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Evaluation of posterior segment ocular parameters in patients with pediatric familial mediterranean fever

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Abstract

Aim: We aimed to compare the ocular posterior segment parameters in pediatric patients with Familial Mediterranean Fever (FMF) with a healthy control group.

Materials and Methods: We evaluated 40 pediatric FMF patients and 36 healthy children in this study. Choroidal thicknesses from the subfoveal, nasal and temporal 500 µm, 1000 µm, and 1500 µm points; the subfoveal macular thickness; macular volume; optic nerve head (ONH) parameters; and peripapillary retinal nerve fiber layer (RNFL) thickness were measured. An optical coherence tomography (OCT) device was used for measurements.

Results: The choroidal thickness in the temporal 1500 µm was significantly thinner, and average peripapillary RNFL thickness was significantly lower in the FMF group compared to the control group ($p = 0.015$ and $p = 0.023$, respectively). The groups were similar in terms of macular thickness and macular volume. Among the ONH parameters, the rim area thickness was also significantly higher in the FMF group ($p = 0.013$).

Conclusion: This study shows that the recurrent inflammation caused by FMF can affect choroidal thickness and peripapillary RNFL in children.

Introduction

Familial Mediterranean fever (FMF) is a common multisystem disorder which is characterized by recurrent acute inflammation attacks of all serosal tissues such as the pleura, peritoneum and synovium [1]. It is especially common in Mediterranean and Middle Eastern populations [2]. The Mediterranean fever gene (MEFV), which is on the short arm of chromosome 16, causes production of a mutant pyrin protein that is responsible for controlling apoptosis, inflammation, and the cytokines [3, 4]. Studies have reported uncontrolled interleukin (IL)-1β secretion in FMF patients [5]. This uncontrolled secretion causes tumor necrosis factor (TNF)-α production and activation and these cytokines are the real cause of the inflammation in FMF patients [6]. TNF-α has been associated with certain ocular disorders in studies [7, 8].

The studies show that in the attack-free periods of FMF, subclinical inflammation continues, and causes endothelial dysfunction, platelet activation, and atherothrombosis [9-11]. The choroid is the posterior part of the uvea. In the human body, it is one of the tissues with the highest blood supply and constitutes 85% of the ocular blood flow [12]. The endothelial involvement and systemic inflammatory nature of FMF could therefore affect the retinal and choroidal vascular structures, and the peripapillary retinal nerve fiber layer (RNFL) thickness.

Enhanced Depth Imaging (EDI), as performed with the Spectral domain optical coherence tomography (SD-OCT) device, has now minimized loss of light due to scattering thanks to its high resolution. It therefore enables obtaining more information about the deep choroidal structures.

We are aware of only a few studies investigating the posterior segment structures of pediatric FMF patients in the literature [13-16]. We aimed to evaluate the macular and choroidal thickness, macular volume, optic nerve head (ONH) parameters and peripapillary RNFL of pediatric FMF patients in the remission period. We used an OCT device to compare these measurements with the healthy control group of patients.

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Material and Methods

The ethics committee approval for our retrospective and sectional study was obtained from Amasya University (20.01.2021-1776). The study was conducted in accordance with the Helsinki Declaration. All parents of the participants gave informed consent for the study. Patients who consecutively presented to the Pediatrics Department, met the Tel-Hashomer diagnostic criteria [17], were found to have the MEFV gene mutation, and attended regular follow-ups were included in the study. Based on the Tel-Hashomer criteria, 2 major or 1 major and 2 minor criteria are needed for definitive diagnosis, and 1 major and 1 minor criteria are required for probable diagnosis. Major criteria are recurrent fever attacks accompanied by peritonitis, synovitis or pleuritis, amyloidosis of the AA-type without predisposing disease, and a favorable response to continuous colchicine treatment. Minor criteria are recurrent febrile episodes, erysipelas-like erythema, and FMF in a first-degree relative. All of our patients were using colchicine and had been in remission for at least the last 3 months. The therapeutic dose of colchicine was given as 0.02-0.03 mg/kg/per day (maximum 2 mg/ per day), and treatment was started on the day of the diagnosis. The control group consisted of healthy individuals without any systemic or ocular problems who consecutively presented to our Ophthalmology Outpatient Department for a routine eye examination. The control group was age- and gender-matched according to the FMF group. The 40 eyes of 40 pediatric FMF patients who presented to the Amasya Sabuncuoğlu Şerafeddin Training and Research Hospital between September 2019 and September 2020 and the 36 eyes of 36 healthy children were included in this study. Only the right eyes of the cases were included because the OCT results were similar in both eyes.

All study subjects underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA) with the Snellen chart, slit lamp examination of the anterior segment, measurement of intraocular pressure (IOP) with Goldman applanation tonometry or a non-contact pneumatic tonometer, and dilated fundus examination with a 90 diopter lens. Exclusion criteria were age $>$ 18 years, previous ocular trauma or intraocular surgery, the presence of amblyopia, glaucoma, proliferative retinopathy, uveitis, cataract or corneal pathology preventing image recording, optic disk anomaly, neurological disorders with possible visual field defects, a systemic disorder like diabetes or hypertension, those who could not comply with OCT instructions, any history of analgesics, decongestant or antihistamine use, and a refractive error above +/- 2.00 diopter on the cycloplegic examination.

The choroidal imaging of all patients was performed by the same clinician using the EDI mode of the SD-OCT device (3D OCT-2000, Topcon, Japan), before pupillary dilatation. The patient was asked to look at the fixation target during the acquisition. The device head was brought close to the eye and the reverse image, which did not normally reflect on the screen, was made to reflect on the screen. All measurements were performed during the same period (09.00-12.00) to decrease the effect of diurnal fluctuation. Manual software was used to measure the choroidal thickness, from the outer edge of the retinal pigment epithelium hyperreflectivity to the internal edge of the choroidoscleral junction. Two independent physicians (MT, NA) performed all choroidal thickness measurements on blind groups, at the central fovea and points 500, 1000 and 1500 µm nasal and temporal to the fovea. When the difference between two measurements was more than 10 µm, the measurement was repeated to prevent bias.

Table 1. Demographic characteristics of all participants

Parameters (Mean±SD), (min-max)	FMF Group	Control Group	p value
Age, (years)	11.9±3.4 (6-18)	12.8±2.5 (8-18)	0.365*
Gender			
Female	15(37.5%)	20 (55.5%)	0.115**
Male	25 (62.5%)	16 (44.5%)	
Visual Acuity	1.0	1.0	1.0*
Intraocular Pressure (mmHg)	15.3±2.9 (10-21)	15.1±2.9 (10-21)	0.713*
Refractive Errors	-0.05±0.8(2.0 to -2.0)	-0.1±0.7(-2.0 to 2.0)	0.765*
Disease duration (year)	3.4±2.7 (1-10)		
Number of attack	6.2±2.8 (2-15)		

FMF: Familial Mediterranean Fever, *: Mann Whitney U test, ** :Chi-square test

Peripapillary RNFL, ONH parameters including disc area, rim area, cup volume, and the vertical and horizontal cup-disc ratio were measured with an automated computer algorithm. A 3.46 mm circular ring surrounding the optic disc was placed automatically by the device while the RNFL and ONH measurements were made. An optic disc scan was performed in an area of 6 × 6 mm2 for ONH analysis. The topographic map of the optic nerve cup and head was created by using 6 radial OCT sections with an interval of 30 degrees passing through the optic nerve center. Average RNFL and RNFL values at the four quadrants (superior, inferior, nasal and temporal) were obtained automatically.

Statistical Analysis

SPSS software for Windows, version 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Mean ± standard deviation or frequencies were used to summarize the data according to variable type. The Kolmogorov–Smirnov was used to for normality analysis. The gender difference between the groups was determined with the chi-square test. Student's t-test or the Mann-Whitney U test was used to analyze the mean differences between the two groups. $p < 0.05$ was accepted as the statistical significance level.

Results

A total of 40 pediatric patients with FMF and 36 healthy children were included in the study. All children in the FMF group were in remission for the past 3 months and were receiving colchicine treatment Patients who were found to have ocular involvement during the study in the FMF group were excluded from the study. The mean age

Table 2. Choroidal thickness, total macular thickness and volume in patients with Familial Mediterranean fever and control groups.

Parameters (Mean±SD), (min-max), µm	FMF group (n=40)	Control group (n=36)	p*
Choroidal thickness			
Fovea center	308.3±24.3 (257-354)	329.3±28.1 (268-378)	0.131
Nasal-500	283.8±29.9 (221-336)	312.3±28.3 (244-363)	0.341
Nasal-1000	270.3±32.1 (215-327)	306.6±31.8 (231-375)	0.334
Nasal-1500	257.1±33.8 (192-318)	292.6±31.3 (213-352)	0.234
Temporal-500	294.9±25.5 (250-342)	316.3±27.2 (262-385)	0.740
Temporal-1000	287±29.7 (241-349)	308.6±24.6 (250-352)	0.152
Temporal-1500	275.9±34.3 (224-336)	301.6±26.6 (242-357)	0.015
Total macular thickness	215±11 (192-235)	213.4±11.2 (192-238)	0.746
Total macular volume	7.7±0.3 (6.93-8.61)	7.9±0.3 (7.13-8.98)	0.561

FMF: Familial Mediterranean Fever, *: Independent t-test, Boldfaced values are statistically significant (p < 0.05).

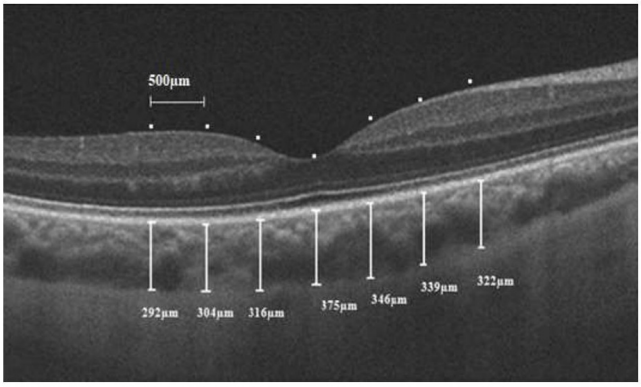

Figure 1. A representative SD-OCT image showing choroidal thickness measurements

was 11.9±3.4 (6-18) years in the FMF group and 12.8±2.5 (8-18) years in the control group (p = 0.365). There were 15 (37.5%) females and 25 (62.5%) males in the FMF group, and 20 (55.5%) females and 16 (44.5%) males in the control group. No significant difference was determined between the groups in terms of gender (p = 0.115). Refractive values, BCVA, and IOP (p = 0.765, p = 1.00, p = 0.713, respectively) were also similar between the patients and the healthy group. The characteristics of the groups are summarized in Table 1.

Although the choroidal thickness values were found to be lower in the FMF group, this difference was only significant for the temporal 1500 µm point (p = 0.015). No statistical difference was present between the two groups in terms of subfoveal macular thickness and macular total volume (p = 0.746, p = 0.561, respectively). The parameters related to macular and choroidal thickness are summarized in Table 2.

The average RNFL value was significantly thinner in the

Table 3. Segmental analysis peripapiller thickness and optic nerve head parameters in patients wtih in patients with Familial Mediterranean fever and control groups.

Parameters (Mean±SD), (min-max)	FMF group (n=40)	Control group (n=36)	p value
RNFL(µm)			
Superior RNFL	121.8±11.1 (102-149)	126.4±15.6 (92-157)	0.066 *
Inferior RNFL	118.3±12.6 (90-152)	123±15 (94-152)	0.071**
Nasal RNFL	82.7±9.1 (68-111)	84.2±12 (57-111)	0.144*
Temporal RNFL	80.3±11.4 (62-119)	82.2±11.7 (64-122)	0.652*
Average RNFL	100.6±8 (84-121)	106.1±11.3 (85-125)	0.023*
Optic nerve head			
Disc area	2.7±0.3 (2.08-3.40)	2.7±0.3 (2.31-3.44)	0.391**
Rim area	2.1±0.5 (0.45-2.82)	1.9±0.4 (1.27-2.9)	0.013**
Lineer cup/disc ratio	0.3±0.1 (0.11-0.59)	0.3±0.1 (0.17-0.57)	0.133**
Vertical cup/disc ratio	0.3±0.1 (0.1-0.61)	0.4±0.1 (0.19-0.58)	0.111**
Cup volume	0.1±0.1 (0.01-0.5)	0.1±0.1 (0.01-0.41)	0.104**

FMF: Familial Mediterranean Fever, RNFL: retina nerve fiber layer, *: Independent t-test, **: Mann Whitney U test, Boldfaced values are statistically significant (p < 0.05).

FMF group than the control group (p = 0.023). There was no significant difference in the optic disc parameters of disc area, linear and vertical cup-disc ratio, and cup volume between the groups (p = 0.391, p = 0.113, p = 0.111, p = 0.104, respectively), but the rim area value was higher in the FMF group compared to the control group and this difference was statistically significant (p = 0.013). The optic disc parameters are summarized in Table-*III*.

Discussion

FMF is an inflammatory disease affecting multiple organs [1]. Although ocular involvement is rare, reported ocular pathologies vary in a spectrum including necrotizing blepharitis, episcleritis, scleritis, anterior uveitis, bilateral panuveitis, bilateral disc edema, optic disc vasculitis, tear film layer and ocular surface dysfunction, amaurosis fugax, oculomotor nerve palsies and ptosis [18-21].

TNF-α, IL-6, and IL -1β levels have been found to increase both during the attack period and attack-free period in FMF patients [6, 22-24]. This shows us that the inflammation continues even outside the acute attacks. Our aim in this study was to investigate how the choroid and macular thickness, macular volume, ONH parameters and peripapillary RNFL are affected in the case of subclinical inflammation in pediatric FMF patients in remission.

Contradictory results regarding the choroidal thickness in FMF patients have been reported in the literature. Gundogan et al. [25] determined that the choroid was significantly thicker in their 50 adult FMF patients than in the control group during an attack period. The authors claimed that increase in choroidal thickness during the acute attack was related to aggravated systemic inflammation and the FMF-related vascular structure changes [25]. There was no difference between the two groups consider-

ing the retinal and choroidal thickness in the study conducted by Erdurmuş et al. on 30 pediatric patients with FMF and 28 healthy children [13]. We found a decrease in choroidal thickness at the temporal 1500 µm point in this study while all our patients were in remission. The choroidal thicknesses at all other measurement points were also lower in the patient group but without statistical significance. Subfoveal macular thickness and total macular volume were also similar between the groups. Supporting our study, Battal et al. reported that choroidal thickness was significantly thinner in the pediatric FMF patients who are in the remission state than in the control group [14]. These results indicate that FMF affects ocular vascular structures in both the acute and chronic remission periods and continues its effect subclinically through the presence of inflammatory cytokines while the patients are in remission. As a result, chronic inflammation may decrease choroid vascular support and lead to choroid atrophy. The difference in the width of the choroidal thinning areas reported by different studies [14, 26] may be due to the duration of the disease and the number of attacks, the duration between the diagnosis and the start of treatment, and thus the difference between the inflammation duration and its being under control. Besides, Adhi et al. suggested that the choriocapillaris and choroid vessel thickness are decreased with normal aging [27]. A decrease in the choroid volume of approximately 0.54 mm3 per decade with aging has also been reported [28]. Therefore, the age factor may have contributed to the detection of choroidal thinning in larger areas in adults. The presence of non-statistical thinning in regions other than the 1500 µm temporal area in our study indicates that the first affected area might be the outer temporal area, and that thinning may continue to develop in other choroid areas during the subsequent chronic inflammatory process.

Apoptosis increases glaucomatous retinal ganglion cell damage mediated by cytokines such as TNF-α, FasL, IL-1α, IL-1β, and IL-6 [29]. The presence of these inflammatory cytokines has been demonstrated in FMF patients [6, 22-24]. The peripapillary RNFL was not different between the groups in the study conducted by Alim et al. on 39 pediatric patients and 36 healthy children [15]. Similar results were also obtained in the study conducted by Yener et al. [16]. In another study of Alim et al. in FMF adult patients, similar results were reported [30]. While there was no significant difference between the groups in terms of the superior, inferior, nasal, and temporal RNFL in our study, similar to the literature, we found the average RNFL to be significantly thinner in the FMF group. Besides, this result shows us that there may be a decrease in the average RNFL thickness secondary to retinal ganglion cell loss developing due to the subclinical inflammation that continues even in remission.

The rim area was the only ONH parameter that was significantly higher in the FMF group in our study. Although there was no significant difference between the groups in terms of ONH parameters in the study conducted by Yener et al., the disc area was found to be larger in the FMF group [16]. The causes of the changes in neuroretinal rim size can be listed as the different lamina cribrosa structures between individuals, different diameters of retinal ganglion cell axons, and differences in the ratio of glial cells in intrapapillary tissue [31, 32]. In recent studies, it has been reported that the rim area increases as the optic disc area increases [33]. Besides, Mansour et al. have reported that males have a larger disc than females [34]. In our study, there was a distribution favoring male patients in the FMF group. We believe that this may have caused the disc area to be larger in the FMF group compared to the control group, although not statistically significant, and consequently the rim area to be found to be larger in the FMF group.

Age, gender, race, refractive error, and axial length are factors that affect the choroidal thickness [35,36] and peripapillary RNFL [37] measurements in the studies conducted. Age and gender were similar in the FMF and control groups in our study. Although the axial lengths were not evaluated in the current study, the difference in refractive values between the groups was not statistically significant.

Our study had some limitations. First, all of our patients were in remission. We could have obtained more meaningful results in terms of posterior segment parameters if an evaluation had been made during the acute attack. Secondly; our study was conducted at a single center and with a small sample group, so our results cannot be generalized to all FMF patients. Another limitation of our study was the manual measurement of choroidal thickness. However, the measurements were taken from 7 different points by two experienced physicians and repeated when there was a difference of more than 10 µm between the measurements to alleviate the effects of this limitation.

In conclusion, the choroidal thickness in the FMF group was significantly lower at the temporal 1500 µm point in our study. Besides, average RNFL thickness was significantly lower in the FMF group. These results indicate that subclinical inflammation continues due to the presence of inflammatory cytokines even when FMF patients are in remission, and the posterior segment parameters of the eye may be affected even in childhood as a result of this inflammation. However, we believe that it is necessary to evaluate the disease in both the acute and chronic stages in larger patient groups in order to better understand its effects.

Ethical approval

The study was approved by the local ethics committee (protocol number 1776-20.01.2021, Amasya University)

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