HLA antigens in ocular cicatricial pemphigoid

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SUMMARY HLA antigen frequencies were studied in 20 patients with ocular cicatricial pemphigoid and 245 normal persons. HLA-B12 demonstrated an increased frequency of 45% in patients with ocular cicatricial pemphigoid which was statistically significant when compared to a frequency of 19.6% in the general population ($P < 0.02$). In patients with ocular cicatricial pemphigoid the prevalence of HLA-A3 was increased to 35% when compared to 22.9% in the general population, but this was not statistically significant. The frequency of finding either HLA-A3 or B12 in patients with ocular cicatricial pemphigoid was increased to 75% in comparison with 38.8% in the general population ($P < 0.005$). The present study suggests that HLA-B12 and possibly HLA-A3 are genetic markers for ocular cicatricial pemphigoid.

Substantial evidence is accumulating that HLA antigens are correlated with particular disease entities in man (McDevitt and Bodmer, 1974; Dausset and Hors, 1975; Henley and Leopold, 1975; Svejgaard *et al.*, 1975). Many of the diseases associated with HLA antigens are tentatively classified as autoimmune: chronic active hepatitis, multiple sclerosis, myasthenia gravis, Graves's disease, and pemphigus (McDevitt and Bodmer, 1974; Svejgaard *et al.*, 1975). The finding of tissue-fixed immunoglobulins and complement in the conjunctival epithelium and its basement membrane of patients with ocular cicatricial pemphigoid suggests that autoimmune phenomena underlie or are at least associated with this condition (Griffith *et al.*, 1974; Furey *et al.*, 1975; Mondino *et al.*, 1977). Because of these immunopathological features in ocular pemphigoid and because of the postulated linkage of HLA antigens with immune response genes (McDevitt and Bodmer, 1974; Katz and Benacerraf, 1975), histocompatibility antigen testing was performed on 20 patients with ocular pemphigoid to determine if one or more HLA antigens were more prevalent in this population.

Materials and methods

Twenty unrelated Caucasian patients with the clinical

diagnosis of ocular cicatricial pemphigoid were included in this study. Patients with other causes of conjunctival scarring and shrinkage such as radiation or chemical burns, membranous conjunctivitis, or erythema multiforme were excluded. The control population comprised 245 normal Caucasian individuals from the Pittsburgh area. There was a normal distribution of ABO blood groups in this population.

HLA tissue typing was performed by lymphocyte cytotoxicity (Amos, 1974). A total of 96 HLA typing sera were employed to define 16 different A-locus antigen specificities and 15 different B-locus antigen specificities. Statistical analysis was performed by the chi-square test with Yates's correction.

Results

The HLA antigen frequencies in the patient and control groups are presented in Table 1. HLA-B12 showed an increased frequency of 45% in patients with ocular cicatricial pemphigoid, which was statistically significant when compared with a frequency of 19.6% in the general population ($P < 0.02$). In the group with ocular cicatricial pemphigoid the prevalence of HLA-A3 was increased to 35% when compared with 22.9% in the general population, but this was not statistically significant. The frequency of finding either HLA-A3 or B12 in patients with ocular cicatricial pemphigoid was increased to 75% in comparison with 38.8% in the general population ($P < 0.005$). Only one patient in

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Table 1 Frequencies of HLA antigens

General population			Ocular cicatricial Pemphigoid	
No. = 245			No. = 20	
	No.	(%)	No.	(%)
A1	62	(25.3)	6	(30.0)
A2	118	(48.2)	10	(50.0)
A3	56	(22.9)	7	(35.0)*
A9	37	(15.1)	4	(20.0)
A10	19	(7.8)	2	(10.0)
A11	27	(11.0)	0	—
A28	20	(8.2)	2	(10.0)
A29	7	(2.9)	1	(5.0)
AW23	5	(2.0)	0	—
AW24	21	(8.6)	2	(10.0)
AW25	6	(2.4)	0	—
AW26	4	(1.6)	0	—
AW30	22	(9.0)	0	—
AW31	8	(3.3)	2	(10.0)
AW32	13	(5.3)	0	—
AW33	2	(0.8)	0	—
B5	24	(9.8)	0	—
B7	41	(16.7)	6	(30.0)*
B8	48	(19.6)	3	(15.0)
B12	48	(19.6)	9	(45.0)†
B13	19	(7.8)	0	—
B15	12	(4.9)	1	(5.0)
B18	30	(12.2)	2	(10.0)
B27	20	(8.2)	2	(10.0)
BW15	24	(9.8)	0	—
BW16	14	(5.7)	2	(10.0)
BW17	23	(9.4)	1	(5.0)
BW21	14	(5.7)	0	—
BW22	5	(2.0)	0	—
BW35	66	(26.9)	3	(15.0)
BW40	32	(13.1)	4	(20.0)
Either B12 or A3	95	(38.8)	15	(75.0)‡

*Not significant.

† $\chi^2=5.64$, $P<0.02$ as compared to general population (Yates's corrected chi-square test).

‡ $\chi^2=8.55$, $P<0.005$ when compared to general population (Yates's corrected chi-square test).

the pemphigoid series had both the HLA-A3 and B12 antigens.

Discussion

To date, several HLA antigens have been associated with ocular disease. HLA-B27 has been associated with Reiter's syndrome and acute anterior uveitis (McDevitt and Bodmer, 1974; Henley and Leopold, 1975; Svejgaard *et al.*, 1975), HLA-B5 with Behçet's disease (Ohno *et al.*, 1975), HLA-BW22J with Vogt-Koyanagi-Harada syndrome (Tagawa *et al.*, 1976), and HLA-A3, B7, and B12 with primary open-angle glaucoma (Becker and Shin, 1977; Shin *et al.*, 1977).

The present study revealed an increased frequency of HLA-B12 and A3 in 20 unrelated patients with ocular cicatricial pemphigoid. This was statistically significant, however, only in the case of HLA-B12 ($P<0.02$). This study also showed that 75% of

patients with ocular cicatricial pemphigoid had either HLA-A3 or B12, and that this prevalence was statistically significant when compared with 38.8% in the general population ($P<0.005$). This latter finding suggests that, as additional patients are studied with ocular cicatricial pemphigoid, an increased frequency of HLA-A3 in itself will be statistically demonstrated. There does not appear to be a linkage disequilibrium between HLA-A3 and B12 in patients with ocular cicatricial pemphigoid, since only 1 patient possessed both antigens.

There is also an increased prevalence of HLA-B12 in patients with primary open-angle glaucoma and HLA-A3 in white patients with primary open-angle glaucoma (Becker and Shin, 1977; Shin *et al.*, 1977). The finding that an HLA antigen is associated with multiple diseases is not without precedent. HLA-B27 has been associated with ankylosing spondylitis, Reiter's disease, and acute anterior uveitis, while HLA-B8 is correlated with Graves's disease, myasthenia gravis, chronic hepatitis, and dermatitis herpetiformis (McDevitt and Bodmer, 1974; Svejgaard *et al.*, 1975). HLA-A3 and B7 have been associated with multiple sclerosis in addition to primary open-angle glaucoma (McDevitt and Bodmer, 1974; Svejgaard *et al.*, 1975).

None of the patients with ocular cicatricial pemphigoid in this series had evidence of primary open-angle glaucoma. Intraocular pressure determinations on numerous occasions by Goldmann tonometry and Alcon pneumo-tonometry were all normal except for 2 patients who developed secondary glaucoma attributable to extensive anterior and posterior synechiae following repair of corneal perforations. Photophobia together with extensive corneal scarring and vascularisation precluded reliable visual field testing in the majority of patients.

The results of the present study suggest that HLA-B12 and possibly HLA-A3 are genetic markers for ocular cicatricial pemphigoid.

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