British Journal of Ophthalmology, 1977, **61**, 699–701

HLA-B27 frequency in Greek patients with acute anterior uveitis

J. ZERVAS, G. TSOKOS, G. PAPADAKIS, E. KABOUKLIS, AND D. PAPADOPOULOS

From the First Department of Internal Medicine of the University of Athens, Vasilevs Pavlos Hospital and the Ophthalmological Clinic of Vasilevs Pavlos Hospital

SUMMARY The histocompatibility antigen HLA-B27 was identified in 12 out of 33 patients with acute non-granulomatous anterior uveitis. This is a frequency of 36·36%, compared with 4·72% in controls. Seven patients had in addition evidence of systemic disease, including ankylosing spondylitis, sacroiliitis, Reiter's disease, Still's disease, and rheumatoid arthritis. Five of these were HLA-B27 positive, which suggests that the uveitis in many of these cases has a similar aetiology to the uveitis in those with rheumatic disease. It appears that the more severe cases of acute anterior uveitis are related more frequently to the presence of HLA-B27.

Associations between HLA-B27 and rheumatic diseases such as ankylosing spondylitis (AS), Reiter's disease (RD), psoriatic arthritis (PA), juvenile rheumatic arthritis (JRA) with sacroiliitis and spondylitis have been described (Brewerton *et al.*, 1973a; Schlosstein *et al.*, 1973; White *et al.*, 1972). Investigations concerning analogous associations between HLA antigens and acute anterior uveitis (AAU) have also been reported (Russell *et al.*, 1972; Brewerton *et al.*, 1973b; Mapstone and Woodrow, 1975; Rebmann *et al.*, 1976). Acute anterior uveitis as a disease of the anterior part of the eye usually accompanies certain rheumatic diseases. The aetiology and pathogenesis of this disease are unknown. Though the exact relationship between AAU and rheumatic diseases is obscure, it is obvious from the study of the histocompatibility antigens that the incidence of HLA-B27 in both conditions is increased. The meaning of this observation for the pathogenesis, aetiology, and epidemiology of these conditions remains to be elucidated.

Since the distribution of HLA antigens varies in different ethnic groups (Kissmeyer-Nielson, 1972) we undertook to examine the distribution of HLA antigens in Greek patients with AAU.

Material and methods

PATIENTS

Thirty-three patients with acute anterior uveitis (non-granulomatous) were referred to the ophthalmological clinic of Vasilevs Pavlos Hospital and carefully documented throughout the attack. Diagnosis was based on clinical symptoms and signs. The latter were obtained by a complete ophthalmological examination, that is, inspection with lateral illumination, slit-lamp examination, ophthalmoscopy, and tonometry. Apart from the symptoms suffered by the patients (photophobia, pain, excessive lachrymation), emphasis was given to the following signs: circumcorneal flush, presence of inflammatory cells in the anterior chamber, inflammatory processes of the iris, precipitates on the posterior surface of the cornea, and increased intraocular pressure.

All patients were submitted to a detailed clinical and laboratory examination. Particular attention was paid to the detection of any rheumatic disease. Routine *x*-rays of chest and sacroiliac joints were carried out, with further *x*-rays being taken when indicated.

Among the 33 patients there were 7 who had in addition evidence of systemic disease—ankylosing spondylitis 3, rheumatoid arthritis 1, juvenile rheumatoid arthritis 1, Reiter's disease 1, and sacroiliitis 1.

HLA TYPING

For the identification of the histocompatibility antigens (HLA) on the surface of the lymphocytes the one-stage lymphocytotoxicity micromethod was used (Terasaki and McClelland, 1964) as modified by Kissmeyer-Nielsen and Thorsby (1976-7). The

Address for reprints: Dr J. Zervas, University of Athens, Medical School, First Department of Internal Medicine, Goudi 609, Athens, Greece

panel consisted of 63 specific antisera, so that each antigen was checked at least twice.

In particular, for HLA-B27 3 monospecific and dispecific (B27 and B7) antisera were used. HLA antisera were kindly provided by the National Institutes for Health, Bethesda, Maryland, and Professor Van Rood (Eurotransplant, Leiden).

Results

The distribution of HLA antigens in 33 Greek patients with acute anterior uveitis and in 233 Greeks who had no blood relationship with them (unbiased sample) is shown in Table 1. HLA-B27 was detected in 12 out of 33 patients with AAU, that is, 36·36% instead of 4·72% in the control sample. The frequency difference of HLA-B27 among patients and healthy persons is statistically significant ($\chi^2 = 63{\cdot}05$, $P < 0{\cdot}001$). The relative risk—mostly an indicator of the strength of the association between HLA-B27 and the disease—is 12·66. Of the 12 patients carrying B27, 4 were males (mean age = 36·02) and 8 females (mean age = 29·50) (Table 2). The sex ratio (males/females) is 1:2, while the mean age is greater among the male patients. Table 2 also shows that the concurrence of AAU and systemic disease is greater in males than in females.

HLA-B27 is more frequent in patients with AAU who in addition have a systemic disease (5 out of 7 with systemic disease were B27-positive) than in those with AAU alone.

Table 3 shows the relationship between B27 and certain clinical findings. Exudates in the anterior chamber are associated with a high frequency of B27 antigen. Furthermore, hyaloid precipitates, recurrent attacks, and disease duration longer than 3 weeks are associated with a higher frequency of B27.

Table 1 *Distribution of HLA antigens (%) in patients with AAU and controls*

HLA series	*Antigen*	*Patients* *No.*	*Frequency (%)*	*No.*	*Sample Frequency (%)*
HLA-A	A1	5	15·15	56	24·03
	A2	12	36·30	123	52·79
	A3	12	36·30	50	21·46
	A9	12	36·30	79	33·91
	A10	2	6·10	36	15·45
	A11	4	12·20	19	8·25
	A28	2	6·10	17	7·73
	AW19	3	9·13	26	11·27
	A29	2	6·10	9	3·97
HLA-B	B5	12	36·30	74	31·76
	B7	7	21·20	31	13·30
	B8	2	6·10	27	11·59
	B12	2	6·10	41	17·60
	B13	1	3·03	11	4·72
	B14	3	9·10	16	6·87
	BW15	1	3·03	17	7.30
	BW16	1	3·03	9	3·86
	BW17	2	6·10	16	6·87
	B18	7	21·20	69	29·62
	AW22	—	—	3	1·29
	B27	12	36·36*	11	4·72*
	BW35	8	24·24	40	17·16
	BW40	5	15·15	26	11·16

*$\chi^2 = 63{\cdot}05$, $P < 0{\cdot}001$, relative risk = 12·66

Table 2 *Age and sex of 33 patients with non-granulomatous iridocyclitis*

HLA—B27	+		-	
No.	12		21	
Sex	M 4	F 8	M 7	F 14
Mean age (years)	36·10	29·50	36·74	47·80
Systemic disease	3	2	2	0

Table 3 *Relationship of HLA-B27 antigen with various clinical manifestations (33 patients)*

Clinical manifestation	*HLA—B27* *Positive (12)* *No.*	(%)	*Negative (21)* *No.*	(%)
Exudates	12	(100)	18	(85·71)
Hyaloid precipications	7	(58·33)	4	(19·04)
Recurrent attacks	11	(91·66)	9	(42·85)
Duration more than 3 weeks	9	(75)	8	(38·09)

Discussion

The findings in this small series of Greek patients did not differ significantly from those in previous studies of acute anterior uveitis. The main finding was that HLA-B27 in AAU is 36·36% compared with 4·72% of controls. Rebmann *et al.* (1976) reported a frequency of 33·2%, though Brewerton *et al.* (1973b) and Mapstone and Woodrow (1975) reported a frequency of 55%. In comparing the reported frequencies the percentage of patients with systemic disease in the samples should be borne in mind. Thus, in the series of Brewerton *et al.* (1973b) 45·5% had systemic disease and in the series of Mapstone and Woodrow (1975) 31%. In our series only 21% had systemic disease. The presence of B27 in patients of this group with AAU who in addition had systemic disease was 71·4%, which is not significantly different from those reported by

Brewerton *et al.* (1973b) (85%) and Mapstone and Woodrow (1975) (82%). The association between non-granulomatous AAU and rheumatic disease deserves emphasis, and at least in this study B27 may represent an important link.

The B27 frequency in patients with AAU who did not have any systemic disease was 27%, about the same as that reported (Brewerton *et al.*, 1973b (29%)). Cases of AAU which had exudates in the anterior chamber were accompanied by a high frequency of B27. This is in accord with ankylosing spondylitis, which is commonly accompanied by exudates. It is well known that the incidence of B27 in ankylosing spondylitis is very high (Brewerton *et al.*, 1973a; Schlosstein *et al.*, 1973; White *et al.*, 1972).

The observation that there is a striking association between B27, acute anterior uveitis, ankylosing spondylitis, Reiter's disease, and psoriatic arthritis provides evidence for a common pathogenesis. The presence of B27 alone does not necessarily lead to a particular clinical disease, but possibly it provides a background for uncommon disease association. Dick and her colleagues (1974) described a family in which out of 2 sibs carrying B27 only 1 had ankylosing spondylitis. There was seemingly a cross-over effect dissociating the gene for B27 antigen from that responsible for increased liability to AS. It was concluded that it is not the possession of antigen B27 alone which determines the manifestation of a certain disease but that the existence of an adjacent gene for disease susceptibility—perhaps an Ir gene—is necessary.

Different strengths of association between B27 and uveitis—or other disease—in different ethnic groups may provide information on the antigen responsible and the co-working factor.

References

Brewerton, D. A., Caffrey, M., Hart, F. D., James, D. C. O., Nicholls, A., and Strurrock, R. D. (1973a). Ankylosing spondylitis and HL-A 27. *Lancet*, **1**, 904–907.

Brewerton, D. A., Caffrey, M., Nicholls, A., Walters, D., and James, D. C. O. (1973b). Acute anterior uveitis and HL-A 27. *Lancet*, **2**, 994–996.

Dick, H. M., Dick, W. C., Sturrock, R. D., and Buchanan, W. W. (1974). Inheritance of ankylosing spondylitis and HLA Antigen W 27. *Lancet*, **2**, 24–25.

Kissmeyer-Nielsen, ed, *Histocompatibility Testing* (1972). Enjar Munksgaard: Copenhagen.

Kissmeyer-Nielsen, F., and Thorsby, E. (1976–7). *Manual of Tissue Typing Techniques*. NIAID.

Mapstone, R., and Woodrow, J. C. (1975). HL-A 27 and acute anterior-uveitis. *British Journal of Ophthalmology*, **59**, 270–275.

Rebmann, D., Raffoux, C., Cordier, J., Streiff, F., and Thomas, C. (1976). A1-A antigen and acute anterior uveitis. In *HLA and Disease Abstracts*. Edition Inserm: Paris.

Russell, J. J., Schultes, L. M., and Kuban, D. J. (1972). Histocompatibility (HL-A) antigens associated with psoriasis. *New England Journal of Medicine*, **287**, 738–740.

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**, 704–706.

Terasaki, P. I., and McClelland, J. D. (1964). Microdroplet assay of human serum cytotoxins. *Nature*, **204**, 998–1000.

White, S. H., Newcomer, V. D., Mickey, M. R., and Terasaki, P. I. (1972). Disturbances of HL-A antigen frequency in psoriasis. *New England Journal of Medicine*, **287**, 740–743.