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Comparison of optical coherence tomography angiography results of adult patients with Familial Mediterranean fever and healthy individuals

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Abstract

Purpose: The aim of this study is to assess the macular ultrastructure measuring by optical coherence tomography angiography in adult patients with Familial Mediterranean fever.

Methods: Participants were 62 Familial Mediterranean fever patients and 54 healthy individuals in control group with similar age and sex. The superficial and deep vascular plexus structures covering the central fovea in an area of 6 mm × 6 mm were measured using AngioVue images taken with optical coherence tomography angiography. Vasculature structure, foveal avascular zone, acircularity index of foveal avascular zone (the ratio of the perimeter of foveal avascular zone and the perimeter of a circle with the equal area), and superficial and deep retinal plexus densities were measured.

Results: The inferior deep vascular density was measured: 49.17% ± 8.59% in Familial Mediterranean fever patients, 55.56% ± 5.92% in the control group. The deep inferior-hemi vascular density was measured: 48.59% ± 10.34% in Familial Mediterranean fever patients, 56.54% ± 8.05% in the control group. Deep inferior and deep inferior-hemi vascular density was significantly reduced in Familial Mediterranean fever patients compared with healthy controls ($p = 0.04$ and $p = 0.03$, respectively).

Conclusion: The vascular abnormalities in optical coherence tomography angiography show subclinical signs of microangiopathy in Familial Mediterranean fever patients. This observation, which can be obtained only through optical coherence tomography angiography, may be an ocular hallmark for Familial Mediterranean fever disease.

Keywords: angiography, Familial Mediterranean fever, macula, optical coherence tomography angiography, vessel density

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Introduction

Familial Mediterranean fever (FMF) is an inherited autosomal recessive and characterized by recurrent fever episodes, serositis (involving the peritoneum, pleura, and synovia), and arthritis.[1] FMF is common among Mediterranean and Middle Eastern populations; however, sporadic cases have been shown in the Far East that usually manifest in childhood.[2] Although it starts during childhood and progresses with attacks, the disease may be diagnosed later as well. Hence, there is usually a long period between the onset of symptoms and the time when patients are diagnosed and when treatment is initiated.[3]

The patients with FMF reside mutation in the Mediterranean fever (*MEFV*) gene, which is found in the short arm of the 16th chromosome. This gene is responsible for pyrin production, resulting in the regulation of apoptosis, inflammation, and cytokines. The mutation leads to dysfunction of pyrin and inhibits its auto-regulatory

function over neutrophil activation and pro-inflammatory cytokine release.[4] The mutations prompt the caspase-1 enzyme and lead to interleukin (IL)-1b production.[5] Afterward, IL-1b regulates tumor necrosis factor (TNF)-a secretion. These cytokines, TNF-a and IL-1b, cause inflammation in FMF patients.[6]

Although eye involvement is rare in FMF, colloidal bodies, anterior uveitis, episcleritis, posterior scleritis, bilateral acute anterior uveitis, frosted branch angiitis, and ocular surface abnormalities have been reported up to date.[7–14] Recently, Bicer and colleagues[15] showed a reduction in choroidal thickness in FMF patients compared with healthy individuals.

Optical coherence tomography angiography (OCTA) is the novel method for imaging of vasculature structure, foveal avascular zone (FAZ), superficial capillary plexus (SCP), and deep capillary plexus (DCP).[16] The quantitative measurements by OCTA could be used in vascular disorders such as macular degeneration and diabetic retinopathy. Dyeless imaging is its main advantage. Changes in erythrocyte movement are measured by repeated B-scans, resulting in OCTA image. Retina is segmented into separate layers: superficial and deep retinal vascular plexus and choriocapillaris images are taken in this way.[17]

The vascular etiology in FMF is unknown. The purpose of this study was to compare the OCTA measurements of the macula in patients with FMF with those of age- and sex-matched healthy controls.

Methods

The study was carried out at a tertiary referral center, Ankara Numune Training and Research Hospital. This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by Ankara Numune Training and Research Hospital Ethics Committee (E-18-2305). Informed consent was obtained from all individual participants included in the study. This study involved patients with FMF. FMF diagnosis was made in a rheumatology clinic with genetical confirmation with *MEFV* mutation and Tel-Hashomer criteria.[18] The patients were in remission using colchicine.

The control group consisted of age- and sex-matched healthy individuals who applied to rheumatology and internal medicine clinics and had no diseases. People with chronic drug use (FMF patients using drugs other than colchicine), alcohol and tobacco use, cataract surgery, posterior segment surgery, history of eye trauma, uveitis, glaucoma, hypertension, diabetes mellitus, acute FMF attack within the previous 1 year and refractive error $\geqslant$3 diopters were excluded from the study. Patients above 50 were also excluded from the study.

Sixty-two eyes of 62 patients (Group 1) and 54 eyes of 54 controls (Group 2) were included in this study. Because the eyes have similar OCTA outcomes, one of the eyes was selected randomly. All patients and controls underwent a detailed ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA) using a Snellen chart, intraocular pressure (IOP; Tonopachy NT-530P, Nidek Co, Ltd, Tokyo, Japan), and axial length measurement (Lenstar LS 900, Haag-Streit AG, Koeniz, Switzerland). The ocular surface and fundus were evaluated with a slit-lamp biomicroscope in both cases and controls. The imaging was performed by the same technician, blinded to examination details of patients.

OCTA

OCTA was applied with the RTVue-XR Avanti (Optovue, Inc., Fremont, CA, USA), which is a 70-kHz spectral-domain optical coherence tomography (SD-OCT) system using the Split-Spectrum Amplitude-Decorrelation Angiography (SSADA) algorithm to quantify vasculature structure, FAZ, and superficial and deep retinal vascular plexus densities. The same technician performed the OCTA scans of the patients during morning hours (8.00 a.m.–11 a.m.). All of the patients were dilated with 1% tropicamide eye drops before scanning. An internal fixation target was used to focus on the people. Five scans were acquired for each participant, and the best quality image was chosen for statistical analyses. An experienced ophthalmologist (E.E.K.) identified poor quality scans due to motion artifacts and blurred images, and these images were excluded.

A 6 mm $\times$ 6 mm scanning area centered on the fovea was used for analyses.[19–21] The location of the foveal center was confirmed by cross-referencing with the OCT scans associated with the OCTA image. This analysis was performed relative to the density of vascular flow, which was measured in a 1- to 2.5-mm diameter parafoveal

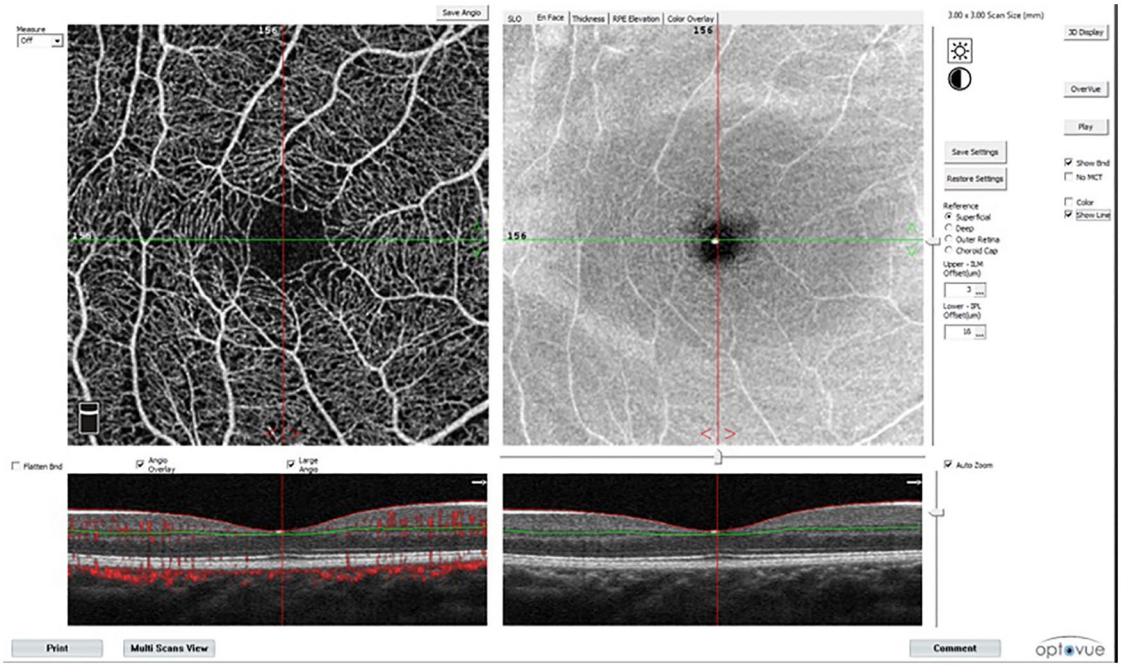

Figure 1. Optic coherence angiography image of superficial capillary plexus in FMF patient.
FMF: Familial Mediterranean fever.

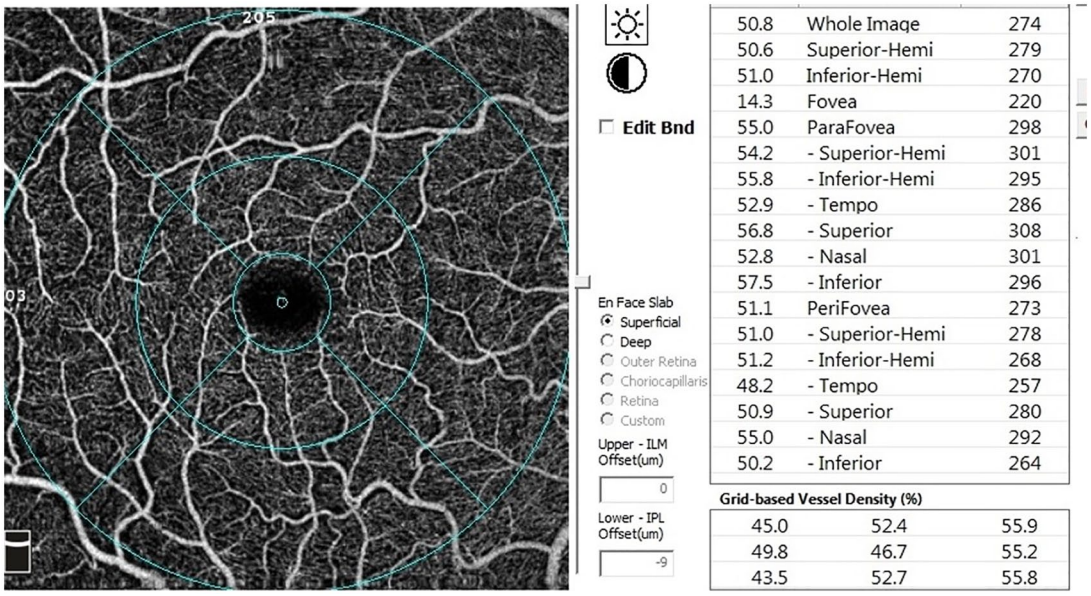

Figure 2. Optic coherence angiography density assessment tool for superficial capillary plexus in FMF patient.
FMF: Familial Mediterranean fever.

ring, proportional to the total area. The FAZ dimension was examined in non-flow mode in the SCP and DCP. Vessel flow density was measured by using the automated density measurement tool in the software. Vascular density of SCP and DCP and FAZ were automatically detected through software. The non-flow area in the SCP, FAZ area, FAZ perimeter, acircularity index (AI), and foveal density (FD-300) as well as the vessel density values for the SCP and DCP in the foveal, parafoveal, and perifoveal zones were recorded for each participant (Figures 1–3).

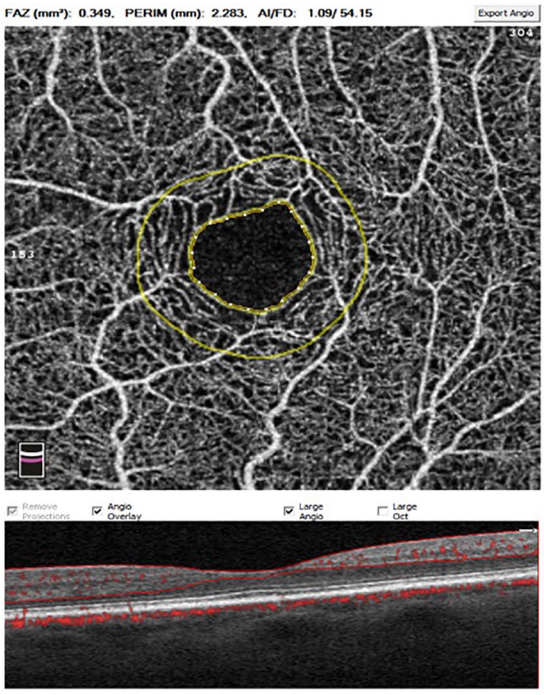

Figure 3. FAZ assessment tools of optical coherence tomography angiography in FMF patient.
FAZ area (mm^2) in whole retina, FAZ perimeter (mm), acircularity index of the FAZ, and foveal density (FD-300) are demonstrated. FAZ: foveal avascular zone; FMF: Familial Mediterranean fever.

Statistical analyses

The statistical analyses of this study were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive data were given as mean ± standard deviations. Continuous variables were expressed as mean ± standard deviation, and categorical data were expressed as number (n) and percentage (%). The normal distribution of the data was assessed. Comparisons of continuous variables between the groups were performed using the independent-samples t test. A value of $p < 0.05$ was considered statistically significant.

Results

This study included 62 eyes of 62 patients (40 female, 22 male) in the FMF group (Group 1), and 54 eyes of 54 patients (36 female, 18 male) in the control group (Group 2). The mean age of Group 1 was 32.15 ± 10.05, and mean age of Group was 40.41 ± 5.61. No significant difference was determined between the groups with respect to age and sex. The demographic data of the patients are given in Table 1.

The mean values of the non-flow and FAZ assessment tool parameters in Group 1 and 2 are documented in Table 2. The differences in the mean values for FAZ perimeter, AI, and foveal density were significant between Group 1 and Group 2 ($p = 0.001$, $p = 0.008$, and $p = 0.016$, respectively). The non-flow area in the SCP and FAZ area in the whole retina did not show a significant difference between the groups. ($p > 0.05$).

The inferior deep vascular density was measured: 49.17% ± 8.59% in FMF patients, 55.56% ± 5.92% in the control group. The deep inferior-hemi vascular density was measured: 48.59% ± 10.34% in Group 1, 56.54% ± 8.05% in Group 2. Deep inferior and inferior-hemi vascular density was significantly lower in Group 1 in comparison with Group 2 ($p = 0.04$ and $p = 0.03$, respectively; Table 3).

Discussion

In the present study, using OCTA, we investigated how FAZ area and vascular density changed in FMF patients compared with healthy control individuals. FAZ perimeter and AI were significantly higher in FMF patients. Foveal density (FD), deep inferior, and inferior-hemi vascular density was significantly lower in FMF patients compared with the control group, but there was no significant difference in the non-flow area in the SCP and FAZ area in the whole retina.

FMF is a chronic auto-inflammatory disease with recurrent arthritis or serositis attacks.[3] Colchicine treatment is the main therapy option for avoiding attacks and amyloid deposition in FMF patients. A high level of inflammation is seen during the attack phase of FMF, and in some patients, there is a persistent chronic subclinical inflammation between attack phases. This persistent chronic inflammation leads to oxidative stress and oxidative tissue damage.[22] Pro-inflammatory cytokines, including TNF-a, IL-1b, and IL-6, are released during acute attack periods but persist at a certain level in the absence of attacks as well.[23,24] Thus, there is an inflammatory status in FMF patients during both attack and attack-free periods. In this study, we examined FMF patients in remission by colchicine. We hypothesized that chronic inflammation in patients with FMF can affect the vascular structure in the retina.

Table 1. Demographic data of the patients.

	Group 1	Group 2	*p*
Age (years)	32.15 ± 10.05	40.41 ± 5.61	0.22
Female/male	40/22	36/18	0.15
Age at the time of diagnosis	26.5 ± 11.1	–	–
Disease duration (months)	98.4 ± 76.8	–	–
FMF attack (total)	32 ± 10.4	–	–

Data are shown as mean ± standard deviation or number (%). FMF, Familial Mediterranean fever.

Table 2. Non-flow and FAZ assessment tool parameters in both groups.

	Group 1	Group 2	*p*
Non-flow area (mm^2), SCP	0.51 ± 0.17	0.48 ± 0.16	0.735
FAZ area (mm^2), whole retina	0.28 ± 0.13	0.27 ± 0.10	0.546
FAZ perimeter (mm)	2.09 ± 0.41	1.89 ± 0.39	0.001*
Acircularity index	1.09 ± 0.08	1.03 ± 0.07	0.008*
Foveal density (%)	53.97 ± 3.61	57.02 ± 3.45	0.016*

Values are stated as mean ± standard deviation. FAZ, foveal avascular zone; SCP, superficial capillary plexus.
*Statistically significant.

Recently, some studies investigating FMF and ocular involvement have been reported. Alim and colleagues[25] found no significant differences in peripapillary retinal nerve fiber layer (RNFL) and retinal ganglion cell–inner plexiform layer (GCIPL) thickness in patients with adult-onset FMF and controls. Tanyildiz and colleagues investigated the effect of oral colchicine on the peripapillary RNFL of FMF patients. They claimed that oral colchicine did not have a significant effect on peripapillary RNFL. Erdurmus and colleagues[26] measured retinal and choroidal thickness in children with FMF using OCT. They found no significant difference in retinal and choroidal thickness between children with FMF and controls. They reported that most of their patients were in remission. They pointed out that retinal and choroidal thickness may change during FMF attacks. Similarly, all of our patients were in remission.

Bicer and colleagues[15] showed a reduction in choroidal thickness in adult patients with FMF compared with healthy individuals. In another study, the choroid was shown to be thicker in patients with FMF in an acute attack.[27] These studies were conducted with enhanced depth imaging (EDI) modality of SD-OCT. Standard EDI-OCT is only capable of showing the structure of choroid and choriocapillaris; however, with OCTA, FAZ and capillary density can be measured at both the SCP and DCP.[28] OCTA, which is a new and non-invasive technology, is capable of taking images of high-resolution with three-dimensional mapping of the retinal and choroidal circulations by using endoluminal flow as a contrast.[29] Although OCTA has emerged in recent years, it is increasingly used as a diagnostic tool for some retinal diseases such as identifying the presence of choroidal neovascular (CNV) membrane in neovascular age-related macular degeneration (nAMD) and areas of non-perfusion associated with diabetic retinopathy.[17] Despite the lack of standardized protocols for image acquisition and interpretation of image scans, OCTA is widely used for the detection of pathophysiology, early diagnosis, treatment, and determination of the progression in patients, especially

Table 3. Superficial and deep foveal and parafoveal vessel density (%) values.

	Group 1	Group 2	*p*
sFoveal	22.05 ± 5.2	23.57 ± 5.18	0.29
sParafoveal	51.24 ± 10.5	48.24 ± 11.2	0.25
sP.superior	43.13 ± 5.4	44.18 ± 9.14	0.28
sP.inferior	49.04 ± 11.3	48.42 ± 8.15	0.24
sP.nasal	43.78 ± 17.4	45.56 ± 10.13	0.14
sP.temporal	48.15 ± 9.4	49.58 ± 4.04	0.24
sP.superior-hemi	53.13 ± 14.6	50.45 ± 12.12	0.19
sP.inferior-hemi	49.16 ± 11.50	53.32 ± 13.41	0.25
dFoveal	20.29 ± 5.89	22.35 ± 8.11	0.21
dParafoveal	43.36 ± 7.03	47.50 ± 8.59	0.06
dP.superior	51.18 ± 15.72	55.43 ± 9.30	0.07
dP.inferior	49.17 ± 8.59	55.56 ± 5.92	0.04*
dP.nasal	54.83 ± 5.03	55.63 ± 22.06	0.07
dP.temporal	52.23 ± 8.5	53.12 ± 10.35	0.11
dP.superior-hemi	54.41 ± 31.05	55.69 ± 15.76	0.06
dP.inferior-hemi	48.59 ± 10.34	56.54 ± 8.05	0.03*

Values are stated as mean ± standard deviation. dP, deep plexus; sP, superficial plexus.
*Statistically significant.

with vascular pathology. Preliminary studies claim that attack-free periods of FMF are characterized by subclinical inflammation and are associated with endothelial dysfunction, increased atherothrombosis, and platelet activation.[30–32] The ongoing inflammation and amyloidosis were shown to be related to pericarditis, valvular diseases, coronary artery disease, cardiomyopathies, subclinical atherosclerosis, and pulmonary hypertension.[33] Therefore, FMF may also affect choroid and retinal vessels. In this study, we did not evaluate choriocapillaris; however, deep inferior and inferior-hemi vascular density was significantly lower than the control group. In addition, FAZ perimeter and AI of FMF patients were significantly higher than the control group. Recent studies reported FAZ shape alterations in diabetic eyes, and this may affect FAZ perimeter and AI.[34,35] FAZ boundaries could be irregular due to capillary occlusion, vascular remodeling, endothelial dysfunction, altered blood flow, and increased vascular endothelial growth factor levels.[36,37] Foveal vessel density gives information about macular perfusion and does not alter with FAZ diameter when measured at a distance of 300 μm. In this study, FD was lower in FMF patients compared with the control group.

FMF is one of the most common auto-inflammatory diseases and may be associated with vasculitis.[38] Hence, retinal vessel density decreases, perifoveal microvascular network changes, and FAZ irregularity may be valuable markers for indicating ocular involvement in FMF such as other rheumatologic diseases. Although eye involvement and FMF relation are not well known, FMF is a systemic chronic inflammatory process, and retinal vasculature is prone to be affected from systemic inflammation and vasculitis. Therefore, this study may precede for future studies by

establishing an association between FMF and retinal vasculature changes.

The major limitations of this study were the small sample size, short-term follow-up time, inability to check the vessel density at attack period of FMF, and possible variation of vessel density over time. Another limitation was the absence of treatment-naïve FMF patients. In addition, all of the patients were in remission.

In conclusion, this is the first OCTA study in the literature that compares FMF patients with the control group. It is significant that reduced FD, vessel density in DCP, and increased FAZ perimeter, AI can be determined on OCTA before any change in fundus examinations. Further studies including larger patient series and patients who were in periods of acute attack are required to clarify the long-term findings of vascular changes determined on OCTA to determine whether it could be utilized as a screening test. In addition, the impact of colchicine treatment on vascular changes should be further investigated in future studies.

Authors' Note

The authors are responsible for the content and writing of the paper.

Conflict of interest statement

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