HLA antigens in glaucoma and ocular hypertension

ROBERT DAVID,¹ GUNTILT MAIER,² INGRID BAUMGARTEN,² AND CYRIL ABRAHAMS¹

From the ¹Department of Ophthalmology, Medical School, University of the Witwatersrand, Johannesburg, and the ²Tissue Bank, Department of Immunology of the School of Pathology of the South African Institute for Medical Research and the University of the Witwatersrand, Johannesburg, South Africa

SUMMARY Forty-five white patients (32 with open-angle glaucoma and 13 with ocular hypertension) and 63 black patients (41 with open-angle glaucoma and 22 with ocular hypertension) were tissue typed for a total of 38 HLA antigens and the results compared to normal, unrelated, panels of 248 white donors and 150 black volunteers, respectively. No statistically significant differences with regard to the frequencies of 38 HLA antigens were detected among the various groups.

It is now generally accepted that genetic factors are involved to a considerable extent in the pathogenesis of primary open-angle glaucoma (OAG). An increased incidence of the disease has been reported among sibs and offspring of patients with glaucoma (Miller and Paterson, 1962; Leighton, 1968; Jay and Paterson, 1972). Furthermore, some of the features found in patients with glaucoma have been shown to be heritable, such as the cup/disc ratio (Armaly, 1967a), the hypersensitivity to topically administered corticosteroids (Armaly, 1967a, b) and the level of the intraocular pressure (Armaly, 1967c). While the exact mode of transmission in primary OAG has not been fully elucidated, evidence at present suggests a multifactorial mode of inheritance (Armaly, 1965; Jay and Paterson, 1972).

With the development of tissue typing, and the identification of the various HLA antigens, correlations have been found between some eye diseases and the increase in the frequency of certain HLA antigens in the affected population (Brewerton *et al.*, 1973; Brewerton *et al.*, 1974).

With evidence that certain features in OAG are genetically determined search for an association between HLA antigens and the disease has been undertaken. The results, however, are rather conflicting. Aviner *et al.* (1976) found an increased incidence of HLA Bw35 among their 49 patients with OAG, while Shin and Becker (1977) reported the opposite, the presence of HLA Bw35 apparently providing protection from glaucoma. In another study by the same group primary OAG was found

to be associated with an increased incidence both of HLA B7 and of HLA B12 (Shin *et al.*, 1977), while Grabner and Mayr (1977) found no correlation between OAG and an increased or decreased frequency of any particular HLA antigen.

In the present study we report on our results of HLA typing in white and black patients with glaucoma and ocular hypertension.

Definition of criteria

Primary open-angle glaucoma: patients with glaucomatous visual field defects, excavation with atrophy of their optic disc in the presence of an intraocular pressure of 21 mmHg or more, and an open filtration angle.

Ocular hypertension: patients with intraocular pressure of 21 mmHg or more when tested repeatedly, a normal optic disc, no glaucomatous visual field defect, and an open filtration angle.

Patients and methods

One hundred and eight patients were included in the study. There were 45 white patients, 32 with OAG and 13 with ocular hypertension, and 63 black patients, 41 with OAG and 22 with ocular hypertension. All patients attended the Glaucoma Clinics at the Johannesburg General Hospital and St John's Eye Hospital, Baragwanath. The control panel consisted of 248 healthy, unrelated white donors and 150 unrelated black volunteers belonging to various Southern African tribes.

Tissue typing was performed at the Tissue Bank of the South African Institute for Medical Research. The method used was the Standard 2 Stage NIH

Address for reprints: G. Maier, MD, Tissue Bank, Department of Immunology, South African Institute for Medical Research, Johannesburg, South Africa

Lymphocyte Microcytotoxicity Test at an incubation temperature of 37°C throughout the test and trypan blue as the indicator dye. A total of 174 different typing sera were used to identify 38 HLA antigens: 17 of the A locus, 18 of the B locus, and 3 of the C locus.

The statistical analysis of the results was performed by χ^2 test with Yates's correction. The P values obtained were corrected by multiplication with the number of antigens tested, Pc.

Results

The distribution of the frequencies of the various HLA antigens in the two races differ widely (Payne *et al.*, 1977). Therefore the 2 race groups in this

Table 1 HLA antigen frequencies in white patients with glaucoma

	Controls N=248 %	OAG patients N=32 %	χ^2y	P	Pc
HLA A1	27.0	25.0	0.001	NS	
Aw36	0.0	0.0			
A2	38.3	50.0	1.17	NS	
A3	31.5	12.5	4.04	<0.05	NS
A9	28.2	31.3	0.02	NS	
A10	3.2	3.1	0.25	NS	
Aw25	2.4	0.0	0.06	NS	
Aw26	4.8	15.6	4.05	<0.05	NS
Aw34	0.8	0.0	0.37	NS	
A11	12.1	6.3	0.47	NS	
A28	9.3	9.4	0.09	NS	
A29	7.2 ¹	3.1	0.10	NS	
Aw30	1.8 ¹	3.1	0.12	NS	
Aw31	9.1 ¹	3.1	0.38	NS	
Aw32	5.5 ¹	0.0	0.54	NS	
Aw33	1.8 ¹	9.4	1.19	NS	
Aw43	0.0	0.0			
HLA B5	12.1	9.3	0.03	NS	
B7	29.0	18.8	1.02	NS	
Bw42	0.0	0.0			
B8	18.1	25.0	0.48	NS	
Bw16	8.9	15.6	0.81	NS	
B12	29.4	28.1	0.003	NS	
B37	1.6	6.3	1.12	NS	
B13	6.5	6.3	0.12	NS	
Bw35	17.3	21.9	0.15	NS	
B15	11.7	6.3	0.39	NS	
B18	4.0	3.1	0.06	NS	
B14	8.9	9.4	0.06	NS	
Bw21	3.2	3.1	0.25	NS	
Bw22	4.8	6.3	0.01	NS	
B27	9.7	3.1	0.80	NS	
B40	12.1	12.5	0.05	NS	
Bw41	0.0 ²	6.3	1.46	NS	
B17	14.1	9.4	0.21	NS	
HLA Cw2	5.0 ²	3.1	0.01	NS	
Cw3	18.3 ²	28.1	0.67	NS	
Cw4	20.0 ²	18.8	0.02	NS	
HLA B7 or B12	51.2	46.9	0.07	NS	
HLA A11 or Bw35	39.5	43.8	0.07	NS	

¹ Tested 55. ² Tested 60.

Table 2 HLA antigen frequencies in white patients with ocular hypertension

	Controls N=248 %	OHT patients N=13 %	χ^2y	P	Pc
HLA A1	27.0	38.5	0.34	NS	
Aw36	0.0	0.0			
A2	38.3	30.8	0.06	NS	
A3	31.5	30.8	0.07	NS	
A9	28.2	15.4	0.48	NS	
A10	3.2	0.0	0.03	NS	
Aw25	2.4	7.7	0.07	NS	
Aw26	4.8	0.0	0.02	NS	
Aw34	0.8	0.0	1.71	NS	
A11	12.1	15.4	0.01	NS	
A28	9.3	15.4	0.06	NS	
A29	7.2 ¹	7.7	0.29	NS	
Aw30	1.8 ¹	0.0	0.63	NS	
Aw31	9.1 ¹	0.0	0.29	NS	
Aw32	5.5 ¹	7.7	0.12	NS	
Aw33	1.8 ¹	0.0	0.63	NS	
Aw43	0.0	0.0			
HLA B5	12.1	7.7	0.002	NS	
B7	29.0	23.0	0.02	NS	
Bw42	0.0	0.0			
B8	18.1	23.0	0.01	NS	
Bw16	8.9	0.0	0.37	NS	
B12	29.4	15.4	0.60	NS	
B37	1.6	7.7	0.27	NS	
B13	6.5	0.0	0.12	NS	
Bw35	17.3	15.4	0.04	NS	
B15	11.7	7.7	0.00	NS	
B18	4.0	7.7	0.005	NS	
B14	8.9	23.0	1.47	NS	
Bw21	3.2	23.0	7.64	<0.01	NS
Bw22	4.8	7.7	0.04	NS	
B27	9.7	0.0	0.47	NS	
B40	12.1	7.7	0.0	NS	
Bw41	0.0 ²	0.0			
B17	14.1	0.0	1.08	NS	
HLA Cw2	5.0 ²	7.7	0.08	NS	
Cw3	18.3 ²	15.4	0.02	NS	
Cw4	20.0 ²	0.0	1.82	NS	

¹ Tested 55. ² Tested 60.

study were dealt with separately. The frequencies of the 38 HLA antigens investigated in the glaucoma patients and ocular hypertensives as compared to the controls are presented in Tables 1 and 2 for the white groups and in Tables 3 and 4 for the black groups.

WHITE GROUPS

In the white glaucoma group a decrease of the frequency of A3 and an increase in the frequency of Aw26 was found (see Table 1). These values did not reach statistical significance when P was corrected.

An increased incidence of the antigens Bw21 and Cw2 were noted in white ocular hypertensives (see Table 2). These results, however, are most probably attributable to the small number of patients in this group and were no longer statistically significant when P was corrected.

Table 3 HLA antigen frequencies in black patients with glaucoma

	Controls N=150 %	OAG patients N=41 %	χ^2y	P	Pc
HLA A1	6.0	4.9	0.01	NS	
Aw36	0.0	0.0			
A2	25.3	22.0	0.06	NS	
A3	12.0	9.8	0.02	NS	
A9	17.3	19.5	0.01	NS	
A10	0.7	2.4	0.02	NS	
Aw25	0.0	0.0			
Aw26	15.3	19.5	0.16	NS	
Aw34	7.3	9.8	0.03	NS	
A11	0.7	0.0	0.49	NS	
A28	22.7	17.1	0.31	NS	
A29	11.3	14.6	0.09	NS	
Aw30	28.7	39.0	1.17	NS	
Aw31	16.0	4.9	2.51	NS	
Aw32	2.7	4.9	0.05	NS	
Aw33	2.0	0.0	0.04	NS	
Aw43	2.7	2.4	0.19	NS	
HLA B5	4.7	4.9	0.13	NS	
B7	18.7	17.1	0.00	NS	
Bw42	19.3	12.2	0.69	NS	
B8	8.7	9.8	0.01	NS	
Bw16	2.0	7.3	1.50	NS	
B12	24.0	26.9	0.03	NS	
B37	0.0	0.0			
B13	1.3	2.4	0.04	NS	
Bw35	10.7	14.6	0.18	NS	
B15	2.7	2.4	0.22	NS	
B18	13.3	7.3	0.61	NS	
B14	5.3	2.4	0.13	NS	
Bw21	0.7	0.0	0.49	NS	
Bw22	3.3	4.9	0.00	NS	
B27	0.7	0.0	0.49	NS	
B40	2.0	0.0	0.04	NS	
Bw41	10.3	2.4	0.04	NS	
B17	34.7	39.0	0.11	NS	
HLA Cw2	36.7	26.8	0.98	NS	
Cw3	20.0	4.9	4.25	< 0.05	NS
Cw4	22.7	46.3	7.86	< 0.01	NS
HLA B7 or B12	41.3	43.9	0.01	NS	
HLA A1 or A11	6.7	4.9	0.00	NS	

BLACK GROUPS

Cw3 showed a decreased frequency and Cw4 an increased frequency in the black glaucoma patients, but again when P was corrected no statistical significance resulted (see Table 3). There was no deviation from the normal HLA antigen distribution in the black ocular hypertensives (Table 4).

Discussion

The results in this series are in accordance with the findings of Grabner and Mayr (1977), who found no difference in the incidence of any of the 36 HLA antigens tested in their 41 white patients with OAG when compared to 450 controls. Their and our results, however, are in discordance with reports which found associations (positive and negative) between certain HLA antigens and glaucoma. Shin

et al. (1977) and Shin and Becker (1976) found a highly significant association between the B locus antigens B7 and B12 in both their white and black patients with OAG. The significance increased further when the presence of either 1 of the 2 antigens was considered. In our series these 2 antigens were not found to be present more frequently in patients with OAG, white or black.

Becker and Shin (1977) observed also an increased prevalence of HLA A3 in their white but not in their black patients with OAG. This is to be expected, as HLA A3 and HLA B7 occur in a marked positive linkage disequilibrium in the white population but not in the black (Payne *et al.*, 1977; Hammond *et al.*, 1977). Therefore an increase in the frequency of HLA B7 in the white group would probably be accompanied by a concomitant increase in HLA A3. Far more importance could be attached to an increase in HLA A3 if it should occur in a group of black patients.

Table 4 HLA antigen frequencies in black patients with ocular hypertension

	Controls N=150 %	OHT patients N=22 %	χ^2y	P	Pc
HLA A1	6.0	4.5	0.05	NS	
Aw36	0.0	0.0			
A2	25.3	18.2	0.21	NS	
A3	12.0	9.1	0.00	NS	
A9	17.3	9.1	0.45	NS	
A10	0.7	0.0	1.25	NS	
Aw25	0.0	0.0			
Aw26	15.3	13.6	0.01	NS	
Aw34	7.3	9.1	0.02	NS	
A11	0.7	0.0	1.25	NS	
A28	22.7	27.3	0.04	NS	
A29	11.3	27.3	2.94	NS	
Aw30	28.7	22.7	0.11	NS	
Aw31	16.0	9.1	0.28	NS	
Aw32	2.7	0.0	0.00	NS	
Aw33	2.0	4.5	0.00	NS	
Aw43	2.7	0.0	0.04	NS	
HLA B5	4.7	4.5	0.27	NS	
B7	18.7	18.2	0.06	NS	
Bw42	19.3	13.6	0.12	NS	
B8	8.7	4.5	0.06	NS	
Bw16	2.0	0.0	0.04	NS	
B12	24.0	31.8	0.28	NS	
B37	0.0	0.0			
B13	1.3	0.0	0.27	NS	
Bw35	10.7	13.6	0.00	NS	
B15	2.7	0.0	0.00	NS	
B18	13.3	9.1	0.05	NS	
B14	5.3	0.0	0.32	NS	
Bw21	0.7	0.0	1.25	NS	
Bw22	3.3	4.5	0.11	NS	
B27	0.7	0.9	1.25	NS	
B40	2.0	0.0	0.04	NS	
Bw41	1.3	0.0	0.27	NS	
B17	34.7	54.5	2.45	NS	
HLA Cw2	36.7	36.4	0.04	NS	
Cw3	20.0	18.2	0.01	NS	
Cw4	22.7	36.4	1.28	NS	

Furthermore, confusion exists with regard to the association of Bw35 and OAG. Aviner *et al.* (1976) found an increased incidence of HLA Bw35 in a group of patients with OAG, whereas Shin and Becker (1977) and Becker and Shin (1977) found that this antigen provides protection from OAG in whites. Our findings confirm the results of Grabner and Mayr (1977), who were unable to find a relationship between the antigen Bw35 and OAG. The observation of Aviner *et al.* (1976) should be interpreted with reserve, as they compared a racially mixed group of patients with an exclusively Caucasian control panel.

The decrease in the antigen HLA A11 in both white and black patients with glaucoma, and hence the assumed protection afforded by this antigen as stated by Shin and Becker (1977) and Becker and Shin (1977), was not borne out by our results. In the white patients this can be partly attributed to the difference in the control groups. Our controls were unselected, whereas those of Shin and Becker were preselected corticosteroid nonresponders and had a frequency of HLA A11 much higher than one would expect from a random white panel (Payne *et al.*, 1977). In addition the reported low incidence of HLA A11 (Becker and Shin, 1977) in their black patients is in fact the figure one would expect in any normal black population, HLA A11 being an extremely rare antigen in negroid people (Ward and Biegel, 1976; Hammond *et al.*, 1977; Payne *et al.*, 1977). The unusually high frequency of HLA A11 in their black controls was established from the extremely small number of 28 controls.

The only related patients in our series were 2 HLA identical sisters. Their antigen typing was as follows: HLA A2-B12, w22. One of the patients has advanced primary OAG while the sister is an ocular hypertensive followed up untreated for more than 8 years.

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