Choroidal thickness and retinal nerve fiber layer analysis in acute systemic brucellosis

Kürşad Ramazan ZorMD1, Tuğba Arslan Gülen2, Gamze Yıldırım Biçer1, Erkut Küçük1, Ayfer İmre2, İlker Ödemiş3 and Üner Kayabaş2

Abstract

Introduction: This study aims to detect changes in choroidal thickness and retinal nerve fiber layer (RNFL) thickness in acute stage brucellosis.

Methods: Fifty-five newly diagnosed patients with acute brucellosis and 19 healthy individuals as control group were included in the study. Choroidal thickness and RNFL thickness were measured using the Spectral Domain Cirrus OCT Model 400 (Carl Zeiss Meditec, Jena, Germany) for each participant in the patient and control group.

Results: In the brucella group, in the right eyes, the mean nasal choroidal thickness was 272.77 ± 50.26 μm (p = 0.689), the mean subfoveal choroidal thickness was 321.14 ± 33.08 μm (p = 0.590), the mean temporal choroidal thickness was 278.86 ± 48.84 μm (p = 0.478), and the mean RNFL thickness was 90.43 ± 8.93 μm (p = 0.567). In the left eyes, the mean nasal choroidal thickness was 282.29 ± 48.93 μm (p = 0.715), the mean subfoveal choroidal thickness was 316.79 ± 39.57 μm (p = 0.540), the mean temporal choroidal thickness was 284.93 ± 50.57 μm (p = 0.392), and the mean RNFL thickness was 92.64 ± 8.95 μm (p = 0.813).

Conclusion: No difference was found between the control and the brucella groups regarding to all choroidal regions and RNFL thickness.

Keywords
brucellosis, choroidal thickness, retinal nerve fiber layer, spectral domain optical coherence tomography

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Introduction

Brucellosis is a common zoonotic infection worldwide and it is spread through contact with infected animals or feeding with uncooked meat, milk, and dairy products.1,2 Brucellosis is a systemic disease that begins acutely with fever and if the disease is not treated properly in the acute period, it can proceed to the chronic stage. Both acute and chronic brucellosis can cause ocular involvement.3 Various ocular findings such as keratitis, episcleritis, cataract, recurrent iridocyclitis, panuveitis, chorioiditis, and optic neuritis have been reported in brucellosis patients.3,4

1School of Medicine Department of Ophthalmology, Niğde Omer Halisdemir University, Niğde, Turkey
2School of Medicine Department of Infectious Diseases and Clinical Microbiology, Niğde Omer Halisdemir University, Niğde, Turkey
3Department of Infectious Diseases and Clinical Microbiology, Niğde Omer Halisdemir Education and Research Hospital, Niğde, Turkey

Corresponding author:
Kürşad Ramazan Zor, Department of Ophthalmology, Niğde Omer Halisdemir University School of Medicine, Niğde 51240, Turkey.
Email: kursadzor@hotmail.com
In some of the case series, the most common involvement was reported to be anterior uveitis, choroiditis, and panuveitis. Although optic neuritis cases due to brucellosis were reported less frequently, nervous system involvement has been reported to occur between 2.7% and 17.8% of brucellosis patients in general. Moreover, electromyography (EMG) studies have shown that subclinical peripheral neuropathy can also be observed in brucellosis. To investigate if there is microinvasive involvement in the optic nerve and choroid due to brucellosis, we evaluated choroidal thickness and retinal nerve fiber layer (RNFL) analysis in patients with brucellosis in the acute stage. Based on these data, we evaluate choroidal thickness and RNFL thickness using spectral domain optical coherence tomography (SD-OCT) device in cases with acute brucellosis without ocular involvement in the patient’s clinical examination.

**Material Method**

This cross-sectional study was conducted in the infectious diseases and ophthalmology departments of Niğde Omer Halisdemir University Hospital between 2019 and 2020. The study protocol was approved by Niğde Omer Halisdemir University Ethics Committee (Protocol No: 2019/08) and written consent was obtained from each patient before the eye examination. The study was conducted in accordance with the principles of the Helsinki Declaration.

The study group was selected from the patients who were diagnosed as having acute brucellosis by the infectious diseases department and referred to ophthalmology department for evaluation of the eye involvement. We included all consecutive patients in the considered time period. Standard agglutination tube (SAT) test was used to diagnose human brucellosis. Fourteen newly diagnosed patients with acute brucellosis who have not yet started treatment and 19 healthy individuals for the control group were included in the study. The control group was selected from individuals who admitted to the ophthalmology clinic for control purposes without any complaints and had similar age and gender characteristics to the patient group. In both groups, children under the age of 18, those with systemic disease other than brucellosis, those with pregnancy and breastfeeding, patients with myopia higher than 3D, hyperopia and astigmatism, patients with ocular pathology and surgery history were excluded.

Age, gender, clinical information, and detailed medical history of all cases were recorded for all participants. For all individuals: best corrected visual acuity, color vision, relative afferent pupil defect (RAPD), eye movements, biomicroscopic anterior segment examination, intraocular pressure measurements using Goldmann applanation tonometer, and dilated fundus examination were performed.

The right and left eyes of the patient and control groups were compared among themselves. In addition, the total eyes in the groups were compared among themselves.

**Choroidal thickness measurement with SD-OCT**

Optical coherence tomography examination using Spectral Domain Cirrus OCT Model 400 (Carl Zeiss Meditec, Jena, Germany) was performed after pupil dilation with 5% tropicamide. HD 5 Line Raster protocol was shot down to a single line. Measurements with a signal quality less than 6 were excluded from the study. Choroid was evaluated in Cirrus HD-OCT using enhanced depth imaging (EDI) mode. The center of the fovea was the first measurement point. Retinal pigment epithelium (RPE) was accepted as the starting point, and the border formed at the choroido-scleral junction was accepted as the end point. Measurements were taken from 6 points in the temporal and nasal directions at 500-micron intervals, up to 1500 microns at 3 temporal and 3 nasal points. Temporal and nasal choroidal thicknesses were calculated by averaging 3 choroid thicknesses measured at 500-1000-1500 micron intervals from subfoveal region. Since manual measurement was made, measurements were repeated by two independent examiners.

**RNFL thickness measurement with SD-OCT**

RNFL thickness was measured using Spectral Domain Cirrus OCT Model 400 (Carl Zeiss Meditec, Jena, Germany). Scans with a signal strength of six or more were included for the study. 30 min after the pupil dilation, the OCT examination was performed. A 6 × 6 mm cubic optical disk scan was obtained from the 200 A scans made for each 200 B scans. From this cube of data, the instrument automatically determined the center of the disk and created a 3.4 mm diameter computing circle around the disk. After RNFL thickness analyzing, results compared with normative data.

**Statistical analysis**

Statistical analysis of the data was performed using STATISTICA Version 13.3 program. Normality check was performed with Shapiro–Wilk test. Since all numerical values are normally distributed, average ± standard deviation and minimum–maximum values were calculated.

Since the assumption of normal distribution was provided, the means of 2 independent groups (patient-control) were compared with the Student t-test. The averages of two dependent groups were compared with Paired t-test. G-power test was used for power analysis. Correlation analysis between the right and left eyes was performed with
Pearson correlation test. A p value lower than 0.05 was accepted as statistically significant for all comparisons.

**Results**

All patients’ best corrected visual acuity was 10/10 and color vision, RAPD, eye movements, biomicroscopic anterior segment examination, intraocular pressure, and fundus examination were all normal in both groups.

Fourteen patients (6 men, 8 women) with brucellosis and 19 healthy subjects (12 men, 7 women) were included in the study. There was no statistically significant difference in terms of gender among two groups. The mean age of the brucellosis group and the control group was 39.1 ± 15.5 years and 40.6 ± 13.1 years, respectively. There was no statistically significant difference in age between two groups (Table 1).

The mean subfoveal choroidal thickness, the mean nasal choroidal thickness, the mean temporal choroidal thickness, and the mean RNFL thickness values for the right and left eyes of the participants were given in Table 2. In the brucella group, in the right eyes, the mean nasal choroidal thickness was 272.77 ± 50.26 µm (p = 0.689), the mean subfoveal choroidal thickness was 321.14 ± 33.08 µm (p = 0.590), the mean temporal choroidal thickness was 278.86 ± 48.84 µm (p = 0.478), and the mean RNFL thickness was 90.43 ± 8.93 µm (p = 0.567). In the left eyes; the mean nasal choroidal thickness was 282.29 ± 48.93 µm (p = 0.715), the mean subfoveal choroidal thickness was 316.79 ± 39.57 µm (p = 0.540), the mean temporal choroidal thickness was 284.93 ± 50.57 µm (p = 0.392), and the mean RNFL thickness was 92.64 ± 8.95 µm (p = 0.813). There was no statistically significant difference among the groups with respect to the choroidal and RNFL thickness measurements in both eyes. In all eyes in the brucella group, the mean nasal choroidal thickness was 277.5 ± 48.9 µm (p = 0.583), the mean subfoveal choroidal thickness was 318.9 ± 58.9 µm (p = 0.085), the mean temporal choroidal thickness was 282.5 ± 48.7 µm (p = 0.234), and the mean RNFL thickness was 91.5 ± 8.8 µm (p = 0.234). There was no statistically significant difference regarding to the nasal, temporal, and subfoveal choroidal thickness and RNFL thickness of all eyes between two groups (28 eyes in brucellosis group—38 eyes in control group) in the patient and control groups (Table 3). In the correlation analysis between the right and left eyes, p = 0.001 and r = 0.790 for choroidal thickness, p = 0.166 and r = 0.392 for RNFL thickness.

**Discussion**

Both anterior and posterior uveitis have been reported frequently in patients with brucellosis. Rolando et al. Zor et al.
detected ocular involvement in 58 patients in their large brucellosis case series including 1551 cases. In this series, they detected uveitis in 43 patients, the largest presentation form with 21 patients had posterior uveitis and 9 patients had panuveitis. Among these patients, legal blindness developed in 4 of 21 patients with posterior uveitis and in 8 of 9 patients with panuveitis despite treatment. Sungur et al. also detected ocular involvement in 21% of the cases with brucellosis and reported that 41% of these cases had anterior uveitis, 32% posterior uveitis, and 9% panuveitis. Despite the treatment, complications such as cataracts and macular edema that cause vision loss developed in these patients. In another study, 14 cases with ocular brucellosis were reported in 70 brucellosis cases, eight of which were posterior uveitis, five were anterior uveitis, and one was panuveitis. In our study, in which we examined choroidal thickness in the acute stages of the disease since posterior and panuveitis were among the common findings of ocular involvement in cases with brucellosis, the choroid was thicker in the subfoveal, nasal, and temporal areas in the patient group with brucellosis compared to the control group. However, this increased thickness was not statistically significant. If the number of our patients were higher, it would be possible that the results were statistically significant.

Ronaldo et al. reported that the circulating immune complexes, which are similar to the pathogenesis of Fuch’s uveitis or Behçet’s disease, may cause brucellar uveitis. Infiltration of different cell types, including neutrophils, monocytes and lymphocytes, and different degrees of necrosis and vasculitis, have been shown in the affected tissues of pets with brucellosis. Therefore, diffuse or focal infiltration with inflammatory cells in choroidal involvement may cause changes in the choroidal structure in brucellosis patients. SD-OCT allows the understanding of choroidal aberrations underlying some chorioretinal diseases by providing clearer imaging of the choroid and measurements of choroidal thickness. Kim et al. found an increase in subfoveal choroid thickness in Behçet’s patients with posterior uveitis at the active and inactive phases of the disease. With these result, they suggested that SD-OCT may be helpful in determining subclinical choroidal involvement even in the inactive phases of Behçet’s posterior uveitis. Due to the increase in the choroidal thickness in all measurement areas in both the eyes in OCT images, we think that choroidal thickness may begin to increase in the acute period in patients with brucellosis before posterior uveitis findings begin.

Posterior and panuveitis cases were mostly reported in the chronic stage of the disease. Sungur et al. detected all cases of anterior uveitis in the acute stage of the disease, while they detected all cases of posterior uveitis in the chronic stage. Rolando et al. also detected 10 out of 14 brucellosis uveitis cases in the chronic period of the disease. Woods reported that not only posterior and panuveitis, but also all ocular brucellosis cases were seen in the chronic phase of systemic disease. Therefore, we think that if we planned our study for the chronic period of brucellosis, we would see the thickening of the choroidal layer more prominently. However, our aim with our study was to evaluate the OCT changes in the acute period.

Neuroophthalmological involvement appears to be less common in cases with brucellosis compared to ophthalmic involvement. Nervous system involvement has been reported between 2.7% and 17.8% in brucellosis cases. In their study including 60 brucellosis patients, Sanivar et al. found impairment in EMG in all patients and claimed that brucellosis may effect on the nervous system, including clinical or subclinical peripheral neuropathy. Although the prevalence of optic nerve involvement was reported as 10% in brucellosis cases, these reports are generally in the form of case reports in the literature. Rolando et al. reported that papilledema developed in 5 patients and optic neuritis in 1 patient in their series of 1551 patients with brucellosis. In this study, in which we aimed to determine the change of RNFL in patients with brucellosis in the acute stage, especially in patients without ocular involvement, we found that there was no significant difference in RNFL compared to the control group.

Optic neuritis cases reported in patients with brucellosis were mostly reported in the chronic phase of the disease. Moreover, in cases of optic neuritis, thinning in RNFL is an expected finding in the chronic period. Therefore, in the long-term follow-up of patients with brucellosis, RNFL thinning may be seen in OCT examinations, but no change has been detected in the acute period.

The strength of our study was that it is the first study to examine the choroid and RNFL thickness in brucellosis. In

### Table 3. Comparison of choroidal thickness and RNFL values for the all eyes.

|                                      | Brucella group (n:14; 28 eyes) | Control group (n:19; 38 eyes) | p       |
|--------------------------------------|-------------------------------|-------------------------------|---------|
| Nasal choroidal thickness (µ) Avg ± SD| 277.5 ± 48.9                  | 270.0 ± 58.6                  | 0.583   |
| Subfoveal choroidal thickness (µ) Avg ± SD | 318.9 ± 35.9                  | 299.8 ± 49.2                  | 0.085   |
| Temporal choroidal thickness (µ) Avg ± SD | 282.5 ± 48.7                  | 267.5 ± 51.1                  | 0.234   |
| RNFL thickness (µ) Avg ± SD          | 91.5 ± 8.8                    | 93.1 ± 12.7                   | 0.577   |

SD: standard deviation.
addition to comparing the right and left eyes of the patient and control groups among themselves, all eyes in the patient and control groups were also compared. The limitations of our study were small sample size and shorter follow-up time. These findings from a noninvasive and practical imaging can allow to identify complications and understand the pathophysiology of ocular brucellosis. Future studies involving more patients and patients in the chronic period of the disease may help determine the role of SD-OCT in the diagnosis of ocular brucellosis and other inflammatory lesions affecting the retina and choroid.

Conclusions
In conclusion; we did not find a significant difference in the choroid and RNFL thickness between patients with acute brucellosis who did not have ocular involvement and the control group, but it is thought-provoking that the choroid is numerically thicker. This may be due to the fact that we evaluated the patients in the acute phase of brucellosis and the number of patients was low in our study.

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Ethics approval
This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent
Written informed consent was obtained from all subjects before the study. All participants were informed verbally and in writing about the study. Informed consent form was signed by participants included in the study.

Trial registration
Not applicable.

ORCID iDs
Kursad R Zor https://orcid.org/0000-0002-3233-7906
Tugba Arslan https://orcid.org/0000-0003-3058-6308

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