

Measurements of Retinal Nerve Fiber Layer and Macular Thickness in Patients with Ankylosing Spondylitis, Using Optical Coherence Tomography

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Abstract

Purpose: To evaluate the retinal nerve fiber layer and macular thickness in patients with ankylosing spondylitis (AS) without ocular involvement.

Methods: Group 1 consisted of patients with AS who were HLA-B27-positive; group 2 consisted of patients with AS who were HLA-B27-negative; and group 3 consisted of healthy controls. Central macular thickness (CMT), central subfoveal choroidal thickness (CSCT), and retinal nerve fiber layer (RNFL) thickness were measured for all participants using spectral domain optic coherence tomography (SD-OCT).

Results: The average CSCT for patients in Group 1, Group 2, and Group 3 were 316.47 μm , 328.77 μm and 317.93 μm , respectively. The average CMT of patients in Group 1, Group 2 and Group 3 were 261.50 μm , 270.29 μm and 256.96 μm , respectively. The average RNFL of patients in Group 1, Group 2, and Group 3 were 102.80 μm , 99.19 μm and 99.63 μm , respectively. In RNFL analysis, the average of N quadrants in Group 1 was 76.7 μm ; in Group 2, it was 71.9 μm ; and in Group 3, it was 78.51 μm .

Conclusions: Patients with AS had thicker CMTs and thinner nasal quadrants (according to RNFL measurements) than control group ($p = 0.02$, $p = 0,04$). There were no significant differences between patients with HLA-B27-positive AS and those with HLA-B27-negative AS.

Keywords: Ankylosing Spondylitis; HLA-B27; Optic Coherence Tomography (OCT); Macular Thickness

Abbreviations

CMT: Central Macular Thickness; CMV: Central Macular Volume; TMV: Total Macular Volume; CSCT: Central Subfoveal Choroidal Thickness; G: Median Retinalnerve Fiber Layer; Ns: Nasal Superior; N: Nazal; Ni: Nasal Inferior; Ti: Temporal Inferior; T: Temporal; Ts: Temporal Superior

Introduction

Ankylosing spondylitis (AS) is one of several seronegative spondyloarthropathic diseases. It engages the axial skeleton, especially spinal articulations. AS, which engages peripheral articulations, may have extra-articular features, including ocular and cardiovascular system involvements [1]. Diagnosis of AS is made based on clinical findings and the results from specific radiologic monitors [1]. Although the etiology of AS is not completely understood, immune impulse, genetic factors, and environmental factors are the most attributed causes. T cell responses, including production of the immune-mediated cytokine TNF- α , are important contributors to AS, suggesting genetic susceptibility due to HLA-B27-positive status¹. Major functional losses due to AS occur within 10 years after diagnosis [2]. Progression occurs rarely, especially in patients who are HLA-B27-positive [3-5].

Acute anterior uveitis (AAU) is the most frequent extra-articular finding with AS, with an incidence of 20 - 40% [6-8]. AS can also cause functional losses of vision by affecting posterior tissues of the eye, and, over time, may cause complications including cataracts, glaucoma, vitritis, cystoid macular edema, macular hole, papillitis, and epiretinal membrane [9,10]. These effects are more obvious for patients who are HLA-B27-positive [6,9].

The frequency of HLA-B27-positive is approximately 10% in normal populations, with some differences between ethnic groups [2,3]. In AAU cases, which do not have systematic coalescence, HLA-B27-positivity is seen 3 - 4 times more frequently. Data suggest that AS progresses over time [11,12]. The level of TNF- α is high in serum and aqueous during active uveitis in patients who are HLA-B27-positive [13]. TNF- α is responsible for inflammatory, edematous, neovascularization, and neurodegenerative responses in the eye [14].

The changes that AS makes in the eye have been investigated in some studies [15-17], but there is no study that compares the posterior eye structure of HLA-B27-positive patients with AS to that of HLA-B27-negative patients with AS. The purpose of this study was to investigate whether HLA-B27 brings about any differences in ocular tissues in AS patients without ocular involvement.

Materials and Methods

This study was conducted in the ophthalmology department at the Kayseri Training and Research Hospital Ophthalmology Department between May 2015 and August 2015. All research was performed according to the Helsinki declaration, and approval for the study was received from the ethics committee. Verbal and written consents were obtained from study participants. This study was registered with trial registration number 2015/40.

This was a prospective and controlled study. Subjects in the study were selected from patients who were followed up in the hospital's rheumatology department because of AS, who were referred to the eye department. The control group was composed of volunteers with demographic characteristics similar to those of the patients who were examined in the eye department. Group 1 consisted of patients who had HLA-B27-positive AS; group 2 consisted of patients who had HLA-B27-negative AS; and group 3 consisted of volunteers in the control group who did not have AS.

The criteria for patients to be involved in this study were the absence of ocular pathology and history, best corrected visual acuity of 0.8 and above, axial length (AL) below 25 mm, spherical equivalent (SE) values in the range of ± 4 , and lack of evidence of previous ocular inflammation, intravitreal injection, or intraocular surgery. Data for only one eye of each patient meeting these criteria were included in the study. Visual acuity, biomicroscopy with slit lamp, intraocular pressure (IOP) measurement by tonometry, and fundus examination after dilatation were performed on all patients.

Patients with an IOP greater than 20 mmHg were excluded from the study. Biometry was performed using a Zeiss® IOLMaster device (Carl Zeiss Meditec, Dublin, CA, USA). Subsequently, macula, choroid, and retinal nerve fiber layer (RNFL) analyses were performed by SD-OCT (Spectralis®, wavelength: 870 nm; Heidelberg Engineering, Heidelberg, Germany) on each patient.

Procedure of Image Acquisition

The RNFL, CMT, and CSCT measurements were obtained using the SD-OCT. The procedure of obtaining SD-OCT has been described previously [18]. CSCTs were measured using SD-OCT (Spectralis, wave-length: 870 nm, Heidelberg Engineering, Heidelberg, Germany). CSCT was defined as the vertical distance from the hyper-reflective line of Bruch's membrane to the hyper-reflective line of the inner surface of the sclera. All subjects were imaged by the same experienced technician. Two independent clinicians measured CSCT, and the average of these measurements was used in the analysis. The peripapillary RNFL thickness parameters that were automatically calculated by the SD-OCT device and divided into regions included average (G) thickness (360 degrees), temporal (T) quadrant thickness (90 degrees), temporal superior (Ts) quadrant thickness (45 degrees), nasal superior (Ns) quadrant thickness (45 degrees), nasal (N) quadrant thickness (90 degrees), nasal inferior (Ni) quadrant thickness (45 degrees), and temporal inferior (Ti) quadrant thickness (45 degrees).

Statistical Analysis

Data were analyzed using SPSS for Windows, version 22.0 (SPSS Inc, Chicago, IL, USA). Data were expressed as mean ± standard deviation. Discrete variables were compared using the Pearson’s chi-squared test. Normal distributions were assessed by the Kolmogorov-Smirnov test.

We tested homogeneity of variances using Levene’s test. We compared groups with normal distributions using the one-way ANOVA test. When we obtained a significant result, we used the Scheffe’s test for post-hoc comparisons. We evaluated nonparametric statistical data using the Kruskal-Wallis test. When we obtained a significant result, we used the Mann-Whitney U test with Bonferroni’s correction for pos-hoc comparisons. We set statistical significance at p values <0.05.

Results

We included 94 patients with AS. Of these, 45 were female and 49 were male. In Group 1, there were 30 patients (16 male and 14 female). In Group 2, there were 31 patients (16 male and 15 female). In Group 3, there were 33 patients (17 male and 16 female). We have presented demographic data in table 1.

	A	G(M/F)	SE	IOP	AI
Group 1 (n = 30)	37.80 ± 11.40	16/14	0.05 ± 0.97D	16.13 ± 2.73 mmHg	23.54 ± 0.71 mm
Group 2 (n = 31)	41.26 ± 12.23	16/15	-0.23 ± 1.05D	15.19 ± 2.31 mmHg	23.35 ± 0.55 mm
Group 3 (n = 33)	37.84 ± 10.41	17/16	-0.64 ± 0.92D	15.48 ± 2.77 mmHg	23.59 ± 0.80 mm
p value	0.16	0.89	0.10	0.36	0.35

Table 1: Summary of Demographics.

Abbreviations: A: Age; G: Gender; M: Male; F: Female; SE: Spherical Equivalent; IOP: Intraocular Pressure; AI: Axial Length

When we analyzed posterior ocular structures, we found some important values. The average CMT in Group 1 was 261.52 µm; in Group 2, it was 270.292 µm; and in Group 3, it was 256.962 µm. The average CSCT in Group 1 was 316.47 µm; in Group 2, it was 328.77 µm; and in Group 3, it was 317.93 µm. In RNFL analysis, the average of N quadrants in Group 1 was 76.7 µm; in Group 2, it was 71.9 µm; and in Group 3, it was 78.51 µm. We have presented the posterior ocular measurements we found in Groups 1, 2, and 3 in detail in table 2.

	Group 1 (n = 30)	Group 2 (n = 31)	Group 3 (n = 33)	p-value
CMT	261.5 ± 21.48 µm	270.29 ± 24.23 µm	256.96 ± 9.40 µm	0.02
CMV	0.21 ± 0.01 mm ³	0.21 ± 0.01 mm ³	0.20 ± 0.01 mm ³	0.77
TMV	8.80 ± 0.35 mm ³	8.83 ± 0.29 mm ³	8.85 ± 0.29 mm ³	0.76
CSCT	316.47 ± 63.37µm	328.77 ± 83.95 µm	317.93 ± 75.39 µm	0.78
G	102.8 ± 9.23 µm	99.19 ± 13.37 µm	99.63 ± 10.40 µm	0.27
Ns	119.20 ± 21.73 µm	122.23 ± 19.19 µm	116,51 ± 20.44 µm	0.52
N	76.7 ± 13.60 µm	71.9 ± 11.21 µm	78.51 ± 10.29 µm	0.04
Ni	117.13 ± 17.42 µm	107.77 ± 22.21 µm	107,57 ± 20.71 µm	0,11
Ti	143.23 ± 23.76 µm	147.52 ± 22.04 µm	140,48 ± 10.81 µm	0.12
T	76.33 ± 13.70 µm	74 ± 11.48 µm	74,90 ± 11.61 µm	0.78
Ts	136.5 ± 13.70 µm	139.16 ± 17.88 µm	132,42 ± 10.26 µm	0.37

Table 2: Posterior Ocular Measurements.

Abbreviations: CMT: Central Macular Thickness; CMV: Central Macular Volume; TMV: Total Macular Volume; CSCT: Central Subfoveal Choroidal Thickness; G: Median Retinal Nerve Fiber Layer; Ns: Nasal Superior; N: Nasal; Ni: Nasal Inferior; Ti: Temporal Inferior; T: Temporal; Ts: Temporal Superior

In the posterior tissue analysis, we did not find a difference in CSCT, CMV, TMV, G, Ns, Ni, Ts, T, and Ti measurements between groups ($p > 0,05$). The CMT measurement in Groups 1 and 2 was significantly thicker than in Group 3 ($p = 0,02$). In RNFL analysis, N quadrants in Groups 1 and 2 was significantly thinner than in Group 3 ($p = 0,04$). There was no statistically significant difference between Groups 1 and 2 in any measurement of the entire posterior ocular structure.

Discussion

Anterior uveitis does not affect the choroid and retina directly, it may affect them indirectly because of mediators that are released. Findings on the retina cannot be examined macroscopically, but they can be examined using OCT measurements [19,20]. The most frequent form of ocular involvement for AS patients is AAU, in which the disease occasionally affects posterior tissues. While clinical examination findings for AU were normal, macular edema was identified by OCT [19,20]. Szepeessy, *et al.* [21] found thickening in spondyloarthropathies with AAU and indicated that this thickening increases with AAU levels.

In a study by Tuzcu, *et al.* [16], researchers found no meaningful difference in CMT and RNFL thickness levels between AS patients without AAU and healthy controls. In a similar study, retina and RNFL measurements were not different from healthy controls, however choroidal thickness was found to be greater in AS patients without AAU [15]. In another study with AS patients with AAU but without posterior involvement, researchers observed thinning in the retina [17]. This result suggested the presence of subclinical inflammation and cytokines in the posterior tissues, as we mentioned above.

In our study, CMT was significantly thicker in AS patients compared to the control group. Although our patients did not have AAU diagnoses and history, the difference we found could be due to subclinical attacks, or it could be totally accidental. Tuzcu, *et al.* [16] stated that there may be some differences in RNFL over time among people who have not had any ocular involvement. We did not find significant differences between patients with HLA-B27-positive and HLA-B27-negative.

Many studies state that RNLF reacts very quickly to hypoxia and increases intraocular pressure. Tuzcu, *et al.* [16] could not find a meaningful difference in RNFL thickness between the group with AS and controls. In the same study, they detected a negative relationship between disease duration and temporal quadrant thickness. The author stressed that this might be related to the duration and severity of the disease [16]. Again, they demonstrated that there was no difference in RNLF thickness between controls and patients with AU and AS [15]. When we compared our control group with patients with AS, we found that the N quadrant of RNLF was thinner. The nasal quadrant is the most affected area, especially in cases where there are ischemic situations, such as decreases in blood flow [22]. When we compared patient's N quadrant of RNLF with AS, there was no significant difference between HLA-B27-positive and HLA-B27-negative. This topic requires longer term studies, which can be monitored more carefully. Researchers have been able to evaluate choroidal tissue with more precision since the development of the enhanced depth imaging optical coherence tomography (EDI-OCT) mode [23]. Earlier studies clearly show that cause of posterior uveitis can change choroid and retina thickness [23-27]. In a study measuring the thickness of the choroid for patients with AAU without any posterior involvement in AS, researchers found that the choroid was thicker in patients than it was in healthy controls [14]. In the same study, researchers found no relationship between choroidal thickness and the activity and duration of the disease. Also, there was no significant difference between the control group and patients in terms of other parameters (e.g. CMT, RNLF). In our study, there was no significant difference between the control group and AS patients regarding choroidal thickness. When we compared patients with AS to each other there was no significant difference between HLA-B27-positive and HLA-B27-negative patients. When we consider that TNF- α increases in serum and ocular tissues during an active attack, it is not surprising that there is no significant difference without attacks. To the best of our knowledge, no other study has investigated this finding. Therefore, further studies with broader series and longer observation periods.

In our study, we investigated whether being HLA-B27-positive or HLA-B27-negative creates a difference in thickness of the ocular tissue for people who have not exhibited any sign or history of AS. Indeed, there were considerable significant differences on CMT and N between healthy controls and patients with AS. When we compared patients with AS, there was no considerable difference regarding posterior tissue thickness between HLA-B27-positive and HLA-B27-negative. More fruitful results could be obtained with further studies that make observations during attacks and normal times with similar groups but with more participants.

There are several limitations in our study that we need to acknowledge. First, the number of observations was limited to N = 94. Second, we selected normal patients, because if the level of TNF- α is high in serum and it active uveitis for patients who are HLA-B27-positive.

We found that in AS patients without ocular involvement, there was no difference in choroidal thickness between those with HLA-B27-positive and those with HLA-B27-negative. Observations on similar individuals during attacks and normal times could provide researchers with more information regarding this issue.

Conflict of Interest

The authors declare no conflict of interests.

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