

HLA antigens in acute anterior uveitis in South African blacks

GUNTHILT MAIER,¹ BENJAMIN MILLER,² JEFFREY FREEDMAN,³ AND INGRID BAUMGARTEN¹

From the ¹Tissue Bank, Department of Immunology of the School of Pathology of the South African Institute for Medical Research and the University of the Witwatersrand, the ²Department of Ophthalmology, Medical School, University of the Witwatersrand, Johannesburg, and the ³Division of Ophthalmology, Department of Surgery, Down State Medical Centre, State University of New York

SUMMARY Fifty-three black patients with acute nongranulomatous anterior uveitis (AAU) were tissue typed and the results compared to those from a panel of 200 healthy unrelated black volunteers. No statistically significant deviation from the norm with regard to the frequencies of 38 HLA antigens could be observed.

The striking association between HLA B27, acute anterior uveitis (AAU), certain rheumatic disorders like ankylosing spondylitis, Reiter's disease, reactive arthritis, and juvenile rheumatoid arthritis has been described by several authors and is well documented (Brewerton *et al.*, 1973a, b; Schlosstein *et al.*, 1973; Caffrey and James, 1973; Brewerton *et al.*, 1974; Rachelefsky *et al.*, 1974; Brewerton, 1975; Mapstone and Woodrow, 1975; Zervas *et al.*, 1977; Ohno *et al.*, 1977).

However, in several series of patients investigated for AAU there was a considerable number of patients who possessed the antigen HLA B27 but did not show rheumatic or any other systemic disorders, the percentages of this type of patient ranging from 30% to 45%. The frequency of the antigen in the relevant control groups ranged from 4% to 8% (Brewerton and colleagues, 1974; Mapstone and Woodrow, 1975; Zervas *et al.*, 1977; Brewerton and James, 1975). All these investigations were undertaken in white patients, in whom it is now generally accepted that idiopathic AAU, that is, without rheumatic or other obvious systemic diseases, shows a significant association with the antigen HLA B27.

Perkins (1976) observed the absence of AAU due to rheumatic conditions in immigrant negroes from West Africa living in London and related this finding to the reported absence of HLA B27 in this ethnic group. Ayanru (1977) also reported the rarity of acute nongranulomatous anterior uveitis associated with rheumatic diseases among Nigerian patients and attributed this to the absence of the genetic

marker HLA B27 among Africans. In his series most of the cases showed posterior uveitis, anterior uveitis being relatively rare.

In contrast Freedman (1974) observed a different distribution in South African blacks, as most of his 355 cases suffered from anterior uveitis, and posterior uveitis was seen far less commonly. Furthermore the rate for anterior uveitis among the South African blacks, 24 per 100 000, was significantly higher than the rate of 12 per 100 000 found in Rochester. During his investigation into the aetiology of uveitis in Bantu adults Freedman (1976) observed 2 patients out of 311 in whom ankylosing spondylitis was the associated disease and described these patients as being unique, ankylosing spondylitis being extremely rare among South African blacks (Baum and Ziff, 1970).

Though the antigen HLA B27 is not altogether absent in South African blacks, it does occur at a very low frequency of 0.6% to 0.7% (Hammond *et al.*, 1977; David *et al.*, 1979). It is completely absent in the normal healthy Japanese population (Tsuji and Fukunishi, 1973). Yet when Sonozaki *et al.* (1975) investigated 27 Japanese patients who presented with ankylosing spondylitis they found the antigen present in 67% of their cases.

It was of interest, therefore, to investigate whether the association of HLA B27 and AAU, with or without systemic disease, as reported in white populations, would also hold true for a black population group.

Patients and methods

PATIENTS

Fifty-three black patients suffering from acute non-

Correspondence to Dr G. Maier, Tissue Bank, Department of Immunology, South African Institute for Medical Research, Hospital Street, Johannesburg, South Africa.

granulomatous anterior uveitis were chosen for this study out of hundreds of uveitis cases seen at the St John's Eye Hospital, Baragwanath, during the years 1976 and 1978. All the patients were examined by 2 of the authors (B.M. and J.F.), and the particulars were recorded indicating history, age, sex, clinical description of the disease, and results of laboratory investigations. Diagnosis was based on clinical symptoms such as pain, photophobia, lacrimation, and recurrence, and signs such as circumcorneal injection, keratic precipitates (not mutton fat), cells and flare in the anterior chamber, and increased intraocular pressure.

All the patients underwent the routine battery of investigations adopted for uveitis which includes: x-rays of the chest, sinuses, and sacroiliac joints, full blood count, erythrocyte sedimentation rate, anti-streptolysin titre, blood sugar level, gonococcal complement fixation test, toxoplasma dye and complement fixation tests, serum protein electrophoresis, fluorescent treponemal antibody test, Rose latex test for arthritis, and a delayed hypersensitivity skin test for tuberculosis. The control panel consisted of 200 healthy unrelated black volunteers belonging to various Southern African tribes.

HLA TYPING

Tissue typing was performed at the Tissue Bank of the South African Institute for Medical Research in Johannesburg. The method used was the Standard 2 Stage NIH Lymphocyte Microcytotoxicity test at an incubation temperature of 37°C throughout the test, 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. Although the first group of 16 patients were investigated in 1976 and the remaining patients in 1978, the range of antisera remained essentially the same. The exception was the introduction of antisera against Aw30, Aw31, and Aw33. For the typing of the first group only antisera with the specificity Aw30/Aw31 were available, whereas for the 1978 group antisera which allowed differentiation between Aw30 and Aw31 and later on Aw33 were at the typing team's disposal. The statistical evaluation of the results was performed by employing the χ^2 test with Yates's correction.

Results

There were 28 males and 25 females among the patients. The mean age of the males was 35.3 years and that of the females was 31.1 years.

Twenty of the patients, on questioning, reported previous episodes of ocular symptoms which might from the patients' descriptions have been attacks of

Table 1 HLA antigen frequencies in black patients with acute anterior uveitis (AAU)

	Controls No. = 200 %	AAU patients No. = 53 %	χ^2y	P
HLA-A1	7.0	13.2	1.38	NS
Aw36	0.5	3.8	1.54	NS
A2	26.0	17.0	1.40	NS
A3	10.0	11.3	0.0007	NS
A9	18.0	18.9	0.0029	NS
A10	0.0	0.0	—	—
Aw25	0.5	1.9	0.199	NS
Aw26	14.5	17.0	0.054	NS
Aw34	9.0	1.9	2.11	NS
A11	0.5	3.8	1.54	NS
A28	20.0	32.1	2.84	NS
A29	12.0	17.0	0.529	NS
Aw30	27.0	13.2 ²	2.358	NS
Aw31	15.0	5.4 ²	1.71	NS
Aw32	4.0	3.8	0.10	NS
Aw33	4.3 ¹	8.7 ³	0.155	NS
Aw43	0.5	1.9	0.0199	NS
HLA-B5	4.5	1.9	0.222	NS
B7	20.0	26.4	0.68	NS
Bw42	20.0	11.3	1.58	NS
B8	8.0	5.7	0.079	NS
B12	24.0	17.0	0.948	NS
B13	1.0	1.9	0.0336	NS
B14	6.0	3.8	0.0855	NS
B15	2.5	3.8	0.001	NS
B17	34.0	39.6	0.3604	NS
B18	14.0	11.3	0.0795	NS
B27	1.0	5.7	2.60	NS
B37	0.0	1.9	0.51	NS
B40	2.0	1.9	0.252	NS
Bw16	2.0	3.8	0.06	NS
Bw21	1.0	1.9	0.0336	NS
Bw22	2.5	3.8	0.001	NS
Bw35	11.0	17.0	0.8932	NS
Bw41	1.0	2.7 ²	0.0025	NS
HLA-Cw2	36.0	21.6 ²	2.279	NS
Cw3	18.5	18.9	0.0188	NS
Cw4	25.0	34.0	1.286	NS

¹Tested 62. ²Tested 37. ³Tested 23.

acute anterior uveitis. None of the 53 patients had any overt clinical evidence of rheumatic or other systemic disease. Ten patients had a raised ESR, 6 had a positive serological test for syphilis, 3 had a positive test for toxoplasmosis, 3 had a raised antistreptolysin titre, 1 had active sinusitis radiologically, and 5 had a positive skin test for tuberculosis but no evidence of active tuberculosis.

None of the 3 HLA B27 carriers, 2 males and 1 female, showed any of the above clinical findings.

The frequencies of 38 HLA antigens in 53 black South African patients suffering from acute, non-granulomatous anterior uveitis, as compared to 200 controls, are presented in Table 1.

Discussion

The antigen HLA B27 was represented slightly more frequently in the patient group (3/53) than in the control group (2/200). However, this did not reach statistically significant proportions. None of the

remaining antigens showed any statistically significant deviation from the norm.

Antigen frequencies of the A, B, and C locus of the major histocompatibility complex of man vary between different racial groups (Payne *et al.*, 1977). The same applies to the linkage disequilibria which have been found to exist between these antigens (Ward and Biegel, 1976; Hammond *et al.*, 1977). Positive or negative linkage disequilibria occur when antigens of the different HLA loci are found together more frequently, or less frequently, on the same chromosome than would be expected by the frequency of the single antigen alone in a given population group. The association of HLA B27 or any other HLA antigen with a certain disease has been attributed tentatively to the location, on the genome, of specific immune response (Ir) genes in close proximity to the gene coding for HLA B27, or to the indicated HLA antigen, and to the occurrence of positive linkage disequilibria between these HLA markers and the, in man as yet, hypothetical Ir genes (Brewerton and James, 1975; Dausset and Hors, 1975; Sveigaard *et al.*, 1975).

Should this hypothesis be true, it is conceivable that the linkage disequilibria found in one racial group are not repeated in another racial group, consistent with the established racial variations in linkage disequilibria between antigens of the A, B, and C locus. This could be one reason why this study has not revealed an association between AAU and any of the HLA antigens in a group of 53 black patients. In this connection it is interesting to mention the well documented association of HLA B17 with psoriasis in whites (Russel *et al.*, 1972; White *et al.*, 1972). B17 is the antigen with the highest frequency, 33%–41%, on the B locus in blacks (Payne *et al.*, 1977; Hammond *et al.*, 1977; David *et al.*, 1979). Yet psoriasis is hardly present in the blacks of South Africa.

We thank Mr A. R. Sayed, biostatistician, for the statistical evaluation of the results, and Mrs M. J. Landsman for excellent secretarial assistance.

This study was supported in part by grant 1324064 from the South African Institute for Medical Research.

References

- Ayanru, J. O. (1977). The problem of uveitis in Bendel State of Nigeria: experience in Benin City. *British Journal of Ophthalmology*, **61**, 655–659.
- Baum, J., and Ziff, M. (1970). Arthritis, Rheumatism, 13: 305A.
- Brewerton, D. A. (1975). HL-A27 in Reiter's disease and psoriatic arthropathy. *International Journal of Dermatology*, **14**, 39–40.
- Brewerton, D. A., Caffrey, M., Nicholls, A., Walters, D., and James, D. C. O. (1974). Acute anterior uveitis and HL-A27. *Lancet*, **1**, 464.
- Brewerton, D. A., Caffrey, M., Nicholls, A., Walters, D., and James, D. C. O. (1973a). Acute anterior uveitis and HL-A27. *Lancet*, **2**, 994–996.
- Brewerton, D. A., Caffrey, M., Nicholls, A., Walters, D., Oates, J. K., and James, D. C. O. (1973b). Reiter's disease and HL-A27. *Lancet*, **2**, 996–998.
- Brewerton, D. A., and James, C. O. (1975). The histocompatibility antigen (HL-A27) and disease. *Seminars in Arthritis and Rheumatism*, **4**, 191–207.
- Caffrey, M. F. P., and James, D. C. O. (1973). Human lymphocyte antigen association in ankylosing spondylitis. *Nature*, **242**, 121.
- Dausset, I., and Hors, I. (1975). Some contributions of the HL-A complex to the genetics of human diseases. *Transplantation Reviews*, **22**, 44–74.
- David, R., Maier, G., Baumgarten, I., and Abrahams, C. (1979). HLA antigens in glaucoma and ocular hypertension. *British Journal of Ophthalmology* (in press).
- Freedman, J. (1974). Incidence of uveitis in Bantu speaking Negroes of South Africa. *British Journal of Ophthalmology*, **58**, 595–599.
- Freedman, J. (1976). A clinical approach to the aetiology of uveitis in Bantu adults. *British Journal of Ophthalmology*, **60**, 64–69.
- Hammond, M. G., Appadoo, B., and Brain, P. (1977). HLA and cancer in South African Negroes. *Tissue Antigens*, **9**, 1–7.
- Mapstone, R., and Woodrow, J. C. (1975). HL-A27 and acute anterior uveitis. *British Journal of Ophthalmology*, **59**, 270–275.
- Ohno, S., Kimura, J. S., O'Connor, G. R., and Char, D. H. (1977). HLA antigens in uveitis. *British Journal of Ophthalmology*, **61**, 62–67.
- Payne, R., Feldman, M., Cann, H., and Bodmer, J. G. (1977). A comparison of HLA data of the North American black with African black and North American Caucasian populations. *Tissue Antigens*, **9**, 135–147.
- Perkins, E. S. (1976). Epidemiology of uveitis. *Transactions of the Ophthalmology Societies of the United Kingdom*, **96**, 105–107.
- Rachelefsky, G. S., Terasaki, P. I., Katz, R., and Stiehm, E. R. (1974). Increased prevalence of W27 in juvenile rheumatoid arthritis. *New England Journal of Medicine*, **290**, 892–893.
- Russel, T. J., Schultes, L. M., and Kuban, D. J. (1972). Histocompatibility (HL-A) antigens associated with psoriasis. *New England Journal of Medicine*, **287**, 738–739.
- Schlosstein, L., Terasaki, P. I., Bluestone, R., and Pearson, C. M. (1973). High association of an HL-A antigen, w27, with ankylosing spondylitis. *New England Journal of Medicine*, **288**, 704–796.
- Sonozaki, H., Seki, H., Chang, S., Okuyama, M., and Juji, T. (1975). Human lymphocyte antigen HL-A27 in Japanese patients with ankylosing spondylitis. *Tissue Antigens*, **5**, 131–136.
- Sveigaard, A., Platz, P., Ryder, L. P., Nielsen, L. S., and Thomson, M. (1975). HL-A and disease associations—A survey. *Transplantation Reviews*, **2**, 3–43.
- Tsuji, K., and Fukunishi, T. (1973). Distribution of HL-A antigens in the solitary islands of Japan. *Excerpta Medica*, International Congress Series No. 300: 2.
- Ward, F. E., and Biegel, A. A. (1976). HL-A antigens in North American black families. *American Journal of Human Genetics*, **28**, 1–8.
- White, S. H., Newcomer, V. D., Mickey, M. R., and Terasaki, P. I. (1972). Disturbance of HL-A antigen frequency in psoriasis. *New England Journal of Medicine*, **287**, 740–743.
- Zervas, J., Tsokos, G., Papadakis, E., Kabouklis, E., and Papadopoulos, D. (1977). HLA-B27 frequency in Greek patients with acute anterior uveitis. *British Journal of Ophthalmology*, **61**, 699–701.