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Estimation of HLA-B27 Positivity by Peripapillary Retinal Nerve Fibre Layer Thickness in Patients with Acute Anterior Uveitis

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ABSTRACT

Purpose: To compare the thickness of retinal nerve fiber layer (RNFL) in HLA-B27 positive and HLA-B27 negative acute anterior uveitis (AAU) patients with active inflammation.

Methods: Thirty-seven patients with HLA-B27-positive AAU and 32 patients with HLA-B27-negative AAU were analyzed. Clinical characteristics, HLAB27 typing and retinal nerve fiber layer thickness measurements were recorded. All data were compared with 35 age and sex matched healthy subjects. ROC analysis was used to determine the RNFL threshold in patients with HLA B27 positive AAU.

Results: There was no significant difference between the HLA-B27 (-) group and the control group in terms of RNFL thickness in the temporal, temporal inferior and nasal inferior quadrants. (P = 0.293, p = 0.064, p = 0.033, respectively) In all other quadrants, RNFL thickness of the HLA-B27 (+) and HLA-B27 (-) groups was thicker than the control group. RNFL thicknesses in temporal superior, nasal superior and nasal inferior quadrants were significantly thicker in the HLA-B27 (+) group compared to the HLA-B27 (-) group. (P = 0.008, p = 0.012, p = 0.016, respectively) According to ROC analysis, RNFL thresholds were 139 µm, 111.50 µm and 110.50 µm in temporal superior, nasal superior and nasal inferior quadrants, respectively. A significant and positive correlation was found between RNFL and anterior chamber cell counts in all quadrant AAU patients.

Conclusion: RNFL thickness increases more in HLA-B27 positive patients than in negative patients. RNFL thickness above the threshold values determined by ROC analysis may indicate HLA-B27 positivity.

Key words: HLA-B27 positivity, Acute anterior uveitis, Retinal nerve fiber layer thickness, ROC analysis, Idiopathic uveitis.

INTRODUCTION

Acute anterior uveitis (AAU), which is the most common type of intraocular inflammation, is characterized by anterior chamber inflammation ending in 3 months.[1] It is responsible for approximately 15 to 42% of all uveitis cases.[2-4] The HLA-B27 antigen is strongly associated with AAU. Previous studies have demonstrated HLA-B27 positivity in 12 to 88% of anterior uveitis cases.[5-7] In one study performed in Turkey, in 40% of patients with AAU, HLA-B27 was determined.[8] Several studies have compared HLA-B27 positive and negative AAU in terms of clinical outcomes. Some works have shown that HLA-B27 positive AAU has a better prognosis,[9,10] whereas others have found the opposite relation.[11,12] There is also research demonstrating that there is no statistically significant difference in this regard.[7,12] However, many studies have found that fibrinous reaction and hypopyon formation rates are significantly higher in HLA-B27-positive AAU.[8,11-14] Therefore, HLA-B27 positive AAU may be thought to be characterized by a more severe inflammation than HLA-B27 negative AAU in the active phase regardless of clinical prognosis.

Retinal nerve fibre layer (RNFL) thickness has been found to be significantly increased in both uveitic eyes without glaucoma but with active inflammation than normal and quiescent uveitis eyes.[15-17] Increased retinal thickness has been reported in various forms of uveitis, and a correlation between retinal thickness and disease activity has been

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demonstrated.[18-20] In studies comparing HLA-B27 positive and negative AAU patients, an objective measurement method such as RNFL thickness has not been used previously. The aim of this study was to compare RNFL thickness of HLA-B27 positive and HLA-B27 negative AAU patients with active inflammation.

PATIENTS AND METHOD

Clinical records of all patients with AAU seen at the Uveitis Unit of the University of Health Sciences, Ulucanlar Eye Education and Research Hospital in Ankara, Turkey from January 2015 to May 2017 were reviewed. The study protocol was approved by the institutional board of the Numune Research and Training Hospital, Ankara, the Turkey ethics committee and was adherent to the Declaration of Helsinki. All participants provided informed written consent. Sex, age at onset, HLA-B27 typing, clinical features, diagnosis and possible systemic disease relationship were recorded. Anterior chamber cells were classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group criteria.[4] Peripapillary RNFL measurements were measured and recorded 3 times by spectral domain optical coherence tomography (SD-OCT) (Spectralis v. 4.0; Heidelberg Engineering, Heidelberg, Germany). Peripapillary RNFL thickness values were divided into 4 quadrants. The upper and lower quadrants are also divided into nasal and temporal sectors. Patients with OCT image quality score <20 were excluded; hence, patients with hypopion and fibrinous reactions were not included in the study. RNFL thicknesses were compared to the normal population, and only patients with the first episode of AAU were included in the study.

Laboratory investigations (blood cell count, angiotensin converting enzyme test, etc.) were performed to determine the possible systemic relationship in all patients, and radiological examinations were performed in suspected cases. In addition, all patients underwent HLA-B27 typing. Diagnoses of ankylosing spondylitis were made according to the criteria of Dougados et al.[21] A biopsy was performed to confirm the diagnosis in patients with suspected inflammatory bowel disease (ulcerative colitis and Crohn's disease). Patients with Fuchs uveitis or systemic diseases other than those mentioned above were excluded from the study.

All patients were treated with topical corticosteroids or systemic corticosteroids according to the severity of intraocular inflammation.

Statistical analysis was performed using IBM SPSS Statistics v21.0 (IBM, Armonk, NY, USA). The normality of data distribution was evaluated by a Shapiro-Wilk test. One way analysis of variance (ANOVA) and Bonferroni post hoc tests were performed to investigate the differences. Pearson' correlation coefficient was used to correlate the variables. All values are reported as mean±standard deviation (SD). The statistical significance level was set at $p < 0.016$. ROC analysis was used to determine threshold RNFL thickness in patients with HLA B27 positive AAU.

RESULTS

The mean age of 34 (51%) HLA-B27 positive patients with AAU was 36.23±6.91 years, the mean age of 32 (49%) patients with HLA-B27 negative AAU was 33.50±11.34 years and the mean age of 35 control groups was 32.71±5.87 years. There was no significant difference between the groups in terms of mean age ($p = 0.083$). HLA-B27 positive patients had male predominance (male / female ratio = 1.8), whereas HLA-B27 negative patients had no significant gender difference (male / female ratio = 0.7). There was no significant difference between HLA-B27 positive and negative patient groups in terms of age and sex ($p = 0.681$, $p = 0.137$, respectively). In addition, there was no gender difference between the 3 groups ($p = 0.200$). Bilateral simultaneous uveitis in both eyes was significantly higher in the HLA-B27 negative group (n = 10, 31%) than in the positive group (n = 4, 11%) ($p = 0.043$). The general characteristics of the groups are summarized in Table 1. Ankylosing spondylitis was detected in 12 (35.3%) of HLA-B27 positive patients. One (2.9%) patient had ulcerative colitis and only one (2.9%) patient had reactive arthritis. There was no relationship between systemic disease in the HLA B27 negative group.

There was no significant difference between the HLA-B27 (-) group and the control group in terms of RNFL thickness in the temporal, temporal inferior and nasal inferior quadrants. ($P = 0.293$, $p = 0.064$, $p = 0.033$, respectively) In all other quadrants, RNFL thickness of the HLA-B27 (+) and HLA-B27 (-) groups was thicker than the control group. RNFL thicknesses in temporal superior, nasal superior and nasal inferior quadrants were significantly thicker in the HLA-B27 (+) group compared to the HLA-B27 (-) group. ($P = 0.008$, $p = 0.012$, $p = 0.016$, respectively) (Table 2) There was a significant and positive correlation between RNFL and anterior chamber cell counts in AAU patients (global $r = 0.525$, $p < 0.001$; temporal $r = 0.456$, $p < 0.001$; nasal $r = 0.289$, $p = 0.018$; temporal superior $r = 0.649$, $p < 0.001$; nasal superior $r = 0.576$, $p < 0.001$; temporal inferior $r = 0.467$, $p < 0.001$; and nasal inferior $r = 0.490$, $p < 0.001$).

Table 3 summarizes the threshold RNFL thicknesses that provide HLA-B27 positive and negative patient distinction and generate ROC analysis values. According to ROC analysis, RNFL thresholds were 139 μm, 111.50 μm and 110.50 μm in temporal superior, nasal superior and nasal inferior quadrants, respectively.

Table 1. *Characteristics of patients with acute anterior uveitis.*

	HLA-B27 (+) group	HLA-B27 (-) group	Control group
No.of patients	34	32	35
Gender (Male/Female)(n)	22/12	14/18	21/14
Male/Female Ratio	1.8	0.7	1,5
Mean age at onset(years)	36,23±6,91	33,50±11,34	32,71±587
Eye involvement (n) Unilateral Bilateral alternating Bilateral simultaneous	 25 5 4	 14 8 10	
Anterior chamber cells (n) Grade 1 Grade 2 Grade 3 Grade 4	 5 8 11 10	 4 13 10 5	

Table 2. *Comparison of RNFL Thickness Between Groups.*

		HLA-B27 (+) group	HLA-B27 (-) group	Control group	P value
RNFL Thickness (μm)	global	105,73±9,22	100,68±9,37	92,02±4,79	p^a<0.032 p^b<0.001 p^c<0.001
	Nasal superior quadrant	117,91±13,90	110,06±12,90	93,37±7,12	p^a =0.012 p^b<0.001 p^c<0.001
	Nasal quadrant	80,41±11,11	80,96±11,24	72,48±4,71	p^a =1.000 p^b=0.002 p^c=0.001
	Nasal inferior quadrant	119,11±16,72	109,59±18,15	100,37±6,37	p^a =0.016 p^b<0.001 p^c=0.033
	Temporal superior quadrant	146,20±11,19	137±17,18	121,28±6,19	p^a =0.008 p^b<0.001 p^c<0.001
	Temporal quadrant	79,29±11,28	75,21±11,17	71,11±7,25	p^a = 0.307 p^b=0.003 p^c=0.293
	Temporal inferior quadrant	144,94±12,04	137,68±13,43	131,60±4,64	p^a=0.020 p^b<0.001 p^c=0.064

RNFL= retina nerve fiber layer; p^a= comparison between HLA-B27(+) group and HLA-B27(-) group; p^b=comparison between HLA-B27(+) group and control group; p^c= comparison between HLA-B27(-) group and control group

Table 3. *Receiver Operating Characteristic (ROC) analysis of the RNFL Thickness.*

	Temporal superior quadrant	Nasal superior quadrant	Nasal inferior quadrant
CP= Cut off point (μm)	139	111.50	110.50
AUC= Area under the curve	0.640	0.642	0.639
$CI_{\%95}$	0.503-0.777	0.509-0.776	0.504-0.774
Sensitivity	%70	%70	%67
Specifity	%57	%50	%54
P value	0.050	0.047	0.050

RNFL= retina nerve fiber layer

DISCUSSION

Posterior segment involvement in HLA-B27-associated AAU was observed at different rates.[2,10,22] In one study, the rate of cystoid macular edema (CME) was found to be 13.7%.[22] Retinal thickening and increase in RNFL thickness were also determined by other studies.[17-19] In accordance with the literature, our research also found an increase in RNFL thickness in active AAU patients. In addition, temporal superior, nasal superior and nasal inferior quadrants were found to be thicker in HLA-B27 positive AAU patients than HLA-B27 negative AAU patients. According to ROC analysis, the threshold value that could distinguish HLA-B27 positivity in temporal superior, nasal superior and nasal inferior quadrants was determined.

The prevalence of HLA-B27 antigen in a healthy Turkish population has been reported as 6.8%.[23] Tuncer et al.[8] detected HLA-B27 antigen positivity in 40% of AAU patients. In our study, this rate was 51%. To avoid the effect of OCT image quality, we excluded patients with hypopyon and fibrinous reactions. Previous studies have shown that the presence of hypopion and fibrinous reaction is more common in HLA-B27 positive patients than in HLA-B27 negative patients.[7,10,13] D'Alessandro et al.[24] reported that the rate of hypopion was 14.5% in HLA-B27 positive patients and 2.2% in HLA-B27 negative patients. Therefore, the 51% rate found in our work could be larger if all patients were included in the study. According to the literature, 50 to 80% of patients with HLA-B27-positive AAU are male.[8-12] In our study, this rate was 64%. No gender differences have been reported in HLA-B27 negative patients with AAU.[12,25] Our study showed a similar result. The onset of AAU was between 20 and 40 years in most patients in the literature.[2,7-12] There was no statistically significant difference between HLA-B27 positive and negative patients at the age of onset of the disease. Many studies have demonstrated that the majority of HLA-B27 positive AAU patients are associated with spondyloarthropathy.[7,9-11,13,25] Among systemic diseases, ankylosing spondylitis is the most common. Some authors have identified ankylosing spondylitis in 22 to 39% of HLA-B27-related uveitis patients.[7-11,13] In our work, the prevalence of this disease was 35.3%. In HLA-B27-positive AAU patients, involvement is usually unilateral or bilateral alternating and is characterized by non-granulomatous recurrent iridocyclitis.[7,11,12] These clinical findings may distinguish this group of patients from those patients associated with HLA-B27 negative AAU. The results of our study confirm this important difference between the two groups. We found that most HLA-B27 positive patients (88%) were characterized by unilateral or bilateral alternan AAU, and 31% of HLA-B27 negative patients had bilateral simultaneous AAU.

Changes in the retinal anatomy of patients with AAU have been reviewed in the literature. Castellano et al.[18] found significant retinal thickening in patients with active iridocyclitis and observed that the condition returned after anti-inflammatory treatment. They also found a moderately positive relationship between retinal thickness and anterior chamber cells; however, there were highly different groups of patients with varying aetiology in their study. Traill et al.[19] detected retinal thickening in patients with AAU, and HLA B27 antigen was positive in 14 of 15 patients. Balaskas et al.[20] demonstrated retinal thickening in all quadrants in HLA-B27 positive AAU patients compared to the other eye, a thickening which correlated with the severity of inflammation. In this study, retinal thickening lasted for 3 months and suggested that inflammation caused a chronic change in the retina.[20] Studies have shown that RNFL thickness increases in AAU patients. In one research paper, an increase in RNFL thickness was reported in patients with active uveitis compared to non-uveitic eyes.[17] Din et al.[16] found a significant increase in RNFL thickness in active uveitic eyes and showed that this thickening improved at a quiescent stage. Similarly, RNFL thickness was increased in all quadrants in HLA-B27 positive patients compared to the control group. This increase in thickness may be due to an increase in inflammatory cytokines, an increase in prostaglandin level and an increase in vascular permeability in the blood retinal barrier. Many studies have shown that hypopion and fibrinous reactions are more common in HLA-B27 positive patients than in HLA-B27 negative patients.[7,10,13] This observation may indicate that inflammation is more severe in HLA-B27 positive patients in the active phase. In one study, IL-1b, IL-1Ra, IL-36Ra and IL-37 levels were increased significantly in aqueous humour of HLA-B27 positive patients.[26] In addition, the aqueous humour level of IL-18 was shown to be higher in HLA-B27 positive patients than in negative patients. Elevation of these cytokines may be responsible for the severity of the local inflammatory reaction. At the onset of the disease, RNFL thickness in HLA-B27 positive patients is higher than that of HLA-B27 negative patients, a result which may be due to the severity of inflammation.

Higher RNFL thickness in HLA-B27 positive patients may help predict HLA-B27 positivity by RNFL analysis in patients presenting with AAU. According to ROC analysis, 139µm, 111.50µm and 110.50 µm were determined as threshold values in temporal superior, nasal superior and nasal inferior quadrants, respectively. Early detection of HLA-B27 positivity in patients presenting with AAU may provide early consultation and more effective treatment. To our knowledge, this is the first study to compare RNFL thickness of HLA-B27 positive and negative patients.

The most significant limiting factor of our study is its retrospective design. Patients with hypopyon and fibrinous reaction were excluded from the study to ensure OCT

signal quality. For this reason, we could not compare the clinical outcome, treatment protocol, and other aspects of our study. The aim of this study, however, was to compare the RNFL thickness of HLA-B27 positive and negative patients with active anterior uveitis and not associated with hypopion and/or fibrinous reaction.

In conclusion, RNFL thickness was significantly increased in patients with HLA-B27 positive AAU than HLA-B27 negative AAU patients. This difference in RNFL thickness may be a predictor of HLA-B27 positivity. RNFL thickness above the threshold values determined by ROC analysis may suggest HLA-B27 positivity.

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