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Abstract- Uveitis is a common ocular disease characterized by inflammation of iris, choroid, and ciliary body. HLA-B27 is the strongest known genetic risk factor for acute anterior uveitis. The prevalence of HLA B27 and associated diseases varies widely across different racial groups and have massive clinical implications. DNA typing was done using amplification of genomic DNA by the polymerase chain reaction (PCR) and hybridization with sequence-specific oligonucleotide probes (SSOP). This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as a predominant clinical feature.

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Molecular Typing of HLA B27 in Uveitis Patients at a Tertiry Care Centre in India and its Clinical Implications

Indu Yadav [α] & Indrani Dhawan [σ]

Abstract- Uveitis is a common ocular disease characterized by inflammation of iris, choroid, and ciliary body. HLA-B27 is the strongest known genetic risk factor for acute anterior uveitis. The prevalence of HLA B27 and associated diseases varies widely across different racial groups and have massive clinical implications. DNA typing was done using amplification of genomic DNA by the polymerase chain reaction (PCR) and hybridization with sequence-specific oligonucleotide probes (SSOP). This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as a predominant clinical feature.

I. Material and Methods

A total of 30 patients of uveitis and 30 healthy controls in blood bank were included in this study of two years from July 2016 to June 2018 in Department of Pathology and Department of Ophthalmology, VMMC AND Safdarjung Hospital, New Delhi. HLA B27 genotyping was performed using PCR-SSP (Fluogene -a fluorescence based HLA gene amplification detection system). It was a tertiary care center based cross-sectional study, and comparison between groups was done using Pearson's Chi-square test/ Fischer's exact test. Ap value≤ 0.05 was considered statistically significant. Patient with any malignancy and treated with radiotherapy or chemotherapy before enrolment in study were excluded. Data were entered in Microsoft excel sheet and Analysis was done on licensed version 21 of SPSS.

II. Results and Discussion

A total of 30 cases of uveitis attending Ophthalmology O.P.D at Safdarjung Hospital and 30 healthy controls from blood bank of Safdarjung Hospital were evaluated in this study by HLA B27 typing done using PCR-SSP method on all the cases and controls.

The age of the cases ranged from 15 to 80 years with a mean age of 35.7±14.08 years. Age of controls ranged from 22 to 46 years with a mean age of 31.43±7.88 years. On comparison of the incidence of HLA B27 positivity between cases and controls, out of 30 cases of uveitis 46.6% (n=14) were positive, and 53.4% (n=16) were negative. In the healthy control group 96.7% (n=29) were negative, and only one 3.3% (n=1) was positive. Chi-square analysis suggests that the cases had a significantly higher incidence of HLA B27 positivity as compared to controls. The study conducted by M. N. Mishra in Asian Indian population concluded that HLA B27 positivity rate was 56.2% among uveitis patients and 3% for control samples.[1] A study conducted in Finland showed HLA B27 positivity rate was 70% in cases of uveitis.[2] Our results were in agreement with the results of these studies. The lower positivity rate than the Finland study is probably explained by the higher frequency of HLA B27 in Caucasians.

Table I: Comparison of incidences of HLA-B27 positivity between two groups

		HLA B27		Total
		Negative	Positive	
Group	Case	16	14	30
	Control	29	1	30
		45	15	60

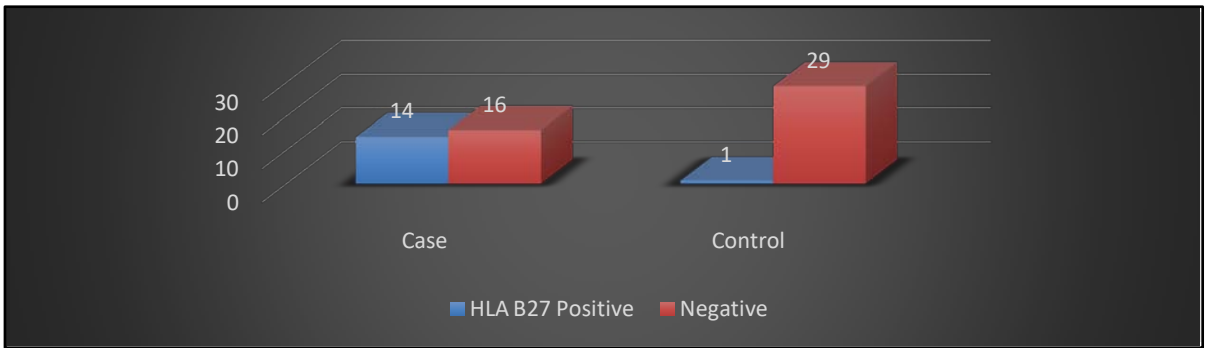

Figure 1: Comparison of incidences of HLA-B27 positivity between two groups.

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In our study out of the 14 HLA B 27 positive cases (n= 8) were in the age group of 20-41 years. In the study by Mishra et al[1], most of the patients were in the age group of 41-50 years. A study conducted by Pathanapitoon K[3] also hypothesized that the HLA B27 associated acute AU represents a distinct clinical entity occurring typically in young adults between the ages of 20 and 40 years, which similar to our study. The possible explanation is that autoimmune diseases present more in the young population.[4] Due to younger age, there is less stimulation of peripheral T regulatory cells hence protective regulatory mechanism is not enhanced.[5]

The mean age at the time of the first attack for HLA-B27 positive cases was 29.50 ± 8.3 years, whereas it was 34.56 ± 15.1 years in case of HLA B27 negative cases. This shows that HLA B27 positive cases have an early age at time of first attack of uveitis. Study by Monnet et al[6] and other authors[7] showed 31 years as mean age at the time of the first attack. Barkenburg[8] showed that there was no difference between male and female in terms of average age of onset of uveitis

Out of 30 cases of uveitis, 66.6% (n=20) were males and 33.3% (n=10) were females. Out of the 20 (66.6%) males clinically diagnosed as uveitis, 39.9% (n=12) were positive for HLA B27, whereas 26.6% (n=8) were negative for HLA B27. Of 10 (33.3%) females clinically diagnosed as uveitis, 6.6% (n=2) were positive and 26.7% (n=8) were negative for HLA B27. Chi-square test suggests that HLA B27 positivity is more frequent in male compared to females presenting of uveitis. In our study there was male preponderance which is similar to studies done by different authors across the world with a male:female ratio varying from 3:1 to 1.5:1. [1,7,9,10] Since HLA B27 molecules are major histocompatibility complex class I gene products which interact with T cells, in particular, CD8+ T cells, it is conceivable that gender-related differences in immune response could play a role in the different manifestations of HLA B27 associated uveitis. Variable environmental exposures, either endogenous (i.e., sex hormone) or exogenous (tendency towards exposure to infectious agents through lifestyle or different susceptibilities), might be expected to play roles as well.[11]

Table II: Gender preponderance in HLA B27 cases

		HLA B27		Total
		Negative	Positive	
Sex	F	8	2	10
	M	8	12	20
Total		16	14	30

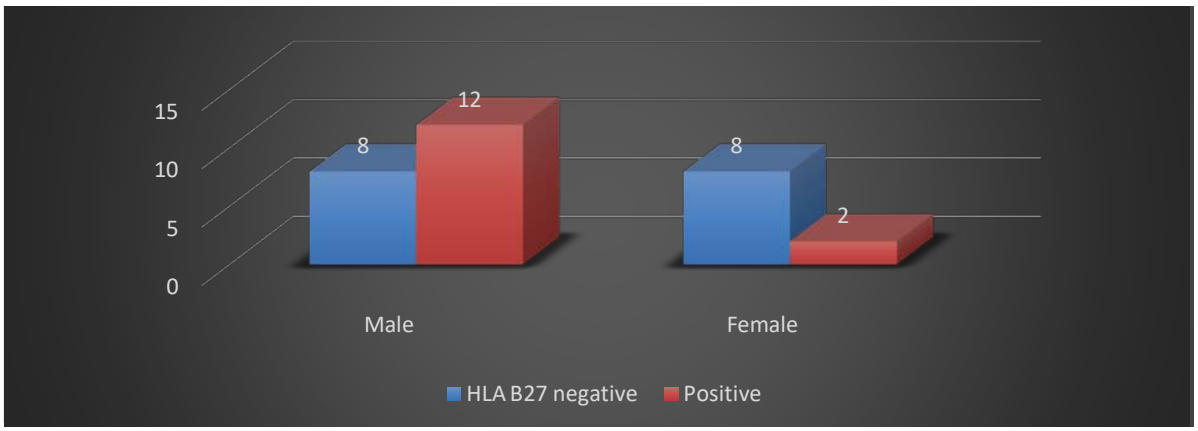

Figure 2: Gender preponderance in HLA B27 case

Our study showed that the most common systemic disease in HLA B27 positive cases is ankylosing spondylitis which constitute 21% of the HLA B27 positive cases of uveitis. Mishra found only 4.5% of uveitis patients had associated systemic disease. The study by Monnet[6] (n=175) showed that HLA B27-associated extraocular disorder was seen in 77.7% and of these, ankylosing spondylitis was diagnosed in 46.3. Similarly, in the study conducted by linseen[12] (n=119), rheumatologic complications occurred in 72% of HLA B27-positive males. So, the most common of the extraocular diseases are spondyloarthropathies. Uveitis is frequently the first indication of a previously undiagnosed HLA B27-associated extraocular disease.[12] The frequency of systemic disease associated with HLA B27 associated uveitis seems to be lower in Japan (1.3%), India (15%), and Thailand (15%) when compared with Western countries (~50%).[3]

Among uveitis cases, a number of episodes was variable ranging from 1 to 12 in all cases included in the study. The HLA B27 tested positive cases for HLA B27 showed 4.36±3.41 mean number of episodes, but the HLA B27 tested negative cases has mean 1.81 ± .911 number of episodes. Our study showed that due to more number of recurrent attack, the HLA B27 positive uveitis are more prone for the development of complication like glaucoma and cystoid macular edema. Denis Wakefield suggested that complication in HLA B27 AU patients are related to the number of recurrent attacks.[13] The patients who were HLA B27 positive,

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either with or without systemic disease, experienced a greater number of complications than did the patients who were HLA B27 negative.[14]Thus the prognosis of anterior uveitis associated with the HLA B27, either with or without associated systemic disease, is less favorable when compared with that of HLA B27-negative patients with idiopathic anterior uveitis.

Table III: Comparison of the number of episodes between HLA B27 positive and negative cases

	HLA B27	N	Mean	Std. Deviation	Std. Error Mean	p-value
No. of episodes	Negative	16	1.81	.911	.228	0.008**
	Positive	14	4.36	3.411	.912	

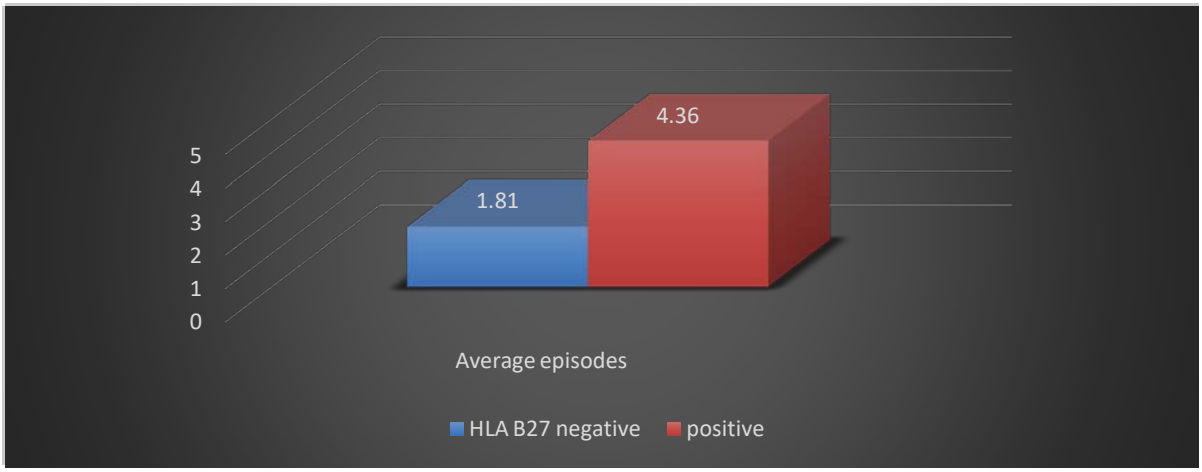

Figure 3: Comparison of the number of episodes between HLA B27 positive and negative cases

Similarly, study conducted in Asian Indian population and at other places [1,15] hypothesized that HLA B27 positive patients have a poorer prognosis than HLA B27 negative patients. On the other hand, contradictory studies are also found in the literature. This can be due to referral bias in a tertiary care centre and small sample size. The prognosis of HLA B27 associated uveitis was rather favorable or similar despite more severe inflammation and a higher recurrence rate[3,8] in these studies.

III. Conclusion

HLA B27 is frequently detected in Indian population. The joint efforts of an ophthalmologist, a rheumatologist and other specialists, can play a positive effect in treating the patients with HLA B27-associated uveitis.[16]Hence, it can be stated that HLA B27 typing in patients with AAU helps the clinician with the prognosis by avoidance of recurrent attacks and complications. This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as a predominant clinical feature. The sample size of our study was small. We recommend further multicentric studies with the large sample size for establishment of typing in uveitis and its importance in prognosis.

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