantly female. No significant association was found between HLA types and lichen planus in this study. A slightly greater incidence of HLA-A 3 and B 5 antigens was seen, but this increased frequency was not as pronounced as reported by others. When combined, available data on HLA and lichen planus indicate a slightly, but significantly, increased frequency of HLA-A 3. None of the HLA antigens known to be associated with insulin-dependent diabetes are associated with lichen planus.

Key words: Lichen planus; HLA-antigens; Diabetes

The aetiology of lichen planus is unknown, but an element of auto-immunity has been suggested. A variety of auto-immune conditions have been found to occur in individuals carrying certain antigens of the HLA major histocompatibility system (14). Saurat (11) found a slight increase in the frequency of HLA-A 3, B 5 and B 8, and Lowe (7) found an increased frequency of HLA-A 3 among patients with lichen planus. He also found an association between the presence of HLA-B 5 and chemical or overt diabetes mellitus in a group of patients with lichen planus (6). Abnormal carbohydrate metabolism has been noted in a group of patients with oral lichen planus (4), and Powell (9) found similar circumstances in patients with cutaneous lichen planus. Severe familial lichen planus has been found to be associated with HLA-B 7 tissue antigen (1), while another study of familial lichen planus did not reveal a prevalence of any particular tissue antigen (12).

Insulin-dependent diabetes is commonly associated with the presence of HLA-B 8 and Bw 15 (2, 8). The following study was conducted to determine the distribution of HLA antigens in a large group of patients with lichen planus, and more specifically to establish the frequency of the antigens commonly associated with abnormal carbohydrate metabolism.

MATERIAL AND METHODS

Eighty-nine patients, 41 males and 48 females, with lichen planus verified by biopsy participated in the investigation. The ages and sex distribution of the patients are set out in Table I. The medical history of the patients included the age at onset of lichen planus, family history of diabetes,

Table I. *Age and sex distribution of eighty-nine patients with lichen planus*

	At the time of examination			At the onset of lichen planus		
Age	Male	Female	Total	Male	Female	Total
0– 9	0	0	0	2	0	2
10–19	2	1	3	5	2	7
20–29	10	4	14	10	6	16
30–39	3	6	9	5	6	11
40–49	6	5	11	5	10	15
50–59	13	14	27	10	12	22
60–69	6	12	18	4	8	12
70–79	1	4	5	0	2	2
80–89	0	2	2	0	2	2
Total	41	48	89	41	48	89

Table II. *Distribution of HLA tissue antigens among 89 patients with lichen planus and 1 967 controls*

HLA antigen	Patients		Controls		Cross ratio (Haldane)	*P* (Fischer)
	No. positive	% of 89	No. positive	% of 1 967		
A 1	25	28.1	611	31.1	0.88	0.32
A 2	53	59.6	1 055	53.6	1.27	0.16
A 3	29	32.6	530	26.9	1.32	0.15
A 9	13	14.6	340	17.3	0.84	0.31
A 10	8	9.0	188	9.6	0.98	0.52
A 11	11	12.4	199	10.1	1.30	0.30
A 28	6	6.7	196	10.0	0.70	0.21
Aw 19	16	18.0	351	17.8	1.03	0.53
B 5	12	13.5	209	10.6	1.35	0.24
B 7	18	20.2	527	26.8	0.71	0.10
B 8	26	29.2	167	23.7	1.34	0.15
B 12	13	14.6	495	25.2	0.52	0.01
B 13	3	3.4	84	4.3	0.90	0.47
B 14	3	3.4	88	4.5	0.86	0.44
B 18	2	2.2	139	7.1	0.37	0.05
B 27	8	9.0	170	8.6	1.10	0.51
Bw 15	19	21.3	352	17.9	1.27	0.24
Bw 16	6	6.7	106	5.4	1.36	0.36
Bw 17	2	2.2	151	7.7	0.34	0.03
Bw 21	2	2.2	69	3.5	0.78	0.40
Bw 22	3	3.4	75	3.8	1.01	0.56
Bw 35	21	23.6	257	13.1	2.08	0.006
Bw 37	4	4.5	32	1.6	3.13	0.07
Bw 40	19	21.3	353	17.9	1.26	0.25
Bw 41	1	1.1	25	1.3	1.29	0.69
Cw 4	26	29.2	73[a]	17.1	1.94	0.008

[a] The number of controls for this antigen was 426.

Table III. *Distribution of HLA-tissue antigens among 89 patients with lichen planus and 1 967 controls according to various clinical subgroups*

Lichen Planus . . .		HLA-A 3		HLA-B 5		HLA-B 8		HLA-B 12	
	N	*N*	%	*N*	%	*N*	%	*N*	%
Controls	1 967	530	26.9	209	10.6	467	23.7	495	25.2
Patients	89	29	32.6	12	13.5	26	29.2	13	14.6
♂	41	13	31.7	7	17.1	10	24.4	3	7.3
♀	48	16	33.3	5	10.4	16	33.3	10	20.8
>1 year ♂ ♀	48	17	35.4	5	10.4	16	33.3	7	14.6
>1 year ♂	24	9	37.5	3	12.5	6	25.0	2	8.3
>1 year ♀	24	8	33.3	2	8.3	10	41.7	5	20.8
≤1 year ♂	17	4	23.5	4	25.3	4	23.5	1	5.9
≤1 year ♀	24	8	33.3	3	12.5	6	25.0	5	20.8
≤40 years ♂	23	9	39.1	4	17.4	7	30.4	2	8.7
≤40 years ♀	14	6	42.9	4	28.6	6	42.9	3	21.4
>40 years ♂	18	4	22.2	3	16.7	3	16.7	1	5.6
>40 years ♀	34	10	29.4	1	2.9	10	29.4	7	20.6
Guttate ♂ ♀	53	20	37.7	7	13.2	13	24.5	9	17.0
Hypertrophic ♂ ♀	20	6	30.0	0	0.0	8	40.0	2	10.0
Familial diabetes ♂ ♀	20	4	25.0	3	15.0	5	25.0	2	10.0
Diabetes ♂	4	0	0.0	0	0.0	2	50.0	0	0.0
Oral lesions ♂ ♀	41	13	31.7	9	22.0	10	24.4	5	12.2
Oral lesions + fam. diab.	10	2	20.0	3	30.0	2	20.0	0	0.0

[a] Studied in only 426 individuals.

and drug intake at the time of onset. Patients taking drugs know to cause lichen planus-like eruptions were excluded from the study. The oral mucosa of each patient was examined clinically for lichen planus lesions, and the distribution of cutaneous lesions was noted. The cutaneous lesions were described as guttate, hypertrophic, or "other". The latter group included bullous, atrophic, and ulcerative lesions.

The HLA antigens were determined by previously described methods (5). The distribution of the antigens listed in Table III was determined. The 1967 controls were healthy, unrelated to one another, but of the same ethnic origin as the patients.

The relative risk of an association between the disease and a particular HLA antigen was expressed by means of the cross-product ratio. Fisher's exact test was used to determine the statistical significance of the deviations of antigen frequencies among the patients as compared with the controls. The risk of false associations, due to the large number of antigens studied, was minimized by the use of conservative significance limits (13). The deviations were considered significant only if the p-values obtained were under 0.05 divided by the number of antigens studied: 26 ($p<2 \cdot 10^{-3}$). The χ^2 test was used to estimate the significance level of the heterogeneity between the three groups of patients listed in Table IV.

RESULTS

The age at onset of lichen planus for the 89 patients is recorded in Table I. Twenty-two of 36 patients with onset before the age of 40 were males, while only 19 of 53 with onset after the age of 40 were males. This difference is statistically significant ($\chi^2=5.5$, $p<0.05$). The disease duration at the time of examination was one year or less for 17 of 41 males and for 24 of 48 females.

Lesions of guttate morphology were seen in 53 patients, while hypertrophic lesions were seen in 20. Both morphologies were seen in 11 patients. Three patients had either atrophic, ulcerative, or bullous lesions, while 2 had only oral mucous membrane lesions. Oral lesions were seen in 41 patients. Twenty patients had a family history of diabetes mellitus, and 4 had overt diabetes, 2 with juvenile and 2 with late-onset diabetes.

The distribution of HLA antigens among the 89 patients and 1967 controls is listed in Table III. The antigens showing the largest deviations in the patients were HLA-B 12 (decreased), B 18 (decreased), B 17 (decreased), Bw 35 (increased), and Bw 37 (increased), but none of these deviations was significant. Because of the increase in Bw 35, the frequency of Cw 4 (which is associated with Bw 35 in the random population) was also studied. It showed approximately the same association as Bw 35. Slightly, but insignificantly, increased frequencies of HLA-A 3 and B 5 were seen, as well as of the diabetes-associated antigens HLA-B 8 and Bw 15. When the patients were grouped on the basis of clinical findings (Table III), increased frequencies of HLA-Bw 35 and Cw 4 were found among male patients with a disease duration of more than a year. A decreased frequency of HLA-B 12 was seen, particularly in male patients over the age of 40. The increased frequency of HLA-B 5 was seen particularly among patients with oral lesions. This subgroup did not have an increased frequency of HLA-B 8 or HLA-Bw 15. When corrections for the number of clinical subdivisions were introduced into the statistical considerations, none of these deviations was statistically significant.

When the available data on HLA tissue typing of patients with lichen planus are pooled (the group of patients of Saurat et al. (11), those of Lowe, Cudworth & Woodrow (7), and the group presented here) a total of 189 patients and 2858 controls have been examined (Table IV). The most marked deviations were seen for HLA-A 3 (present in 33–54% of the patients and 26–30% of the controls), for HLA-B 5 (present in 13–21% of the patients and in

HLA-Bw 15		HLA-Bw 35		HLA-Cw 4	
N	%	N	%	N	%
352	17.9	257	13.1	73[a]	17.1
19	21.3	21	23.6	26	29.2
7	17.1	12	29.3	14	34.1
12	25.0	9	18.8	12	25.0
10	20.8	13	27.1	17	35.4
2	8.3	10	41.7	12	50.0
8	33.3	3	12.5	5	20.8
5	29.4	2	11.8	2	11.8
4	16.7	6	25.0	7	29.2
4	17.4	6	26.1	7	30.3
2	14.3	2	14.3	4	28.6
3	16.7	3	33.3	7	38.9
10	29.4	7	20.6	8	23.5
12	22.6	15	28.3	18	34.0
5	25.0	5	25.0	6	30.0
4	20.0	4	20.0	6	30.0
3	75.0	0	0.0	2	50.0
5	12.2	11	26.8	13	31.7
1	10.0	1	10.0	2	20.0

Table IV. *Distribution of HLA-tissue antigens in the present group of patients combined with those previously reported*

HLA antigen	No. of studies	Patients		Controls		Cross ratio (Haldane)	Significance level (relative risk)	*p*-value (heterogeneity)
		Total	% POS-range	Total	% POS-range			
A 1	3	189	26–33	2 858	23–34	0.97	>0.05	>0.05
A 2	3	189	33–60	2 858	44–54	0.93	>0.05	>0.05
A 3	3	189	33–54	2 858	26–30	1.75	0.00036	>0.05
A 9	3	189	12–16	2 858	17–20	0.78	>0.05	>0.05
A 10	3	189	9–12	2 858	7–10	1.28	>0.05	>0.05
A 11	3	189	7–18	2 858	10–13	1.19	>0.05	>0.05
A 28	3	189	2– 7	2 858	5–10	0.72	>0.05	>0.05
A 29	1	43	9– 9	591	11–11	0.92	>0.05	–
Aw 19	1	89	18–18	1 967	18–18	1.03	>0.05	–
Aw 32	1	43	2– 2	591	5– 5	0.65	>0.05	–
Aw 33	1	43	5– 5	591	1– 1	5.43	0.017	–
B 5	3	189	13–21	2 858	9–13	1.75	0.006	>0.05
B 7	3	189	12–33	2 858	19–31	0.81	>0.05	>0.05
B 8	3	189	26–30	2 858	17–31	1.29	>0.05	>0.05
B 12	3	189	15–32	2 858	25–29	0.83	>0.05	>0.05
B 13	3	189	0– 3	2 858	2– 6	0.80	>0.05	>0.05
B 14	3	189	3–14	2 858	4– 9	1.37	>0.05	>0.05
B 18	3	189	2–14	2 858	4–12	1.14	>0.05	>0.05
B 17	3	189	7–14	2 858	7– 9	1.32	>0.05	>0.05
Bw 15	3	189	7–21	2 858	8–18	1.19	>0.05	>0.05
Bw 16	1	89	7– 7	1 967	5– 5	1.36	>0.05	–
Bw 17	3	189	2– 9	2 858	7– 8	0.82	>0.05	>0.05
Bw 21	2	132	2– 5	2 558	4– 9	0.69	>0.05	>0.05
Bw 22	3	189	2– 3	2 858	4– 5	0.75	>0.05	>0.05
Bw 35	3	189	12–24	2 858	13–19	1.48	0.04	>0.05
Nw 37	1	89	4– 4	1 967	2– 2	3.13	0.02	–
Bw 40	3	189	5–21	2 858	10–18	1.06	>0.05	>0.05
Bw 41	1	89	1– 1	1 967	1– 1	1.29	>0.05	–

9–13% of the controls) and for HLA-Bw 35 (present in 12–24% of the patients and in 15–19% of the controls). The increased frequency of HLA-A 3 was statistically significant ($p=0.00036$); none of the other deviations was statistically significant when the number of comparisons made is taken into account.

DISCUSSION

We found no predominance of the HLA antigens commonly associated with insulin-dependent diabetes among patients with lichen planus. Neither were these antigens predominant in a sub-group of patients with oral lesions. This type of lesion has previously been associated with diabetes (4). The normal distribution of diabetes-associated antigens found in the current study is in agreement with the reports by Jolly (4) and Powell (9). Their patients had lichen planus and chemical or late-onset diabetes which do not appear to be associated with specific HLA antigens (14).

In patients with Addison's disease and myasthenia gravis, which have been reported to occur concurrently with lichen planus (3), the HLA-B 8 antigen has been detected with increased frequency. Saurat (11) reported similar findings in patients with lichen planus. This antigen was not found with increased frequency among the patients in the current study. Nor was there a significant increase in the frequency of HLA-A 3 or B 5, which have previously been associated with lichen planus (7, 11). When the previosly published data were pooled with those of the present study, somewhat increased frequencies of HLA-A 3 and B 5 were found, but only the deviation of A 3 was still significant, indicating that there may be a weak association between this antigen and lichen planus.

There was in the current study a preponderance of males among patients with onset of the disease at

an early age, and a greater proportion of females among patients whose age at onset was 40 years or more than in the group of patients described by Samman (10).

It is concluded that the HLA antigens commonly associated with insulin-dependent diabetes are not found with increased frequency among patients with lichen planus, but that there may be a rather weak association between HLA-A3 and lichen planus.

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