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Iridocyclitis in black Americans: association with HLA B8 suggests an autoimmune aetiology

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SUMMARY Histocompatibility (HLA) testing was performed on a total of 171 black Americans, 129 controls, and 42 patients with iridocyclitis. None of the patients had a history of rheumatological disease. The phenotype frequency of HLA B8 was greatly increased among patients than the control group (exact p = 0·0010). Most striking was the almost identical phenotypic frequency of B27 found in patients and in the control group (exact p = 0·07087). No HLA DR antigen in the patient group was found to be significantly raised when compared with controls. The HLA B8 associated disease was seen more in females, was bilateral and nongranulomatous, had no systemic disease associated with it, and left patients with visual handicap. The HLA B8 antigen has been associated with various entities of presumed autoimmune origin, and these data suggest that iridocyclitis, at least in blacks, may be of similar aetiology.

Genetically determined cell surface markers, particularly the antigens of the major histocompatibility complex (the HLA region), have provided basic as well as clinical researchers with a powerful tool to examine possible involvement of the immune system in the manifestation of certain diseases.[1] Disease associations with certain HLA antigens have been repeatedly shown. One of the earliest associations reported was that of HLA B27 with ankylosing spondylitis[2 3] as well as anterior uveitis[4 5] in Caucasoids. Among Caucasoid patients with ankylosing spondylitis over 90% were reported as having B27, while among Caucasoid controls only 4–6% had B27. Of the above B27 positive patients approximately 30% also have an anterior uveitis.[6] Among Caucasoid patients with anterior uveitis 50–55% have been reported as having B27; a large proportion of these also suffer from rheumatological disease. The increased incidence of B27 in other ocular inflammatory syndromes, including those associated with arthritic conditions, has not been shown,[7–9] and a recent report did not find any significant phenotype deviations in South African blacks with acute anterior uveitis as compared with healthy controls.[10]

Recently it has become possible to type for B cell alloantigens or HLA DR antigens.[11] The HLA DR locus is thought to have an important role in cell-to-cell interactions which regulate the host's immune response.[12 13] Certain studies have demonstrated D or DR locus associations with autiommune disease,[14 15] while the relationship of DR antigens with ocular diseases has only recently begun to be investigated.[16 17]

We have investigated the phenotypic frequencies of HLA A, B, C, and DR antigens in black Americans who had recurrent iridocyclitis with no evidence of rheumatological disease. We have compared their antigen frequencies with those in an appropriate control group of healthy individuals. We report here a significant association between the HLA B8 antigen and this disease. This finding might shed light on the possible aetiology of the disease.

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Material and methods

CONTROLS AND PATIENTS

A total of 171 unrelated black Americans, 129 controls, and 42 patients were studied. All controls were healthy normal volunteers. All patients were examined by at least 2 ophthalmologists. They all had a history and ocular evidence of iridocyclitis. Four of the patients also carried the diagnosis of sarcoidosis. These patients, as well as some patients with no evidence of systemic disease, were felt to have a granulomatous uveitis. This was based on the presence of lardaceous ('mutton fat') keratic precipitates which were seen before the initiation of therapy.

HLA TESTING

All controls and patients were tested for HLA A, B,

Table 1 *Phenotypic frequencies (PF) of the HLA antigens of loci A, B, and C in black Americans with and without iridocyclitis*

HLA antigen	PF (%) Controls n=129	PF (%) Patients n=42	Exact p	Relative risk†
HLA A				
1	8·5	14·3	0·3713	1·8
2	33·3	23·8	0·3368	0·6
3	22·5	7·1	0·0383*	0·3
9	27·9	26·2	1·0000	0·9
10	8·5	11·9	0·5454	1·5
11	5·4	2·4	0·6811	0·4
23	19·4	19·1	1·0000	1·0
24	4·0	11·9	0·0671	3·4
26	7·0	11·9	0·3360	1·8
28	17·8	23·8	0·3788	1·4
29	10·1	7·1	0·7636	0·7
30	22·5	19·1	0·8294	0·8
31	6·2	7·1	0·7324	1·2
32	7·0	9·5	0·7375	1·4
33	11·0	11·9	0·7848	1·1
34	4·0	2·4	1·0000	0·6
36	3·1	11·9	0·0411*	4·2
HLA-B				
5	12·4	11·9	1·0000	1·0
7	20·2	23·8	0·6644	1·2
8	6·2	26·2	0·0010**	5·4
12	23·3	14·3	0·2779	0·6
13	2·3	0·0	1·0000	0·0
14	6·2	7·1	0·7324	1·2
15	9·3	0·0	0·0399*	0·0
16	4·7	7·1	0·6906	1·6
17	24·0	16·7	0·3957	0·6
11	8·6	4·8	0·5242	0·5
21	7·0	7·1	1·0000	1·0
22	3·1	4·8	0·6362	1·6
27	5·4	7·1	0·7087	1·3
35	26·4	16·7	0·2206	0·6
37	0·8	2·4	0·4320	3·1
33	1·6	0·0	1·0000	0·0
39	1·6	7·1	0·0958	4·9
40	4·7	2·4	1·0000	0·5
41	0·8	0·0	1·0000	0·0
42	7·8	11·9	0·5292	1·6
44	10·9	11·9	0·7848	1·1
45	11·6	2·4	0·1229	0·2
49	3·9	7·1	0·4077	1·9
50	1·6	0·0	1·0000	0·0
51	3·9	11·9	0·0671	3·4
52	5·4	0·0	0·1960	0·0
53	3·9	9·5	0·2256	2·6
57	2·3	4·8	0·5974	2·1
58	0·8	7·1	0·0463*	9·9
HLA-C				
1	1·6	2·4	0·5732	1·6
2	17·1	14·3	0·8122	0·8
3	24·0	23·8	1·0000	1·0
4	27·9	35·7	0·3368	0·4
5	1·6	0·0	0·4170	1·0
6	10·9	11·9	0·8505	0·9

* $p<0·05$. ** $p=0·001$.

†Relative risk $= \frac{\text{antigen-positive patients} \times \text{antigen-negative controls}}{\text{antigen-negative patients} \times \text{antigen-positive controls}}$

and C antigens by the standard lymphocyte microcytotoxic test.[18] A total of 59 controls and all patients were also tested for HLA DR antigens by the international method.[11] Briefly, T cells were separated from B cells by rosetting with sheep red blood cells which had been pretreated with 2-aminoethylisothiouranium bromide hydrobromide. The B cell suspensions were incubated with DR antisera for 60 minutes at 37°C, and after addition of rabbit complement they were further incubated for an additional 120 minutes at 22°C prior to addition of eosin and formalin, as described elsewhere.[18]

For comparison of phenotype frequencies between controls and patients the p values were calculated by Fisher's exact method.[19]

Results

The comparisons of phenotype frequencies of the HLA A, B, and C antigens between the control and the patient groups are presented in Table 1. The phenotype frequency of HLA B8 was greatly increased in patients in comparison with that in the control group (exact $p=0·0010$, relative risk 5·4). Other antigens with an increased incidence included Aw36 (exact $p=0·0411$) and Bw58 (exact $p=0·0463$), the last with the highest relative risk of 9·9.

Most striking was the almost identical phenotype frequency of B27 found in the patient and the control groups (exact $p=0·7087$). Of interest was the relative decrease of certain antigens among patients, particularly HLA B15, present in 9·3% of the control group, and in none of the patients tested (exact $p=0·0399$).

The comparison of the HLA DR phenotype frequencies in the 2 groups is given in Table 2. No DR antigen was significantly increased in the patients. However, DR5 and DRw8 had somewhat greater frequencies in the patient group.

Table 2 *Comparison of the HLA DR phenotypic frequencies (PF) in American blacks with and without iridocyclitis*

B cell antigen	PF (%) Controls n=59	PF (%) Patients n=41	Exact p	Relative risk
HLA DR				
1	18·6	14·6	0·7876	0·8
2	32·2	43·9	0·2934	1·7
3	30·5	29·3	1·0000	0·9
4	15·3	12·2	0·7744	0·8
5	28·8	41·5	0·2050	1·8
6	13·6	12·2	1·0000	0·9
7	28·8	12·2	0·0540	0·3
8	3·4	14·6	0·0609	4·9

Table 3 *Comparison of HLA B8 positive and negative black Americans with iridocyclitis*

		HLA B8	
		Positive n=10	*Negative n=31*
Sex	Male	3	15
	Female	7	16
Visual acuity*	20/20–40	5	7
	20/50–80	3	15
	20/100–LP	2	9
Age at onset	1–20 yr	1	1
	20–40 yr	9	30
Uveitis	Bilateral	10	27
	Uniocular	0	4
	Nongranulomatous	10	23
	Granulomatous	0	8
Disease association	None	0	27
	Sarcoid	0	4

*Best visual acuity in worst eye. LP = perception of light.

In order to characterise the B8 positive uveitis group a comparison of the B8 positive and negative patients was done (Table 3). While the B8 negative group of patients was evenly divided between male and female, the B8 positive group showed a female predominance. The B8 positive group in addition had no known systemic disease association, and had disease which was bilateral and nongranulomatous in nature. Some patients had a chronic recurrent pattern, while others had an acute recurrent course to their disease. A sizeable proportion of both groups had a noncorrectable drop in visual acuity due to their disease.

Discussion

In the middle of this century the aetiology of most cases of uveitis was thought to be of an infectious nature. This theory has, at least for many conditions, not survived the years,[20] and an endogenous cause for ocular inflammatory disease has been proposed. The HLA B8 antigen has previously been associated with a variety of presumed autoimmune conditions, including those with ocular involvement.[21–25] The finding of B8 being associated with this disease entity would suggest that this condition may also be of an autoimmune aetiology. Further, this association of HLA B8 antigen to iridocyclitis in black Americans is a strong one (Table 1). The relative risk calculated for this disease, when the antigen is present, is greater than for all well-known B8–associated autoimmune diseases except for coeliac disease and dermatitis herpetiformis.[25]

The B8–associated disease entity reported here is different from the anterior uveitis in Caucasoids associated with B27. Woodrow *et al.*[5] reported that the typical B27 uveitis was one found in males, being uniocular and nongranulomatous, having repeated attacks, and usually not leaving visual handicap. The B8 uveitis in black Americans reported here was bilateral, nongranulomatous, more commonly seen in females, and leaving several patients with visual handicap.

The finding of an increase in only B8 in our patients would suggest that this disease propensity centres about this gene locus, and this is perhaps true of some Caucasoids with autoimmune disease. However, antigens A1, B8, and DR3 are known to be in positive linkage disequilibrium among Caucasoids,[11] and consequently all 3 antigen frequencies may be found elevated in this group. This theory has also been proposed for myasthenia gravis, where the B8 association seems much greater than the DR3 association.[26] Although several entities of autoimmune origin have been associated with the B8 antigen, this is the first report we are aware of associating B8 with intraocular inflammatory disease. Brewerton *et al.*[27] reported that among sarcoid patients, presumably Caucasoid, A1 was increased among those with uveitis, while B8 was elevated in those who had arthritis. None of our B8-positive patients had ocular sarcoid.

The lack of certain antigens in the patient group could be a reflection of the relatively small sample size, with the exception of B15. It has been noted that Caucasoid diabetes mellitus patients bearing B8 and DR3 differ in their immunological response from those patients bearing B15 and DR4. B8, DR3 patients have a higher incidence of anti-B-cell antibodies, while B15, DR4 patients tend to have high antibody titres to exogenous insulin.[28 29] If found valid in a larger patient sample, an absence of B15 in this disease may suggest an association between B15 and some factor causing resistance against this disease.

Some of the more commonly proposed roles for HLA in the pathogenesis mechanisms are the following: (1) certain HLA genes act as immune response genes, or they are closely linked to those that are; (2) certain HLA antigens may serve as receptors for pathogens or toxins; (3) certain invading pathogens may 'mimic' specific HLA antigens, thus making 'non-self' appear as 'self', leading to cross-tolerance; and (4) if pathogens or toxins can alter antigens coded for by the HLA loci, this may result in 'altered self', leading to autoimmunity.[25 30] Apart from the first hypothesis that the HLA region may include the immune response loci, thereby contributing to the pathogenesis of disease, all other theories propose a role of some exogenous factor. Seager and co-workers[31] have reported antigenic similarities between the products

of klebsiella and the B27 associated antigens. This finding may be of importance in understanding the pathophysiology of disease seen in B27-positive patients. Added insight into this type of uveitis has also been gained from the recent finding of an anterior inflammatory response which was induced in animals by immunisation with lipopolysaccharide, a purified component of the cell wall of Gram negative bacteria.[32]

Clues to the role that B8 may play in the pathogenesis of autoimmune disease are not yet evident. As proposed by Strober,[33] the restricted genotype found in this category of very varied disease presentations suggests a common pathophysiological mechanism acting in conjunction with independent environmental and genetic factors to produce specific disease entities.

The variety of clinical entities which are placed under the diagnosis of uveitis are legion. It is clear that more effective diagnostic and descriptive methods are needed to categorise these diseases. Further studies defining the immunological and nonimmunological characteristics of both the B8-associated and nonassociated uveitides may help in defining more precisely this varied and perplexing group of diseases.

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