

# **Immunogenetics in Rheumatology**

**Musculoskeletal Disease  
and D-Penicillamine**

**Editors:**

**R.L. DAWKINS  
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**EXCERPTA MEDICA**

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ANTERIOR UVEITIS

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## INTRODUCTION

Considerable interest has been generated in recent years into the study of the immunogenetics and immunopathology of inflammatory eye disease. The relationship between several HLA antigens and anterior uveitis (AU) is now well established. This is exemplified by the association of HLA B27 with idiopathic AU and with that form of uveitis commonly complicating the seronegative arthritic syndromes such as ankylosing spondylitis and Reiter's syndrome. As well the role of other immunogenetic markers, in particular alpha 1 antitrypsin, has received renewed attention. Progress has been made in understanding of the immunological mechanisms that may underlie HLA B27 AU and into possible aetiological agents that trigger the disease. The aim of this review is to outline recent developments which add to our understanding of this disease.

## HLA STUDIES IN UVEITIS

The HLA B27 antigen is associated with AU in all populations so far studied ranging from 37 - 56% of patients, a notable exception being Negroes from South Africa and the United States (1,2). Confirmation of this close link between HLA B27 and anterior uveitis was provided by groups from the U.S.A., England, India, Netherlands and Australia during this conference.

We recently analysed 62 patients with anterior uveitis looking for possible associations between the DR locus antigens and with the B7 cross reactive groups (Creg) previously reported to be associated with ankylosing spondylitis. No association was found between the DR or B7 Creg group of antigens. This study also failed to show a relationship between HLA antigens and posterior uveitis although the small numbers studied make it impossible to be dogmatic on this issue. These results were in agreement with those from several other groups including Kahn from Cleveland and Woodrow from the United Kingdom. Clemens from Northwick Park confirmed an earlier report of an association of the HLA DR5

antigen with chronic anterior uveitis found in young girls with the pauci articular form of juvenile chronic polyarthritis (3). The DR5 antigen however was not increased in a small group of children with JCA reported by John Edmonds from Sydney.

#### CLINICAL FEATURES

Most would agree that the uveitis associated with the HLA DR5 antigen in pauci articular JCA is a chronic indolent disease with a marked tendency to progress to cataract formation, iris adhesions, glaucoma and blindness. However, there was no such general agreement as to the clinical features of HLA B27 anterior uveitis. This form of AU is usually described as unilateral, non-granulomatous and recurrent. Mapstone and Woodrow (4) found that HLA B27 AU was associated with more severe chronic disease, however, this has not been our experience and we would agree with Ohno et al (5) that the HLA B27 antigen is not a marker of disease severity. In a recent study of 100 consecutive patients referred to a uveitis research clinic, patients with HLA B27 positive AU when compared with B27 negative disease tend to have more frequent attacks ( $5.3 \pm 0.9$  vs  $3.9 \pm 0.9$ ,  $p < 0.01$ ) of shorter duration ( $2.7 \pm 0.2$  vs  $3.4 \pm 0.4$  months,  $p < 0.01$ ) and rarely develop chronic anterior uveitis. The sex of the patient was a major factor in disease pattern. Males with AU compared with females had a higher incidence of HLA B27 (31/41,  $p < 0.05$ ) and were more likely to have rheumatic disease such as ankylosing spondylitis (12/49,  $p < 0.001$ ), Reiter's syndrome (7/49,  $p < 0.001$ ) or seronegative arthritis (3/49,  $p < 0.05$ ). By contrast, HLA B27 positive AU without associated rheumatic disease occurred with equal frequency in male and female patients. With respect to attacks of uveitis, females in this group had a comparatively later age of onset (47 years vs 40 years), had more attacks (11 vs 4.6,  $p < 0.05$ ) each being of longer duration and had a higher attack rate per year (1.4 vs 0.8 attacks per year,  $p < 0.05$ ). These later findings were in agreement with the results of the studies by Kahn, Woodrow and others but were in sharp contrast to Linssen from the Netherlands who described a remarkably high incidence of sacroiliitis - HLA B27 positive females.

#### ROLE OF ALPHA 1 ANTITRYPSIN DEFICIENCY IN ANTERIOR UVEITIS

Previous reports on the association of deficient alpha 1 antitrypsin phenotypes with AU have been controversial. Brewerton et al found that the alpha 1 antitrypsin deficient phenotype MZ was present in 25% of their 80 patients with acute AU compared with an incidence of 3% in the control population. This association

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was refuted by Brown et al (7) who found no increased association of the MZ phenotype in their 133 patients with acute AU. We analysed the relationship between alpha 1 antitrypsin deficient phenotypes and the nature and severity of uveitis in 125 patients. Our results indicated a significant increased incidence of alpha 1 antitrypsin deficiency (MS or MZ) in patients with AU, being most prevalent in those patients with chronic, bilateral or recurrent disease (Table I). As outlined elsewhere in this Symposium such deficient patients may have abnormalities in immunoregulation that predispose to more prolonged and severe uveal inflammation.

TABLE I. Genetic risk factors in uveitis.

	PHENOTYPE %				$\alpha$ 1AT DEF. AND/OR HLA B27+
	MM	MS	MZ	MS/MZ	
Anterior Uveitis					
Acute(36)	100**	0	0	0*	22
Chronic(10)	60**	40**	0	40**	40(8)
Bilateral(5)	40+	40**	20	60**	60(8)
Recurrent(39)	80+	15**	5	20**	69(7.9)
Posterior Uveitis(16)	83	5	12	17	
Retinal Vasculitis(19)	84	11	5	16	
Controls(339)	89	7	4	11	

\* p < 0.001 - 0.05 compared with controls  
+ p < 0.05 compared with acute anterior uveitis  
( ) relative risk compared with acute uveitis

There was a 19% incidence of deficient alpha 1 AT phenotypes (MS or MZ) in the HLA B27 group, but this was not significantly increased compared with the control population. The HLA B27 antigen and alpha 1 AT deficient phenotypes both predispose to recurrent disease and appear to act as independent variables. They may serve therefore not only as genetic markers for the disease but also as important prognostic indicators in early disease.

## IMMUNOLOGICAL ABNORMALITIES IN ANTERIOR UVEITIS

Abnormalities of humoral and cellular immunity have been extensively investigated in uveitis patients but until recently these have not been correlated with immunogenetic markers of the disease. Work in our laboratory has demonstrated a dichotomy of immunological abnormalities depending on the HLA B27 status. HLA B27 AU is characterised by an absolute T cell lymphopenia during active iris inflammation which returns to normal following recovery. This phenomena could not be attributed to

antilymphocyte antibodies and was not observed in B27 negative AU (8). Although these findings suggest an underlying abnormality of immunoregulation this was not substantiated in a further study comparing the autologous mixed lymphocyte reaction (MLR) and T cell subsets (OKT3, OKT4, OKT8) in HLA B27 positive and negative patients and controls. These findings suggest that the T lymphopenia occurring during active AU is due to other mechanisms such as infection or the transit of the cells into inflamed tissues.

HLA B27 negative AU is a more heterogenous disease associated with a raised IgE level and the presence of circulating immune complexes. It is interesting to speculate that the mechanisms involved in B27 negative AU may involve immune complex deposition in the iris and/or an IgE mediated hypersensitivity response, while HLA B27 AU may involve a T cell mediated hypersensitivity response to iris antigen.

#### THE ROLE OF INFECTION

A number of infectious agents have been implicated in HLA B27 related diseases, especially gram negative organisms and Chlamydia in the seronegative arthropathies. Although less attention has been given to the role of these agents in the pathogenesis of AU, a number of recent studies were reported at this conference. Ebringer reported culturing species of Klebsiella pneumoniae from the faeces of patients with AU and ankylosing spondylitis and found an association between the presence of these organisms and exacerbations in the uveitis. These findings have not been verified by other groups and the role of faecal Klebsiella remains controversial. A different approach to this problem has been previously reported by Avakin et al (10) who have shown cross reactivity between Klebsiella pneumonia antibodies and a crude preparation of bovine vitreous. This is a potentially important study although it fails to demonstrate specificity the cross reacting antibody for iris tissue and also fails to address the crucial question of the role of HLA B27 antigens. This challenge has been taken up by Edmonds et al who have shown cytotoxicity to HLA B27 positive ankylosing spondylitis lymphocytes but not B27 positive non-ankylosing spondylitis lymphocytes using an antibody to Klebsiella K43. Furthermore, a culture filtrate of Klebsiella can convert B27 positive ankylosing spondylitis negative lymphocytes into cells susceptible to lysis by the Klebsiella antibody. When we examined this phenomena in patients with AU without evidence of ankylosing spondylitis the B27 positive lymphocytes were not lysed by the Klebsiella antibodies (12). This implies that the antigen present on the B27 positive ankylosing spondylitis lymphocytes is not shared with the B27 positive AU lymphocytes.

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Although these studies implicate *Klebsiella* in the pathogenesis of B27 related disease, the significance of these observations remains unclear. In order to further investigate the role of the B27 antigen in relation to potential microbial pathogens we examined the macrophage response to a number of organisms using the chemiluminescence assay which is a sensitive measure of the oxidation products generated intracellularly during phagocytosis. Studies were performed on two species of *Klebsiella pneumoniae*, *Salmonella typhimurium* and *Shigella flexneri* as well as zymosan. In comparison of HLA B27 positive and negative AU patients the CL response to *Klebsiella* K43, *Shigella* and *Salmonella* was significantly reduced in the B27 positive AU patients compared with B27 negative patients and controls. By contrast, the CL response to an unclassified *Klebsiella* species was greater in the B27 positive AU patients while the response to zymosan showed no significant difference between groups. Thus, the macrophage CL response of HLA B27 positive AU patients is reduced to a number of potentially pathogenic bacteria. The basis of this interaction remains speculative but may involve the HLA B27 antigen acting as a surface receptor on the macrophage or more likely controlling macrophage antigen presentation and perhaps T cell interaction.

## REFERENCES

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## SECTION FIVE ANKYLOSING SPONDYLITIS AND UVEITIS

### Chapter 5.8 Anterior Uveitis

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