

HLA-B27 Association with Uveitis in an Asian Indian Population

Mahendra Narin Mishra¹, Khurshed Minoo Bharucha²

¹Dr. Lal Pathology Reference Laboratory, New Delhi, ²Department of Ophthalmology, Command Hospital (SC), Pune, India

ABSTRACT

Background: Uveitis refers to diseases characterized by intraocular inflammation of the uveal tract. Anterior uveitis is a common ocular disease characterized by inflammation of the iris and the ciliary body. **Objectives:** To establish the frequency of HLA-B27-positive uveitis in Asian Indian population, study their clinical profile and compare it with other reports in literature. **Methods:** We retrospectively reviewed medical data of 89 patients of uveitis referred for HLA B27 typing with predominantly ocular symptoms during the period from April 2006-October 2010. All patients were tested for complete blood count, erythrocyte sedimentation rate, infectious diseases serology, HLA-B27 typing, and prepared radiographs of the sacroiliac joints and lumbar spine if required. **Results:** The HLA-B27 positive rate was 56.2% among patients and 3% for control samples. Most of the patients were in the age group of 41-50 years with a male predominance. **Conclusions:** HLA-B27 was seen to be associated with acute anterior uveitis in Asian Indian males and the test is important for confirmation of diagnosis, prognostication and also for planning the treatment.

Keywords: Asian, HLA-B27, Indian, Uveitis

INTRODUCTION

Acute anterior uveitis (AAU) is a relatively common form of uveal inflammation with typical clinical features for which HLA-B27 typing provides a strong support for diagnosis (1). These patients usually have recurrent, unilateral disease and were previously thought to have less severe disease and less frequent complications than their HLA-B27-negative counterparts (2). Association of HLA-B27 with acute uveitis was first described in 1973 (3). The incidence of uveitis in Asian population is 6-13% (4-6). HLA-B27 positive AAU, as a distinct clinical entity, is now known to be associated with severe ocular complications and sight-threatening effects. Therefore, it is important to distinguish it from HLA-B27 negative ones (6). The prognosis of HLA-B27 negative

Corresponding author: Dr. Mahendra Narin Mishra, Dr. Lal Pathology Reference Laboratory, Sector 18, Rohini, New Delhi, India, Tel: (+) 91 7838101202, e-mail: mnmishra@hotmail.com

uveitis was earlier supposed to be worse but recent literature suggests contradictory findings. This retrospective study was undertaken to examine the clinical profile, establish the frequency of HLA-B27 in 89 cases of uveitis referred to the tissue-typing laboratory of the Pathology department and compare it with that reported in literature. On conducting a Pub Med search we found no recent study on the association of HLA-B27 with uveitis as a predominant feature in Asian Indian population, although there are reports of uveitis as a part of spondylo-arthropathies and this was the unique feature of patients in this study.

MATERIALS AND METHODS

This was a retrospective study conducted on 89 out of 102 patients with ocular symptoms referred to the tissue-typing laboratory of the Pathology Department of a tertiary care centre in Maharashtra. All patients included in this study had predominantly ocular symptoms. Thirteen cases which did not meet the criteria for clinical diagnosis of uveitis were excluded. Diagnosis was based on clinical and ophthalmic examination as per International study group on uveitis (7). All patients had undergone complete laboratory work up including complete blood count, ESR, antinuclear antibody, serology for infectious diseases including syphilis, ELISA and X-Ray chest for tuberculosis, HLA-B27 testing and radiological work up including X-ray and CT scan, where indicated. Clinical and ophthalmological examinations were performed for all patients. None of them had uveitis of infectious aetiology. All the patients had acute anterior uveitis sometime during the course of the disease. Details of the clinical features were not available so have not been discussed in detail.

HLA-B27 typing was done by standard two stage NIH microlympho-cytotoxicity assay for 30 samples, by sequence specific primers (SSP) for 47 samples and by both methods for 12 samples using commercial kits from GTI (USA), and Innotraining and BAG (Germany) as described by the authors in a previous study (8). DNA extraction for B27 typing by SSP was performed manually by column based methods using kits from Qiagen (Germany). Tests were put up in singles in accordance with the procedure mentioned in product insert. The choice of method for HLA-B27 typing was as per the availability of a particular kit at the time of test requisition. One known positive DNA sample was included in each run of SSP typing for HLA-B27. The results were compared with prevalence of HLA-B27 in 200 healthy renal or prospective bone marrow donors without any history of uveitis, for whom the tissue-typing was done by SSP at this centre.

RESULTS

Clinical diagnosis based on onset and clinical presentation was acute uveitis in seventy-five patients, chronic uveitis in four patients and recurrent uveitis in ten patients. Eighty patients had anterior uveitis and six had posterior uveitis as the predominant symptom at the time of testing with a history suggestive of previous anterior uveitis; and three had pan uveitis. Patients had been symptomatic for six weeks to fifteen years. The cases of pan and posterior uveitis were included as they also had only ocular symptoms. Four patients had associated joint related symptoms of which three were positive for

HLA-B27. There were 23 females (25.6%) and 66 males with the age ranging from 2-82 years (mean 38.44 years). Fifty (56.2%) samples were positive for HLA-B27 while 39 samples (43.7%) were negative. In the control population only 3% of the samples tested positive for HLA-B27. Table 1 show the age and sex distribution of the patient population and HLA-B 27 positivity for various age groups. Maximum numbers of patients were in the age group of 41-50 years.

Table 1. Age/sex distribution and B27 typing results for 89 uveitis patients.

Age in years	M	F	positive	negative
≤20	6	0	3	3
21-30	19	2	9	12
31-40	15	10	15	10
41-50	21	5	17	9
> 50	5	6	6	5

DISCUSSION

HLA associations are strongest in diseases of the uvea among all ocular diseases. Anterior uveitis is the most common form of uveitis in most regions of the world. HLA-B27 associated AAU is the most frequent type of endogenous uveitis, accounting for 18-32% of all anterior uveitis cases in western countries and for 6-13% of all anterior uveitis cases in Asia (4-6). The relatively lower frequency in Asia is related to the lower frequency of HLA-B27 found in this population. HLA-B27 associated AAU has a characteristic presentation, so diagnosis is often suggested by clinical assessment, although testing for HLA-B27 status provides strong support for the diagnosis (1). Only seven females (23%) with uveitis were positive for HLA- B27. Among males, the positivity rate was almost three times higher (64.2%) which is in agreement with other reports in literature that showed male predominance (9,10). In patients with AAU, the HLA B27 frequency was 65.7%, as three out of eight patients with RU were positive for HLA B27 and all five patients with bilateral uveitis were negative for HLA-B27. In this study only 4.5 % had systemic disease, unlike some reports with a high association of AAU with systemic diseases and infections (11). In Table 2 we have shown a comparison of some of the features of this study with some similar studies reported in literature. AAU was present in 94 % of cases in an Italian study and this was similar to that in our study where 80 out of 89 (90%) had AAU at the time of clinical evaluation (12). Overall positivity rate of 56.3 % was higher than that reported in another recent Asian study, but lower than that of the Italian study which is probably explained by the higher frequency of B27 in Caucasians (12,13). A study by Deodhar *et al.* on 28 Asian Indian patients with AAU revealed HLA -B27 positivity of 64.3% (14).

Despite intensive clinical and basic scientific research, the precise molecular and pathogenic mechanisms linking HLA-B27 and its associated inflammatory diseases remain unclear. Human uveal cells, with the exception of vascular endothelium do not normally express, or express in low concentration, HLA antigens in vivo (15,16) . The

expression of HLA antigens was found to be upregulated in the iris of patients with anterior uveitis and this correlated directly with the concentration of IFN- γ in the aqueous humor (17). Clinical features of HLA-B27-associated AAU have been extensively reviewed in the literature and include abrupt onset, unilateral involvement, younger age of onset, marked fibrinous reaction and necessity for systemic treatment (6,18). Earlier the prognosis of AAU was supposed to be better, but now there are conflicting reports on the prognosis (2,6) and there is a requirement to perform multicentre studies on larger populations.

Table 2. Previously reported prevalence of HLA B27 in uveitis and special features.

Study	Number of patients	% B 27 positive	special features
Current	89	56.3	Male predominance, unilateral much >> than bilateral. systemic diseases in 4.5% and 0% infections.
Pathanapitoon <i>et al.</i> ⁹	121	44	Male predominance, mainly ocular involvement.
Nguyen <i>et al.</i> ⁸	121	13.2	systemic diseases & infections in 35.5 and 26.4% respectively.
Accorinti <i>et al.</i> ¹¹	165	63.6	unilateral >> bilateral, 50% had associated systemic diseases
Niederer <i>et al.</i> ¹⁰	124	36	AS in 41% of HLA B27 cases. Male preponderance.
Huhtinen <i>et al.</i> ¹²	220	71	HLA B27 associations with AAU and unilateral uveitis were 71 and 79% , respectively.

Pathanapitoon *et al.* found that HLA-B27 positive uveitis was similar to that in Europe and the USA, but the pathogenesis and cause of HLA-B27 negative uveitis in Thailand was different (10). Limitations of our study include its retrospective nature for which follow up data is unavailable and also the fact that a comparison of clinical profile of B27 negative patients has not been carried out. However it was intended as a pilot study and we were successful in documenting the frequency of B27 positivity in patients presenting mainly with ocular symptoms and diagnosed as uveitis on IUSG criteria (7). Noble *et al.* have suggested HLA-B27 typing in all cases of non-granulomatous AAU in adults and additional testing for antinuclear antibodies in children with AAU. The advantage of DNA testing by SSP for HLA-B27 is that samples can be transported across large distances in a country like India where the facility is available at few centres and test is not affected by viability of the cells (19).

This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as predominant clinical feature. HLA-B27 association with uveitis showed a male preponderance and higher B27 positivity in AAU similar to the findings reported in the literature for other populations. The HLA-B27 status is useful for determining the clinical profile, prognostication and outcome of AAU. There is also a need requirement to make all ophthalmologists including those staying in remote areas aware of this test.

ACKNOWLEDGMENTS

Director General Armed Forces medical Services for funding the study and Dr. Seema Sharma for statistical analysis of the data.

REFERENCES

- 1 Smith JR. HLA-B27-associated uveitis. *Ophthalmol Clin North Am.* 2002; 15:297-307.
- 2 Wakefield D, Monanaro A, Mc Cluskey P. Acute Anterior Uveitis and HIA-B27. *Surv Ophthalmol.* 1991; 36:223-32.
- 3 Brewerton DA, Caffrey M, Nicholls A, Walters D, James DC. Acute anterior uveitis and HLA 27. *Lancet.* 1973; 302:994-6.
- 4 Biswas J, Narain S, Das D, Ganesh SK. Pattern of uveitis in a referral uveitis clinic in India. *Int Ophthalmol.* 1996-1997; 20:223-8.
- 5 Kotake S, Furudate N, Sasamoto Y, Yoshikawa K, Goda C, Matsuda H. Characteristics of endogenous uveitis in Hokkaido, Japan. *Graefes Arch Clin Exp Ophthalmol.* 1997; 235:5-9.
- 6 Chang JH, McCluskey PJ, Wakefield D. Acute Anterior Uveitis and HLA-B27. *Surv Ophthalmol.* 2005; 50:364-88.
- 7 Deschenes J, Murray PI, Rao NA, Nussenblatt RB. International Uveitis Study Group (IUSG): clinical classification of uveitis. *Ocul Immunol Inflamm.* 2008; 16:1-2.
- 8 Mishra MN, Singal V. Human Leukocyte Antigen B27 in 453 Asian Indian patients with Seronegative Spondyloarthropathy. *Iran J Immunol.* 2010; 7:252-6.
- 9 Nguyen AM, Sève P, Le Scanff J, Gambrelle J, Fleury J, Broussolle C, et al. Clinical and etiological aspects of uveitis: A retrospective study of 121 patients referred to a tertiary centre of ophthalmology *Rev Med Interne.* 2010; 32:9-16.
- 10 Pathanapitoon K, Suksomboon S, Kunavisarut P, Ausayakhun S, Wattananikorn S, Leetrakool N, Rothova A. HLA-B27-associated acute anterior uveitis in the University Referral Centre in North Thailand: clinical presentation and visual prognosis. *Br J Ophthalmol.* 2006; 90:1448-50.
- 11 Niederer R, Danesh-Meyer H. Uveitis screening: HLAB27 antigen and ankylosing spondylitis in a New Zealand population. *N Z Med J.* 2006; 119(1230):U1886.
- 12 Accorinti M, Iannetti L, Liverani M, Caggiano C, Gilardi M. Clinical features and prognosis of HLA B27-associated acute anterior uveitis in an Italian patient population. *Ocul Immunol Inflamm.* 2010; 18:91-6.
- 13 Huhtinen M, Karma A. HLA-B27 typing in the categorisation of uveitis in a HLA-B27 rich population. *Br J Ophthalmol.* 2000; 84:413-6.
- 14 Sen Gupta S, Jain IS, Jain GC, Deodhar SD. HLA antigens in acute anterior uveitis in North Indians. *Indian J Ophthalmol.* 1978; 26:26-9
- 15 Abi-Hanna D, Wakefield D. Expression of HLA antigens on the human uvea. *Br J Rheumatol.* 1988; 27:68-71.
- 16 Abi-Hanna D, Wakefield D, Watkins S. HLA antigens in ocular tissues. I. In vivo expression in human eyes. *Transplantation.* 1988; 45:610-3.
- 17 Abi-Hanna D, McCluskey P, Wakefield D. HLA antigens in the iris and aqueous humor gamma interferon levels in anterior uveitis. *Invest Ophthalmol Vis Sci.* 1989; 30:990-4.
- 18 Ramsay A, Lightman S. Hypopyon uveitis. *Surv Ophthalmol.* 2001; 46:1-18.
- 19 Noble J, Hollands H, Forooghian F, Yazdani A, Sharma S, Wong DT, et al. Evaluating the cost-effectiveness of anterior uveitis investigation by Canadian ophthalmologists. *Can J Ophthalmol.* 2008; 43:652-7.