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E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

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Research Articles

Comparison of Higher-Order Aberrations After Single-Step Transepithelial and Conventional Alcohol-Assisted Photorefractive Keratectomy
Kemal Özülken and Çağrı İlhan; Ankara, Hatay, Turkey

Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors
Pragati Garg et al.; Lucknow, India

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Effects of Upper Eyelid Blepharoplasty on Contrast Sensitivity in Dermatochalasis Patients
Hilal Nalcı et al.; Ankara, Turkey

Early Results of Stereotactic Radiosurgery in Uveal Melanoma and Risk Factors for Radiation Retinopathy
Gökçen Özcan et al.; Ankara, İstanbul, Turkey

Relationship Between Final Visual Acuity and Optical Coherence Tomography Findings in Patients with Diabetic Macular Edema Undergoing Anti-VEGF Therapy
Seher Eraslan et al.; Nevşehir, Mersin, Turkey

Review

Behçet's Uveitis: Current Diagnostic and Therapeutic Approach
Pınar Çakar Özdal; Ankara, Turkey

Case Reports

In Vivo Confocal Microscopy and Anterior Segment Optical Coherence Tomography Findings in Two Cases with Mucopolysaccharidoses
Yalçın Karaküçük et al.; Konya, Turkey

A Rare Cause of Type II Neovascularization: Unilateral Retinal Pigment Epithelium Dysgenesis
Berrak Şekeryapan Gediz; Ankara, Turkey

Multimodal Imaging in a Case of Fovea Plana Associated with Situs Inversus of the Optic Disc
Berrak Şekeryapan Gediz and Mehmet Ali Şekeroğlu; Ankara, Turkey

Paracentral Acute Middle Maculopathy
Pelin Kıyat et al.; İzmir, Turkey

Letter to the Editor and Response

COVID-19 Pandemic and Ophthalmologists
Joob Beuy and Viroj Wiwanitkit; Bangkok, Thailand, Pune, India

Response to Letter to the Editor
Banu Bozkurt et al.; Konya, İzmir, İstanbul, Mersin, Ankara, Turkey

May June 2020
50 Volume
Issue 3

galenos

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

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Publishing House
Molla Gürani Mah. Kaçamak Sokak No: 21,
34093 Fındıkzade-İstanbul-Turkey
Publisher Certificate Number: 14521
Phone: +90 212 621 99 25 **Fax:** +90 212 621 99 27
E-mail: info@galenos.com.tr
Online Publishing Date: May 2020
International scientific journal published bimonthly.
E-ISSN: 2149-8709

The Turkish Journal of Ophthalmology is an official journal of the Turkish Ophthalmological Association.

On Behalf of Turkish Ophthalmological Association Owner

İzzet CAN
Private Practice, Ankara, Turkey

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Turkish Ophthalmological Association
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IBAN: TR10 0006 7010 0000 0065 7748 42
Annual Subscription: Domestic: 100.-TL (Tax Incl)
Abroad: 100 USD (Tax Incl.)

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Galenos Yayınevi Tic. Ltd. Şti.
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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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CONTENTS

Research Articles

127 Comparison of Higher-Order Aberrations After Single-Step Transepithelial and Conventional Alcohol-Assisted Photorefractive Keratectomy
Kemal Özülken, Çağrı İlhan; Ankara, Hatay, Turkey

133 Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors
Pragati Garg, Aditi Gupta, Nishi Tandon, Priyanka Raj; Lucknow, India

143 The Role of Heredity and the Prevalence of Strabismus in Families with Accommodative, Partial Accommodative, and Infantile Esotropia
Fatma Çorak Eroğlu, Sibel Oto, Feride İffet Şahin, Yunus Terzi, Özge Özer Kaya, Mustafa Agah Tekindal; Ankara, İzmir, Konya, Turkey

151 Effects of Upper Eyelid Blepharoplasty on Contrast Sensitivity in Dermatochalasis Patients
Hilal Nalcı, Melek Banu Hoşal, Ömür Uçakhan Gündüz; Ankara, Turkey

156 Early Results of Stereotactic Radiosurgery in Uveal Melanoma and Risk Factors for Radiation Retinopathy
Gökçen Özcan, Ahmet Kaan Gündüz, İbadulla Mirzayev, Kaan Oysul, Hasan Uysal; Ankara, İstanbul, Turkey

163 Relationship Between Final Visual Acuity and Optical Coherence Tomography Findings in Patients with Diabetic Macular Edema Undergoing Anti-VEGF Therapy
Seher Eraslan, Özlem Yıldırım, Özer Dursun, Erdem Dinç, Gülhan Orekici Temel; Nevşehir, Mersin, Turkey

Review

169 Behçet's Uveitis: Current Diagnostic and Therapeutic Approach
Pınar Çakar Özdal; Ankara, Turkey

Case Reports

183 *In Vivo* Confocal Microscopy and Anterior Segment Optical Coherence Tomography Findings in Two Cases with Mucopolysaccharidoses
Yalçın Karaküçük, Banu Bozkurt, Merve Şahin, Süleyman Okudan; Konya, Turkey

187 A Rare Cause of Type II Neovascularization: Unilateral Retinal Pigment Epithelium Dysgenesis
Berrak Şekeryapan Gediz; Ankara, Turkey

190 Multimodal Imaging in a Case of Fovea Plana Associated with Situs Inversus of the Optic Disc
Berrak Şekeryapan Gediz, Mehmet Ali Şekeroğlu; Ankara, Turkey

193 Paracentral Acute Middle Maculopathy
Pelin Kıyat, Cumali Değirmenci, Serhad Nalçacı, Filiz Afrashi, Cezmi Akkın; İzmir, Turkey

Letter to the Editor and Response

197 COVID-19 Pandemic and Ophthalmologists
Joob Beuy, Viroj Wiwanitkit; Bangkok, Thailand, Pune, India

198 Response to Letter to the Editor
Banu Bozkurt, Sait Eğrilmez, Tomris Şengör, Özlem Yıldırım, Murat İrkeç; Konya, İzmir, İstanbul, Mersin, Ankara, Turkey

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EDITORIAL

2020 Issue 3 at a Glance:

This issue of our journal features 6 original studies, 1 review, and 4 case reports, as well as a letter to editor and response. We believe that these articles, which have been prepared and presented in light of the basic principles of science and the value of sharing information, will make important contributions to your knowledge repertoire.

The first original article of this issue aimed to compare asphericity and higher-order aberration (HOA) outcomes after single-stage transepithelial photorefractive keratectomy (tPRK) and conventional alcohol-assisted FRK (aaPRK) in patients with myopia and myopic astigmatism. Özülken and İlhan evaluated 108 eyes of 54 patients, 27 of whom underwent tFRK and the other 27 of whom underwent aFRK, according to patient preference. They reported that aaPRK yielded better results in terms of the aberration coefficient value, which is affected by all HOAs, while postoperative best corrected visual acuity, spherical equivalent, asphericity, and HOA values were similar with both methods (see pages 127-132).

In an original article from India, Garg et al. share their investigation of the incidence and risk factors of dry eye in patients undergoing cataract surgery. They report that dry eye was quite common after cataract surgery and was nearly independent of variables such as demographic and anthropometric profile, type of surgical intervention, duration of microscope light exposure, and amount of energy used. On a positive note, they stated that dry eye signs and symptoms were generally temporary in these patients, but they also emphasized that longer follow-up studies are needed to determine the timeframe of resolution (see pages 133-142).

In another original article, Eroğlu et al. shared the results of their study on the role of heredity and the prevalence of consanguineous marriage among the relatives of patients with accommodative, partial accommodative, and infantile esotropia. The authors reported that sporadic and non-Mendelian inheritance patterns were more common than autosomal recessive inheritance patterns in these types of deviations, and the frequency of strabismus and microtropias were higher among the relatives of esotropia patients compared to the general population (see pages 143-150).

Nalcı et al. investigated the effects of upper lid blepharoplasty on contrast sensitivity in patients with dermatochalasis and found that their contrast sensitivity at high spatial frequency increased significantly. In their conclusion, they speculated that in light of these objective data, blepharoplasty may have an additional functional indication in older patients (see pages 151-155).

Özcan et al. retrospectively analyzed the early results, side effects, and risk factors for radiation retinopathy in uveal melanoma patients who underwent stereotactic radiosurgery using the CyberKnife device with image-guided non-invasive fixation. They determined that this treatment is an effective method having a safe adverse-effect profile and can be considered among the eye-preserving therapies for uveal melanoma (see pages 156-162).

Diabetic macular edema (DME) is the most common cause of diabetes-related vision loss; therefore, diagnosis and monitoring treatment response are essential. Optical coherence tomography (OCT) enables the objective evaluation of DME and provides valuable information for the detection of serous macular detachment (SD) and vitreoretinal interface pathologies. In their OCT study of patients who will start anti-VEGF therapy due to DME, Eraslan et al. concluded that the presence of SD with DME increases the need for treatment but was not associated with final visual acuity. In addition, they stated that ellipsoid zone irregularity, disorganization of the retinal inner layers, and presence of epiretinal membrane detected on OCT were factors that adversely affected visual acuity (see pages 163-168).

The subject of this issue's review article, written by Pınar Çakar Özdal, is current approaches to the diagnosis and treatment of Behçet's uveitis, which is the leading cause of noninfectious uveitis in Turkey. The article includes valuable information about Behçet's uveitis, and because this disease is more common in young adults and is potentially blinding, it is emphasized that early diagnosis and aggressive treatment with immunomodulator and biological agents when necessary are the main factors in improving visual prognosis (see pages 169-182).

Mucopolysaccharidoses are a group of diseases caused by hereditary lysosomal enzyme deficiencies, resulting in widespread intracellular and extracellular accumulation of

TURKISH JOURNAL OF OPHTHALMOLOGY

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glycosaminoglycans. In their case report evaluating the *in vivo* confocal microscopy and anterior segment OCT findings of 2 patients with mucopolysaccharidosis, Karaküçük et al. report that using these imaging technologies will make useful contributions to our current knowledge regarding the identification of disease-related macroscopic and microscopic corneal changes (see pages 183-186).

Another case report in this issue concerns unilateral retinal pigment epithelial dysgenesis (URPED), which is a very rare clinical condition. Berrak Şekeryapan Gediz states that the aim of this interesting case report was to inform about URPED, which causes vision loss in young people in particular, and the type 2 neovascularization secondary to it (see pages 187-189).

Gediz and Şekeroğlu also refresh our knowledge with another rare case report presenting multiple optic disc anomalies associated with fovea plana and emphasize that the use of multimodal imaging methods facilitates the identification of rare anomalies (see pages 190-192).

A case report from Kıyat et al. draws attention to paracentral acute middle maculopathy, which is a variant of acute macular neuroretinopathy whose etiology is believed to involve retinal ischemia caused by vasopressor exposure or systemic diseases that cause microvascular retinopathy. The authors report that demonstration of a band of hyperreflectivity in the inner nuclear and outer plexiform layers on spectral domain OCT is important in the detection and differential diagnosis of this clinical entity, but they also emphasized the need to support the diagnosis with multimodal imaging (see pages 193-196).

In a Letter to the Editor, Beuy and Wiwanitkit share their views on an article entitled "The COVID-19 Pandemic: Clinical Information for Ophthalmologists", published in the previous issue of our journal. The authors state that the general approach to ophthalmology practice during the COVID-19 outbreak is similar worldwide and that ophthalmologists have a consensus regarding their occupational risk of contracting COVID-19. However, they claim that there have been no reports of ophthalmologists infected with COVID-19, discuss the possible reasons for this, and conclude by emphasizing the universal protective measures that must be taken (see page 197).

In response to the Letter to the Editor, Bozkurt et al. pointed out that Li Wenliang, who was the first to recognize and raise the alarm about COVID-19, was an ophthalmologist working in Wuhan and lost his life after contracting the disease through contact with a glaucoma patient. In addition, according to the article entitled "Symptomatic COVID-19 in Eye Professionals in Wuhan, China" and data from the same region obtained from the China Red Cross Foundation and Wuhan Health Commission, the estimated COVID-19 incidence is similar in ophthalmologists and other health workers. The authors stated that based on these findings, they could not say that the disease is rare among ophthalmologists or that ophthalmology practice involves less risk than other medical services. However, the common point is that measures to protect ophthalmologists, other health workers, and patients are universally similar and essential (see pages 198-199).

Respectfully on behalf of the Editorial Board,

Tomris Şengör, MD

DOI: 10.4274/tjo.galenos.2019.14554
Turk J Ophthalmol 2020;50:127-132

Original Article

Comparison of Higher-Order Aberrations After Single-Step Transepithelial and Conventional Alcohol-Assisted Photorefractive Keratectomy

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Abstract

Objectives: To compare the asphericity and higher-order aberration (HOA) outcomes of single-step transepithelial photorefractive keratectomy (tPRK) and conventional alcohol-assisted PRK (aaPRK) in patients with myopia and myopic astigmatism.

Materials and Methods: Of the 108 eyes of 54 patients enrolled in the study, tPRK was performed on 54 (50%) eyes and aaPRK was performed on 54 (50%) eyes. The following parameters were compared: corrected distance visual acuity (CDVA), spherical equivalent (SE), flat and steep keratometry, intraocular pressure, central corneal thickness, asphericity, and HOAs including horizontal and vertical coma, horizontal and vertical trefoil, spherical aberration, second-order vertical coma, and aberration coefficient.

Results: The demographic and baseline characteristics were similar between the two groups ($p>0.05$, for all). The aberration coefficient value was significantly lower in patients treated with aaPRK compared to patients treated with tPRK at postoperative 3 months, 6 months, and 1 year ($p=0.022$, $p=0.019$, and $p=0.017$, respectively). Differences in the other variables were statistically insignificant ($p>0.05$ for all).

Conclusion: Both tPRK and aaPRK procedures obtain similar postoperative CDVA, SE, asphericity, and HOA outcomes, except the aberration coefficient value.

Keywords: Transepithelial photorefractive keratectomy, alcohol-assisted photorefractive keratectomy, asphericity, higher-order aberration, PRK

Introduction

Transepithelial photorefractive keratectomy (tPRK) was described in the late 1990s as a two-step procedure to create a well-arranged epithelial wound edge. The corneal epithelium is removed with laser phototherapeutic ablation and then laser photorefractive ablation provides the desired refraction corrections.[1] Unlike alcohol-assisted photorefractive keratectomy (aaPRK), using manual mechanical scraping or an alcohol solution is not needed in tPRK and there is no contact of any surgical equipment with the cornea. The lack of contact with the eye during the procedure is appealing to patients, who know this procedure as "no-touch laser" in Turkey.

Theoretically, the risk of epithelial defect and irregularity is minimal, but the predictability of this two-step unstandardized laser surgical procedure is limited due to a lack of adjusted nomograms. With old generation laser technology, this two-stage method was not used worldwide in the early period due

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Received: 29.05.2019 **Accepted:** 18.12.2019

Cite this article as: Özülken K, İlhan Ç. Comparison of Higher-Order Aberrations After Single-Step Transepithelial and Conventional Alcohol-Assisted Photorefractive Keratectomy. Turk J Ophthalmol. 2020;50:127-132

to prolonged time to switch from phototherapeutic keratectomy (PTK) mode to PRK mode, corneal dehydration, and increased postoperative pain.[2,3] Following developments in laser technology and improvements in algorithms over the years, a new modern variant of tPRK was described as no-touch laser tPRK in the Schwind Amaris platform (SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany).[4] The most important methodological innovation in tPRK is the combination of PTK and PRK excimer laser applications in a single-step ablation procedure to remove the epithelium and stroma. This aspheric ablation profile is determined from literature data estimating the corneal epithelial thickness is 55 μm centrally and 65 μm peripherally. Recent studies show that the new generation single-step tPRK method reduces operative time, minimizes the epithelial defect area, eliminates the risk of toxicity on limbal cells because of the absence of alcohol, and causes less postoperative pain and corneal haze with faster healing time and visual recovery.[4,5,6,7]

Although there are many publications comparing the conventional aaPRK and single-step tPRK procedures, the tPRK method has undergone many minor modifications and nomogram adjustments over time. The aim of this study was to evaluate whether the latest version of the tPRK device is superior to that of aaPRK in patients with myopia and myopic astigmatism. The postoperative 1-year asphericity (Q value) and higher-order aberration (HOA) outcomes of tPRK and aaPRK were compared.

Materials and Methods

Design

This retrospective, nonrandomized, comparative study was conducted between January 2016 and June 2018 in the refractive surgery department of a private eye clinic, with approval granted by the local research ethics committee. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki for human subjects and written informed consent was obtained before surgery from each patient after a detailed explanation of the surgical procedures.

Subjects

The study included patients aged over 18 years old with myopic or compound myopic astigmatism within the range of -1.00 to -8.50 diopter (D) manifest refraction spherical equivalent (SE), with better than 0.00 logMAR corrected distant visual acuity (CDVA) and stable refractive error for at least 12 months. Exclusion criteria were a history of ocular surgery, ocular trauma, or ocular disease, irregular astigmatism on corneal topography, estimated central stromal bed thickness less than 350 μm at the thinnest point, history of keloid formation, systemic disease that could affect corneal wound healing, and pregnancy. In total, 108 eyes of 54 consecutive patients were included in the study. Twenty-seven patients underwent tPRK and 27 underwent aaPRK according to patient preference. All subjects underwent bilateral refractive surgery performed by the same experienced and certified refractive surgeon (K.O.).

Clinical Evaluations

Preoperative ocular and medical history was obtained and all preoperative examinations were performed after discontinuing soft contact lens use for at least 4 days. A detailed ophthalmic examination was performed by the same ophthalmologist. Manifest and objective refraction were determined and uncorrected distant visual acuity (UDVA) and CDVA were measured using Snellen chart. Decimal values were converted to logMAR for statistical analysis. Corneal tomography was performed with WaveLight®Oculyzer II (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany) and curvature, elevation, and thickness maps were obtained. Asphericity (Q value) calculations were obtained from the placido-based Allegrato Topolyzer version 1.59 (Alcon, Fort Worth, TX). Total corneal HOAs were analyzed, including horizontal and vertical coma (Z[3, 1] and Z[3, -1]), horizontal and vertical trefoil (Z[3, 3] and Z[3, -3]), primary spherical aberration (Z[4, 0]), second-order vertical coma (Z[5, -1]), and aberration coefficient in the Zernike analysis. The aberration coefficient is calculated from the value of the Zernike polynomial coefficients used to reconstruct the anterior corneal surface. If there are no abnormal corneal aberrations, aberration coefficient is 0.0; otherwise it becomes 1.0 or greater, depending on the degree of aberration.[8] HOAs were evaluated in the 6.0 mm diameter central area with respect to the pupil center in a dark environment, and the pupil was not dilated.

Manifest refraction, UDVA and CDVA, intraocular pressure (IOP) measurement, anterior and posterior segment examination were done at postoperative 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year. Corneal tomography evaluation, asphericity, and HOAs calculations were repeated at postoperative 3 months, 6 months, and 1 year. Postoperative 1 year was defined as the primary end-point of the study.

Surgical Technique

A single experienced surgeon performed all surgeries using the same 6th generation Amaris excimer laser version 750 S (Schwind Amaris, SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany). It was aimed to achieve emmetropia in all eyes.

In the operating room, topical proparacaine hydrochloride 0.5% (Alcaine, Alcon, Fort Worth, TX) was instilled for topical anesthesia and the eyelids were opened using a wire lid speculum. In the tPRK group, the epithelium was removed with excimer laser and the aberration-free tPRK ablation algorithm (SCHWIND eye-tech-solutions) was used. In the aaPRK group, the superficial epithelium was cut using an 8.5 mm diameter trephine and mechanically debrided with a spatula after exposure of the corneal surface to 20% ethyl alcohol solution for 10 seconds. Wavefront optimized ablation was performed according to the aberration-free algorithms calculated with the ORK-CAM software (version 4.63, SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany). Mitomycin C 0.02% was applied for 30 seconds in eyes with SE greater than 3 D and for 60 seconds if greater than 6 D due to increased risk of corneal haze.[9] After laser ablation, a bandage contact lens (Senofilcon A [Acuvue Oasys,

J&J, Vision Care, Inc., Jacksonville, FL]) was applied for 5 days. Postoperative topical moxifloxacin 0.5% (Vigamox, Alcon, Fort Worth, TX) 3 times a day for 1 week, topical dexamethasone (Maxidex, Alcon, Fort Worth, TX) starting after epithelial healing and tapered off over 3 weeks and artificial tears every 2 hours for 2 months were prescribed. No intraoperative or postoperative complications developed in any patient.

Statistical Analysis

The data obtained from the study were analyzed using the Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM Corp., New York, NY). Descriptive statistics were presented as mean ± standard deviations (SD) and minimum-maximum values. The normal distribution of the variables was tested using the Kolmogorov-Smirnov test. The non-parametric tests were used in analysis as the numerical data did not conform to normal distribution. The preoperative and postoperative variables of the same eye were compared using the Wilcoxon test. Postoperative asphericity and HOAs of the two groups were compared using the Mann-Whitney U test. Statistical significance was set at $p<0.05$ for all tests. Power and Sample Size (PASS) version 19 software (NCSS Statistical Software, Il, USA) was used for sample size and power calculations. It was found that at least 24 eyes were needed in each group for power of 80% (δ=6, σ=13, and alpha=0.05).

Results

The tPRK group included 54 eyes of 27 patients (13 male, 14 female) with a mean age of 27.2±6.7 years (18-45 years). The aaPRK group included 54 eyes of 27 patients (12 male, 15 female) with a mean age of 26.1±6.2 years (18-43 years). There was no statistically significant difference in gender or age characteristics between two groups ($p>0.05$ for both).

Preoperative clinical findings including CDVA, SE, flat and steep keratometry, IOP, and CCT values were similar in the two groups ($p>0.05$ for all). When comparing the postoperative 1-year measurements of the two groups, no significant difference was determined in CDVA, SE, flat and steep keratometry, IOP, and CCT ($p>0.05$ for all). No intraoperative or postoperative complications including haze, infection, undercorrections, overcorrections, or dry eye developed in any case. The preoperative and postoperative 1-year mean values of CDVA, SE, flat and steep keratometry, IOP, and CCT of the tPRK and aaPRK groups are presented in Table 1. Additionally, the mean CDVA and SE values are shown in Figures 1 and 2.

Asphericity and all HOAs were similar in the two groups at postoperative 3 months, 6 months, and 1 year ($p>0.05$ for all). The aberration coefficient differed significantly between the tPRK and aaPRK groups at postoperative 3 months, 6 months, and 1 year ($p=0.022$, $p=0.019$, and $p=0.017$, respectively). The postoperative results of asphericity and HOAs of the tPRK and the aaPRK groups are shown in Table 2.

Discussion

Having excellent visual quality without using spectacles or contact lenses is the main rationale of refractive surgery. According to the results of this study, the postoperative CDVA and SE outcomes were highly satisfactory in both methods and there was no statistically significant difference between tPRK and aaPRK except in postoperative aberration coefficient value.

Table 1. Comparison of preoperative and postoperative 1-year values of the tPRK (n=54) and aaPRK (n=54) groups

	tPRK (mean ± SD)			aaPRK (mean ± SD)			p value	
	Preop	**Postop 1 year**	**p value**	**Preop**	**Postop 1 year**	**p value**	**Preop**	**Postop 1 year**
CDVA (logMAR)	**-0.10±0.1** (0.00 to -0.20)	-0.06±0.09 (0.00 to -0.20)	<0.001	-0.10±0.06 (0.00 to -0.20)	-0.06±0.16 (0.00 to -0.20)	<0.001	0.356	0.732
SE (D)	-4.05±1.92 (-1.25 to -8.50)	-0.21±0.28 (0.38 to -0.75)	<0.001	-3.38±2.22 (-1.00 to -7.63)	0.11±0.24 (0.38 to -0.50)	<0.001	0.099	<0.081
K1 (flat) (D)	43.2±1.4 (40.6-47.2)	39.9±2.1 (34.5-44.6)	<0.001	42.7±1.7 (38.5-45.7)	40.5±2.1 (35.5-44.2)	<0.001	0.222	0.059
K2 (steep) (D)	44.0±1.4 (41.8-48.3)	40.7±2.1 (35.6-45.2)	<0.001	44.5±1.5 (40.6-46.8)	41.3±2.2 (36.0-44.7)	<0.001	0.069	0.054
IOP (mmHg)	14.4±1.0 (12-16)	11.5±1.8 (8-14)	<0.001	14.4±2.8 (9-24)	12.0±2.8 (7-18)	<0.001	0.236	0.103
CCT (mm)	519.6±32.1 (449-591)	439.4±45.2 (324-533)	<0.001	514.8±27.5 (463-576)	440.8±50.3 (356-543)	<0.001	0.376	0.956

tPRK: Single-step transepithelial photorefractive keratectomy, aaPRK: Alcohol-assisted photorefractive keratectomy, SD: Standard deviation, Preop: Preoperative, Postop: Postoperative, CDVA: Corrected distance visual acuity, SE: Manifest refraction spherical equivalent, K: Keratometry, IOP: Intraocular pressure, CCT: Central corneal thickness

Table 2. Postoperative asphericity and HOAs of the tPRK (n=54) and aaPRK (n=54) groups									
	tPRK (mean ± SD)			aaPRK (mean ± SD)			p value		
	3 months	6 months	1 year	3 months	6 months	1 year	3 months	6 months	1 year
Asphericity (D)	-0.02±0.82	-0.02±0.77	-0.02±0.61	0.02±0.67	0.02±0.64	0.02±0.55	0.826	0.798	0.940
Z(3, 1) (mm)	-0.17±0.56	-0.16±0.67	-0.14±0.47	-0.18±0.66	-0.15±0.48	-0.14±0.40	0.760	0.802	0.780
Z(3, -1) (mm)	-0.02±0.71	-0.02±0.58	-0.01±0.61	-0.03±0.74	-0.03±0.68	-0.03±0.55	0.670	0.592	0.780
Z(3, 3) (mm)	0.09±0.43	0.08±0.42	0.07±0.29	0.07±0.23	0.06±0.32	0.04±0.19	0.312	0.344	0.236
Z(3, -3) (mm)	0.03±0.31	0.02±0.29	0.02±0.22	0.03±0.24	0.02±0.22	0.01±0.15	0.335	0.298	0.667
Z(4, 0) (mm)	1.11±0.44	1.05±0.51	1.02±0.45	0.99±0.51	0.98±0.52	0.95±0.43	0.468	0.431	0.380
Z(5, -1) (mm)	-0.03±0.22	-0.03±0.19	-0.04±0.15	-0.03±0.32	-0.02±0.19	-0.02±0.14	0.526	0.498	0.436
Aberration coefficient	1.4±0.2	1.4±0.2	1.4±0.1	1.3±0.2	1.3±0.2	1.3±0.2	0.022	0.019	0.017
HOA: Higher-order aberration, tPRK: Single-step transepithelial photorefractive keratectomy, aaPRK: Alcohol-assisted photorefractive keratectomy, SD: Standard deviation									

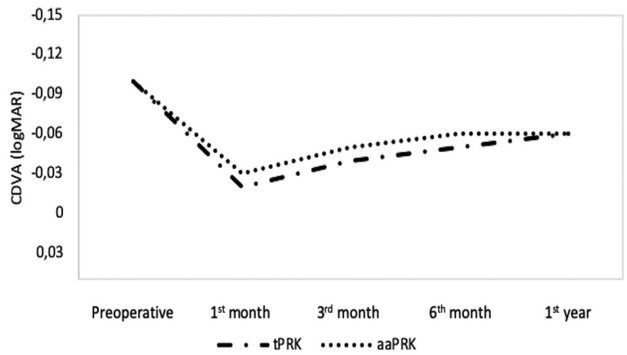

Figure 1. The mean corrected distant visual acuity (CDVA) in transepithelial photorefractive keratectomy (tPRK) and alcohol-assisted PRK (aaPRK) groups

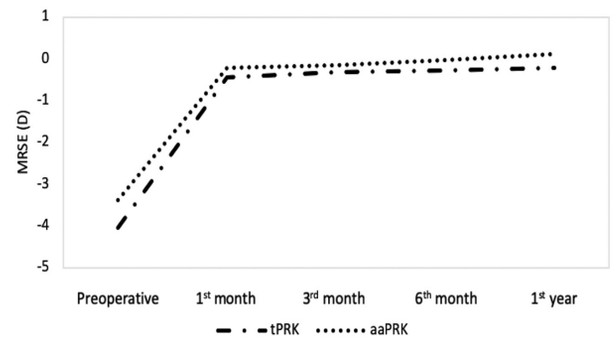

Figure 2. The mean manifest refraction spherical equivalents (MRSE) in transepithelial photorefractive keratectomy (tPRK) and alcohol-assisted PRK (aaPRK) groups

However, visual quality is a very versatile concept and asphericity and HOAs are important factors affecting retinal image quality in patients who have undergone refractive surgery.[10,11] It has been previously shown that excimer laser ablation increases ocular aberration in myopic eyes.[10,12] The purpose of the present study was to compare the surgical outcomes of tPRK to aaPRK and to evaluate whether tPRK was superior to conventional aaPRK.

The profile used during tPRK is calculated based on data in the literature. As a result, the epithelial thickness of the central cornea is taken as 55 mm and the thickness of the epithelium in the 4 mm periphery as 65 mm. Moreover, the photoablative rate is set 20% higher than stroma.[13] In the tPRK method, keratocyte apoptosis is restricted and a smooth uniform corneal surface is created with ideal epithelial regeneration.[14] In contrast, an irregular ablation field and imperfect wound healing after mechanical epithelial removal with or without ethyl alcohol solution exposure can cause postoperative clinical or subclinical epithelial pathologies.[14,15] In this regard, aaPRK and mechanical epithelial removal in PRK without alcohol give comparable outcomes.[16]

Since the tPRK method uses a standard epithelial ablation algorithm regardless of actual epithelial layer topometry, in some eyes less epithelial ablation than required is applied and an amount of ablation to be applied to the stroma may be applied to the remaining epithelium.[4] Many studies have shown that there are differences between CCT and 3D epithelial maps.[5,6] Therefore, refractive results and visual quality may be deteriorated after tPRK using a standard epithelial algorithm. In the current study, the groups were compared in terms of HOAs and only the difference in aberration coefficient value was found to be statistically significant in favor of aaPRK. It may be thought that the aberration coefficient is a general indicator that is affected by all HOAs and despite there being no difference in the individual HOAs, the aberration coefficient differed between the groups.[8] Since aberration coefficient value was lower in the aaPRK patient group, we can conclude that corneas were more uniform after aaPRK and thus abnormal corneal aberrations were less common in this group. Moreover, in the light of this result, it can be said that the quality of vision after aaPRK is slightly better than after the tPRK method because the aberration coefficient is affected by all HOAs.

We did not find a statistically significant difference between the two groups when we evaluated HOAs. Kaluzny et al.[17] evaluated the refractive results, predictability, safety, and efficacy of these two procedures and found that tPRK and aaPRK

provided very similar results after a 3-month follow-up. Fattah et al.[18] and Antonios et al.[19] stated that the postoperative HOAs of two groups obtained by a Scheimpflug analyzer were similar. Luger et al.[5] compared postoperative asphericity and HOAs of two groups using Pentacam HR and wavefront aberrometry and found no statistically significant difference after a 1-year follow-up period. To the best of our knowledge, ours is the first report to compare HOAs after tPRK and aaPRK using a Scheimpflug camera-based system and demonstrate different aberration coefficient results. The current study has filled this gap in the literature by having a long postoperative follow-up time and giving detailed measurements obtained at postoperative 1 months, 3 months, 6 months, and 1 year.

A disadvantage of tPRK is that the total excimer laser energy applied for epithelial removal and stromal ablation is higher than in the aaPRK method. The excimer laser energy can increase the temperature in the stromal tissue and cause postoperative haze formation.[20] On the contrary, there are studies indicating that in aaPRK method more keratocyte apoptosis occurs because of the formation of bigger size of corneal epithelial defect and it provides more limbal cell damage due to use of alcohol and for these reasons aaPRK causes more corneal haze formation than the tPRK method.[20,21] When all surgeries including tPRK and aaPRK in this study were considered, no difference was observed between the two groups in terms of postoperative haze severity, which can be attributed to the use of mitomycin C during the operation in both groups.

In the current study, there were no differences between the groups in terms of mean age or preoperative SE. Nevertheless, these parameters showed a wide range with large differences between maximum and minimum values (18 to 45 years and -1.00 to -8.50 D, respectively). This variability can directly affect postoperative outcomes. For example, the risk of corneal haze increases 2 fold in subjects with more than 6 D myopia.[9] This should be considered an important limitation, and more homogeneous groups of patients in a narrower age range and separated into groups of low, moderate, or high myopia would be able to refine the results and overcome this limitation. Epithelial healing (re-epithelialization) processes and subjective visual parameters (pain, photophobia, photic phenomena, etc.) were not evaluated. In addition, there were no data about the mean operative times of the procedures in the current study; however, we observed that the tPRK method was shorter than the aaPRK method. Similar to these findings, there are studies indicating that the tPRK method performed with new generations of laser systems shortens the duration of surgery and reduces the risk of corneal dehydration compared to conventional aaPRK method.[22]

Conclusion

In conclusion, both tPRK and aaPRK are predictive and effective for the treatment of myopia and myopic astigmatism. Since both procedures provide similar postoperative CDVA, SE, asphericity, and HOAs in patients with myopia and compound myopic astigmatism, these two methods have no superiority over each other in terms of long-term results. When evaluated in terms of the aberration coefficient value, which is affected by all HOAs, aaPRK provides better results.

Ethics

Ethics Committee Approval: Approval granted by the local research ethics committee.

Informed Consent: Written informed consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Ö., Concept: K.Ö., Ç.İ., Design: K.Ö., Ç.İ., Data Collection or Processing: K.Ö., Ç.İ., Analysis or Interpretation: K.Ö., Ç.İ., Literature Search: Ç.İ., K.Ö., Writing: Ç.İ., K.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.45538
Turk J Ophthalmol 2020;50:133-142

Original Article

Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors

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Abstract

Objectives: To study the incidence of dry eye and its determinants in patients undergoing cataract surgery.

Materials and Methods: One hundred twenty patients with senile cataract underwent Schirmer's test, tear break-up time (TBUT) test, lissamine green staining of the cornea and conjunctiva, and Ocular Surface Disease Index (OSDI) for evaluation of dry eye preoperatively and again at first and second follow-up examinations at 1 week and 1 month after cataract surgery.

Results: Mean age of the patients was 59.25+9.77 years and 73 (60.8%) were men. None of the patients had dry eye at the time of enrollment as per the criteria of our study. Postoperatively, Schirmer's test values ranged from 12-35 mm and 8-24 mm at first and second follow-ups, respectively. Mean TBUT was 13.16±2.45 and 9.64±2.20 seconds, while lissamine green staining score was 3 in 67 (55.8%) and 1 in 67 (55.8%) subjects at first and second follow-up, respectively. OSDI values ranged from 1-30 and 10-33 with a mean of 25.97±5.34 and 11.96±7.47 respectively at first and second follow-up. At first follow-up, 89.1% of the 56 patients who underwent phacoemulsification were found to have grade 2 dry eye ($p<0.001$), while 92.2% of the 64 patients who underwent small-incision cataract surgery (SICS) had grade 2 dry eye ($p<0.001$). At second follow-up, grade 0 dry eye was observed in 92.2% of the patients who underwent phacoemulsification and 82.1% of the patients who underwent SICS ($p<0.001$).

Conclusion: The incidence of dry eye after cataract surgery was high and mostly independent of demographic and anthropometric profile, type of surgical procedure, time of microscope exposure, and amount of energy used. This dryness was transient in nature and showed a declining trend, tending to achieve normalization by the end of 1 month.

Keywords: Cataract, dry eye disease, Schirmer's test, Ocular Surface Disease Index, phacoemulsification

Introduction

Dry eye disease (DED) is defined as "a disorder of the tear film due to reduced tear production or excessive tear evaporation, which causes damage to the inter-palpebral ocular surface and is associated with symptoms of ocular discomfort and/or visual symptoms".[1] A more descriptive definition given by the dry eye workshop defines it as "a multifactorial disease of the tear film and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface".[2]

The etiology of dry eye syndrome has been attributed to a number of causes and factors that include old age, gender, disorders affecting the connective tissue, metabolic disorders like diabetes and hypertension, contact lens usage, drugs like antihistamines, anticholinergics, antidepressants, oral contraceptives and topical eye drops containing preservatives, and ocular diseases like blepharitis, chronic conjunctivitis, meibomitis, and pterygium.[3,4,5]

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Received: 31.05.2019 **Accepted:** 27.12.2019

Cite this article as: Garg P, Gupta A, Tandon N, Raj P. Dry Eye Disease after Cataract Surgery: Study of its Determinants and Risk Factors. Turk J Ophthalmol. 2020;50:133-142

Apart from the conventional risk factors of dry eye syndrome, it has been seen that some surgical procedures related to the anterior segment like photorefractive keratectomy, laser-assisted in situ keratomileusis, and cataract surgery are also responsible for causing dry eye syndrome or aggravating existing symptoms of dry eye.[6,7,8] Surgical procedures like cataract surgery cause denervation of the cornea, which results in impaired epithelial wound healing, increased epithelial permeability, decreased epithelial metabolic activity, and loss of cytoskeletal structures associated with cellular adhesion. The incidence of dry eye syndrome among patients undergoing cataract surgery has been shown to be dependent on a host of factors including type of procedure, type of ophthalmic solution being used[9], intraoperative medication[10], coexistent systemic disorders[11], operating microscope light exposure and cumulative dissipated energy (CDE) used during the procedure[12], and time since surgery.[13]

Considering the fact that occurrence of dry eye syndrome after cataract surgery could be dependent on a number of factors like the type of surgery[9], intraoperative exposure[12], and energy used during phacoemulsification[12], it is essential that a proper risk assessment be done in both phacoemulsification as well as small-incision cataract surgery (SICS) procedures. Thus, the present study was carried out with an aim to assess the incidence of dry eye syndrome and its determinants among patients undergoing cataract surgery at a tertiary care center in North India.

Materials and Methods

This hospital-based observational study was carried out in the Clinic of Ophthalmology of Era's Lucknow Medical College and Hospital, Lucknow, a tertiary care-center in North India, over a period of 18 months. We initially enrolled 176 subjects with senile cataract and without pre-existing dry eye syndrome. Subjects underwent detailed history and ocular examination and those with ocular conditions that can contribute to the occurrence of dry eye, such as lid disorders (blepharitis, ectropion, entropion), contact lens wear, allergic conjunctivitis, any past ocular surgeries, chronic conjunctivitis, exposure keratitis, contact dermatitis, and Bell's palsy; those with systemic conditions like diabetes mellitus, hypertension[14], thyroid-associated diseases, lupus, rheumatoid arthritis, scleroderma, Sjögren's syndrome, vitamin A deficiency, and other factors like smoking[15]; and those with continuous long-term use of ocular or systemic medications (antihistaminics, antidepressants, decongestants, beta blocker drugs, diuretics, and aspirin) were excluded from this study. After excluding subjects who failed to meet the inclusion and exclusion criteria, did not give consent, or were lost to follow-up, there were 120 patients.

All the subjects included in the study best corrected visual acuity was assessed by Snellen chart and intraocular pressure by Goldmann applanation tonometer. Detailed slit-lamp examination was done and the fundus was examined by indirect ophthalmoscopy.

Schirmer's test, tear break-up time (TBUT) test, lissamine green staining of the cornea and conjunctiva, and Ocular Surface Disease Index (OSDI) were carried out for evaluation of dry eye.

Schirmer's test was done to test basal and reflex tear secretion using a specialized Schirmer's strip prepared from Whatman filter paper no. 41 measuring 40×5 mm, marked 0 to 35 mm. Depending on the wetting of the strip, the results of Schirmer's test were graded as: >10 mm, normal (grade 0); 5-10 mm, mild (grade 1); 3-4 mm, moderate (grade 2); 0-2 mm, severe (grade 3).[16]

TBUT was assessed to test tear film stability and meibomian gland disorder and the grading was done depending upon the time between the last blink and the appearance of a dry spot. TBUT less than 10 s was abnormal and graded as: >10 s, normal (grade 0); 3.1-6 s, moderate (grade 2); 6.1-10 s, fair (grade 1); <3 s, poor (grade 3).[16]

Lissamine green staining of the ocular surface was done to assess the dead and devitalized cells on the ocular surface. Results were graded as: 0, no dry eye; 1, mild dry eye; 2, moderate dry eye; and 3, severe dry eye. OSDI is a 12-item evaluation for dry eye assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye syndrome. The criteria used for the grading was: 0-12, normal; 13-22, mild; 23-32, moderate; and 33-100, severe.[17,18]

Risk factors such as pre-anesthetic medication, shape of incision, type of cataract surgery (phacoemulsification/SICS), microscope light exposure, CDE manipulation of ocular surface tissue, and intra- and postoperative medications were taken into consideration. Of these factors, all cases had the same pre-anesthetic medication, shape of incision, intra- and postoperative medications (which included a combination of antibiotic and steroid, non-steroidal anti-inflammatory and intraocular pressure-lowering topical eye drops from the same pharmaceutical brands, instilled at similar frequencies), and operating surgeon.

The patients were followed up 1 week and 1 month after the surgery. Evaluations of all dry eye parameters were repeated on both occasions.

The study was conducted after ethical approval by the institutional ethics committee in accordance with international agreements and the Declaration of Helsinki, and informed and written consent was obtained from all the subjects included in the study.

Statistical Analysis

The statistical analysis was done using Statistical Package for Social Sciences version 21.0 statistical software. The values were presented in number (%) and mean ± standard deviation. P values of <0.05 were considered significant and <0.001 as highly significant.

Results

Out of 120 subjects evaluated, the largest age group was 61-70 years (n=43, 35.83%), followed by those aged 51-60 years (n=40, 33.33%), <50 years (n=30, 25%), and >70 years (n=7,

5.83%). The mean age of the patients was 59.25+9.77 years and most were men (n=73, 60.83%). The male to female ratio was 1.55:1.

Most of the patients were from rural areas (n=103, 85.83%); subjects from urban areas comprised only 14.17% (n=17) of the study population. With respect to occupation, the largest group was homemakers (n=42, 35%), followed by farmers (n=33, 27.5%), skilled laborers (n=17, 14.17%), teachers (n=16, 13.33%), and shopkeepers (n=12, 10%). Using body mass index (BMI) criteria, the nutritional status of 114 patients (95%) was adjudged as normal weight (18.5-25.0 kg/m^2) and the other 6 (5%) fell in the overweight category (25.1-30 kg/m^2). None of the patients evaluated were underweight (<18.5 kg/m^2) or obese (>30 kg/m^2) (Table 1).

The most common ocular symptoms of the patients were photophobia (55.83%), itching (50.83%), watering (45.83%), burning sensation (45%), eye pain (41.67%), redness of eyes (39.17%), lid heaviness (36.67%), foreign body sensation (28.33%) and discharge (27.50%) (Table 2).

In preoperative clinical assessment of dry eye, Schirmer's test values ranged from 15 to 35 mm with a mean of 27.23±4.38 mm. Mean TBUT was 13.50±1.89 (range 10-18 s). Lissamine green staining score was 1 in 79 (65.8%) and 2 in 41 (34.2%) cases.

OSDI values ranged from 1 to 12 with a mean of 6.48+2.61. None of the patients had dry eye at the time of enrollment, as per the inclusion criteria of the study (Table 3).

Table 1. Demographic profile of the patients (n=120)

	n	%
Age, years		
≤50	30	25.00
51-60	40	33.33
61-70	43	35.83
>70	7	5.83
Mean age ± SD (range)	59.25±9.77 (40-85)	
Gender		
Male	73	60.83
Female	47	39.17
Place of residence		
Rural	103	85.83
Urban	17	14.17
Occupation		
Homemaker	42	35.00
Farmer	33	27.50
Skilled laborer	17	14.17
Teacher	16	13.33
Shopkeeper	12	10.00
Body mass index, kg/m^2		
18.5-25.0	114	95.00
25.1-30	6	5.00

n: Number of eyes, SD: Standard deviation

Postoperative Schirmer's test values ranged from 12 to 35 mm at 1 week and 8 to 24 mm at 1 month. Mean TBUT was 13.16±2.45 and 9.64±2.20 s, while lissamine green staining score was 3 in 67 (55.8%) and 1 in 67 (55.8%) subjects at 1 week and 1 month follow-up, respectively. OSDI values ranged from 1 to 30 (mean 25.97±5.34) at 1 week and 10 to 33 (mean 11.96±7.47) at 1 month (Table 3).

Cataract surgery was performed using the phacoemulsification technique in 53.33% of patients while remaining 46.67% underwent SICS. The incidence of dry eye was 89.1% and 15.6% in the phacoemulsification group at 1 week and 1 month, compared to 92.9% and 26.8% in the SICS group at the corresponding time points. Although the incidence of dry eye was higher after SICS as compared to phacoemulsification at both time points, the differences were not significant statistically (p>0.05) (Table 4).

We compared OSDI grade among the subjects preoperatively and postoperatively. On evaluating all the subjects together, irrespective of the technique of cataract surgery, all of the 120 subjects (100%) were in grade 0 preoperatively, while at postoperative 1 week, only 8 patients (6.7%) had grade 0, 3 patients (2.5%) had grade 1, and 109 (90.8%) had grade 2 dry eye. At 1 month follow-up, 105 patients (87.5) had grade 0, 14 (11.7%) had grade 1, and only 1 (0.8%) had grade 2 dry eye according to the OSDI scale.

When comparing OSDI grade among the patients according to cataract surgery technique, all 64 (100%) of the patients who underwent phacoemulsification and 56 (100%) patients who underwent SICS had grade 0 dry eye preoperatively. At postoperative 1 week, 89.1% of the phacoemulsification group had grade 2 dry eye (p<0.001) and 92.9% of the SICS group had grade 2 dry eye (p<0.001). At 1-month follow-up, 92.2% of the phacoemulsification group had grade 0 and the other 7.8% had grade 1 dry eye. None of the patients had grade 3 dry eye at 1 month and the results were statistically significant (p<0.001). Of the 56 patients who underwent SICS, 82.1% had grade 0, 16.1% had grade 1, and only 1.8% had grade 2 dry eye at postoperative 1 month and the results were statistically significant (p<0.001) (Table 5).

Table 2. Presenting symptoms of included patients (n=120)

	n	%
Foreign body sensation	34	28.33
Burning sensation	54	45.00
Discharge from eye	33	27.50
Itching	61	50.83
Lid heaviness	44	36.67
Redness of eyes	47	39.17
Photophobia	67	55.83
Watering	55	45.83
Eye pain	50	41.67

n: Number of eyes

On overall evaluation, the majority of patients (n=65, 54.2%) had microscope exposure time within 10-15 minimum (min), followed by 16-20 min (n=34, 28.3%), 21-25 min (n=11, 9.2%), and 26-30 min (n=10, 8.3%). In the phacoemulsification group, most patients (n=53, 82.8%) had microscope exposure time of 10-15 min, followed by 16-20 min (n=10, 15.6%), and 21-25 min (n=1, 1.6%). However, in the SICS group, the most frequent microscope exposure time was 16-20 min (n=24, 42.9%), followed by 10-15 min (n=12, 21.4%), and 21-25 and 26-30 min (n=10, 17.9% each).

On overall evaluation as well as among patients undergoing SICS, microscope exposure time did not show a significant association with the incidence of dry eye at postoperative 1 week or 1 month. However, in the phacoemulsification group, exposure time >15 min was found to be significantly associated with an increased risk of dry eye at 1 week (p=0.009) (Table 6).

Among phacoemulsification cases, the majority (n=33, 51.6%) underwent the procedure with 8.0-11.5% CDE, followed by 11.6-15.5% (37.5%) and 15.6-19.0% CDE (10.9%). On evaluating the relationship between CDE and incidence of dry eye at 1 week and 1 month, the association was not found to be significant (Table 7).

On looking for the pattern of change in values of different dry eye parameters from baseline at 1 week and 1 month, we observed a significant decline in mean Schirmer's test and TBUT values at 1 week compared to baseline; however, by 1 month the change from baseline was not statistically significant. In LG staining, the proportion of those having scores of 3 and 4 was significantly higher at 1 week but returned to baseline by 1 month.

Mean OSDI values were 6.48±2.61 at baseline and reached 25.98±5.34 at 1 week and 10.53±4.99 at 1 month. The change from baseline was statistically significant at both follow-ups. Compared to baseline, when all patients had OSDI grade 0, the proportion of patients having OSDI grades 2 and 3 was significantly higher at 1 week and the proportion having grades 1 and 2 was significantly higher at 1 month (Table 8).

Table 3. Clinical assessment (for dry eye-related tests) preoperatively and at postoperative 1 week and 1 month

	Preoperative n (%)	**Postop 1 week n (%)**	**Postop 1 month n (%)**
Schirmer's test, mean ± SD (range) ≥15 mm, normal 9-14 mm, mild 4-8 mm, moderate <4 mm, severe	27.23±4.38 (15-35) 120 (100%) - - -	24.61±6.32 (12-35) 100 (83.3%) 20 (16.7%) - -	12.91±2.95 (8-24) 15 (12.5%) 103 (85.8%) 2 (1.7%) -
TBUT, mean ± SD (range) >10 s, normal 6.1-10 s, fair 3.1-6 s, moderate <3 s, poor	13.50±1.89 (10-18) 120 (100%) - - -	13.16±2.45 (8-18) 97 (80.8%) 23 (19.2%) - -	9.64±2.20 (5-16) 37 (30.8%) 78 (65.0%) 5 (4.2%) -
Lissamine green staining of cornea/conjunctiva score, mean ± SD (range) 1 2 3 4	1.34±0.48 (1-2) 79 (65.8%) 41 (34.2%) - -	3.10±0.72 (1-4) 3 (2.5%) 16 (13.3%) 67 (55.8%) 34 (28.3%)	1.60±0.75 (1-3) 67 (55.8%) 34 (28.3%) 19 (15.8%) -
OSDI, mean ± SD (range) 0-12, normal 13-22, mild 23-32, moderate 33-100, severe	6.48±2.61 (1-12) 120 (100%) - - -	11.96±7.47 (1-30) 95 (79.2%) 23 (19.2%) 2 (1.7%) -	25.97±5.34 (10-33) 10 (8.3%) 103 (85.8%) 7 (5.8%) -

Postop: Postoperative, n: Number of eyes, SD: Standard deviation, TBUT: Tear film break-up time, OSDI: Ocular Surface Disease Index

Table 4. Comparison of dry eye incidence at postoperative 1 week and 1 month between phacoemulsification and small-incision cataract surgery groups

Surgical technique	**n**	**%**	**Dry eye at 1 week**	**Dry eye at 1 month**
Phacoemulsification	64	53.33	57 (89.1%)	10 (15.6%)
SICS	56	46.67	52 (92.9%)	15 (26.8%)
Significance of difference			χ^2=0.517; p=0.472	χ^2=2.256; p=0.133

n: Number of eyes, SICS: Small-incision cataract surgery

Table 5. Comparison of Ocular Surface Disease Index grade preoperatively and at postoperative 1 week and 1 month (Wilcoxon Signed Rank test)

	OSDI grade 0		OSDI grade 1		OSDI grade 2		Change from preop OSDI grade	
	n	%	n	%	n	%	Z	p
Overall (n=120)								
Preop	120	100.0	0	0.0	0	0.0	-	-
Postop 1 week	8	6.7	3	2.5	109	90.8	10.450	<0.001
Postop 1 month	105	87.5	14	11.7	1	0.8	3.771	<0.001
Phacoemulsification (n=64)								
Preop	64	100.0	0	0.0	0	0.0	-	-
Postop 1 week	5	7.8	2	3.1	57	89.1	7.562	<0.001
Postop 1 month	59	92.2	5	7.8	0	0.0	2.236	<0.001
Small-incision cataract surgery (n=56)								
Preop	56	100.0	0	0.0	0	0.0	-	-
Postop 1 week	3	5.4	1	1.8	52	92.9	7.216	<0.001
Postop 1 month	46	82.1	9	16.1	1	1.8	3.051	<0.001

OSDI: Ocular Surface Disease Index, n: Number of eyes, Preop: Preoperative, Postop: Postoperative

Table 6. Association of microscope exposure time with dry eye at 1 week and 1 month after cataract surgery

Time	n	Dry eye at 1 week	Dry eye at 1 month
Overall (n=120)			
10-15 min	65	59 (90.8%)	13 (20.0%)
16-20 min	34	32 (94.1%)	8 (23.5%)
21-25 min	11	10 (90.9%)	2 (18.2%)
26-30 min	10	8 (80.0%)	2 (20.0%)
Statistical significance		$\chi2$=1.850, p=0.604	$\chi2$=0.228, p=0.973
Phacoemulsification (n=64)			
10-15 min	53	47 (88.7%)	8 (15.1%)
16-20 min	10	10 (100%)	2 (20.0%)
21-25 min	1	0	0
26-30 min	-	-	-
Statistical significance		$\chi2$=9.379, p=0.009	$\chi2$=0.342, p=0.843
Small-incision cataract surgery (n=56)			
10-15 min	12	12 (100%)	5 (41.7%)
16-20 min	24	22 (91.7%)	6 (25.0%)
21-25 min	10	10 (100%)	2 (20.0%)
26-30 min	10	8 (80%)	2 (20.0%)
Statistical significance		$\chi2$=4.236, p=0.237	$\chi2$=1.864, p=0.601

n: Number of eyes

Discussion

Cataract surgery is perhaps one of the most frequently performed ophthalmic procedures.[19] However, like any other surgery, it is not free from post-operative complications. The most common complications are postoperative inflammatory reaction, increase in intraocular pressure, cystoid macular edema, and significant post-operative astigmatism. Along with these complications, the patients also complain of dry eye symptoms of grittiness, foreign body sensation, and burning sensation, which are commonly overlooked.

Table 7. Relationship between cumulative dissipated energy (%) and dry eye (only phacoemulsification cases, n=64)			
Energy used (%)	**Number of eyes**	**Dry eye at 1 week**	**Dry eye at 1 month**
8.0-11.5	33	27 (81.8%)	2 (3.6%)
11.6-15.5	24	24 (100%)	6 (25.0%)
15.6-19.0	7	6 (85.7%)	2 (28.6%)
Statistical significance		$\chi 2$=3.562, p=0.468	$\chi 2$=4.780, p=0.092

Table 8. Changes from baseline (preoperative values) in different clinical parameters at postoperative 1 week and 1 month (n=120)			
	Preop	**Postop 1 week**	**Postop 1 month**
Mean Schirmer's test ± SD (mm)	27.22±4.40	12.91±2.95	24.61±6.32
	Paired "t"-test	"t"=14.308, p<0.001	"t"=4.778, p<0.01
Mean TBUT ± SD (s)	13.50±1.89	9.64±2.20	13.16±2.45
	Paired "t"-test	"t"=17.128, p<0.001	"t"=1.368, p=0.174
Lissamine green staining of cornea/ conjunctiva 0 1 2 3 4	 0 79 (65.8%) 41 (34.2%) 0 0	 0 3 (2.5%) 16 (13.3%) 67 (55.8%) 34 (28.3%)	 0 67 (55.8%) 34 (28.3%) 19 (15.8%) 0
	WSR test	z=9.405, p<0.001	z=3.963, p<0.001
Mean OSDI ± SD	6.48±2.61	25.98±5.34	10.53±4.99
	Paired "t"-test	"t"=34.121, p<0.001	"t"=8.24, p<0.001
OSDI Grades 0 1 2 3	 120 (100%) 0 0 0	 10 (8.3%) 0 103 (85.8%) 7 (5.8%)	 95 (79.2%) 23 (19.2%) 2 (1.7%) 0
	WSR test	z=10.194; p<0.001	z=4.838; p<0.001
Preop: Preoperative, Postop: Postoperative, SD: Standard deviation, TBUT: Tear film break-up time, OSDI: Ocular Surface Disease Index			

Dry eye following cataract surgery has been shown to have a high variability in its incidence, ranging from 9.8 to 96.6.[20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65] The incidence of dry eye among patients undergoing cataract surgery has been shown to be dependent on a host of factors including the type of procedure (SICS/phacoemulsification), type of ophthalmic solution used, intra- and postoperative medications, coexistent systemic disorders, operating microscope exposure time, CDE during phacoemulsification, and time since surgery. But none of them have been confirmed to be individually responsible for causing dry eye.

Hence to study the incidence of dry eye and its determinants in patients undergoing cataract surgery we enrolled 120 patients who were scheduled to undergo unilateral cataract surgery. The mean age of the patients was 59.25±9.77 years, a finding consistent with a study conducted by Dodia et al.[59] in which the mean age of the patients was 60.35 years. However, the majority of patients in our study were males (60.83%), in contrast to previous studies in which the majority of patients were females.[57,13,60,62] This is probably due to estrogen changes related with menopause which results in higher risk of age-related cataract among females as compared to males.[66,67] With respect to domicile and occupational profile of patients, most studies did not report on this aspect. In our study, homemakers (35%) and farmers (27.5%) comprised the most dominant occupational groups. We feel that considering differences in sanitary conditions and environment, place of residence and occupation could have a role in affecting the dry eye prevalence at 1-month follow-up, when patients have resumed their activities of daily living.[68,69,70]

Nearly all of the patients in our study had BMI in normal range (18.5-24.9 kg/m^2) (95%) and remaining 5% of patients were in the overweight category (BMI 25-29.9 kg/m^2). Although no significant associations have been reported between DED and BMI in past, this patient characteristic was included in

our assessment as BMI is known to have association with various systemic illnesses, which in turn might have a contributing role in the development of dry eye following cataract surgery.

Preoperatively, the majority of patients had complaints of photophobia (55.83%) and itching (50.83%). On average, each patient had 3.7 symptoms from amongst foreign body sensation, burning sensation, discharge from eye, itching, lid heaviness, redness of eye, photophobia, watering, and eye pain. None of the previous studies reports any assessment of preoperative symptoms. These symptoms were recorded and analyzed using OSDI grading, which showed all of them to be within the normal limits of dry eye severity grading preoperatively. This was corroborated, as all the patients had dry eye parameters (Schirmer's test, TBUT, lissamine green staining, and OSDI) within the normal range when these investigations were conducted.

In our study, both phacoemulsification and SICS procedures were taken into account in order to assess the impact of the type of surgery on dry eye incidence. Phacoemulsification accounted for 53.33% and SICS 46.67% of the operations in our study. Few studies have included both SICS and phacoemulsification cases.[60,61,71]

At 1 week after surgery, Schirmer's test, TBUT, and OSDI findings suggestive of dry eye were seen in 87.5%, 69.2%, and 91.7% of the patients, respectively. For the purposes of the present study, we accepted OSDI-evaluated dry eye as representing dry eye. Thus, the prevalence of dry eye was 91.7% in the present study. The reported prevalence of dry eye varies considerably in different studies, which might be dependent on various determinants as well as methods of evaluating dry eye. In the present study, we could see that while TBUT criteria detected dry eye in 69.2% of the patients, OSDI resulted in 91.7% prevalence of dry eye, thus increasing the prevalence by 1.33 times.

A considerable difference in the incidence of dry eye can be seen in different studies. Kasetsuwan et al.[20] conducted their study that followed up patients at days 0, 7, 30 and 90, and reported that the severity of dry eye peaked at postoperative 7 days. Venugopal et al.[58] on the other hand, evaluated data for patients from postoperative weeks 2 through 6 in 58.8% of their study population and from 6 weeks to 2 years in remaining 41.2% of their patients. Dodia et al.[59] evaluated dry eye incidence at postoperative day 1, 7, and 45 and reported the peak incidence at day 1. Interestingly, most of the studies did not conduct any preoperative assessment for dry eye, and hence it was difficult to assess whether the dry eye incidence reported in the study was a continuation of preexisting dry eye syndrome or was a response to cataract surgery. In their study following patients for up to 2 years after cataract surgery, Venugopal et al.[58] did not report the environmental and occupational risk and evaluated dry eye incidence as an outcome of cataract surgery without having any baseline data. In another study, Cetinkaya et al.[64] made assessments for up to 2 years but had neither preoperative data nor data related to environmental and occupational risk factors. Moreover, most previous studies did not assess symptomatic risk factors for dry eye. The relatively higher burden of dry eye incidence in our study could be due to the fact that the study population had more than 3 symptomatic risk factors on average even before cataract surgery, and they could have influenced the incidence of dry eye since it is one of the most common comorbid conditions associated with cataract.[24]

In the present study, we also made a detailed assessment of different risk factors and then evaluated their impact on dry eye incidence, but we failed to find any association between age, gender, place of residence, occupation, BMI, or type of surgery (SICS/phacoemulsification) and the incidence of dry eye at postoperative 7 days and 1 month, similar to Venugopal et al.[58]

In the present study, we also evaluated the effect of microscope exposure time on dry eye incidence. We determined that overall and in patients undergoing SICS, microscope exposure time was not significantly associated with the incidence of dry eye at 1-week or 1-month follow-up. However, in the phacoemulsification group, exposure time >15 min was found to be significantly associated with an increased risk of dry eye at first follow-up. Prolonged microscope light exposure time has been correlated with reduced TBUT and temporarily worsened symptoms.[33] In the present study, we did not find a significant association between CDE and incidence of dry eye at 1 week or 1 month among patients undergoing phacoemulsification. This is consistent with observations made by Sahu et al.,[13] Rizvi et al.,[61] and Sengupta and Banerji[68] who also detected no significant difference between the phacoemulsification and SICS groups, similar to the findings of present study. Yu et al.[63] also reported that type of surgery did not have an impact on dry eye incidence.

In the present study, nearly all the dry eye tests indicated mild dry eye (for OSDI and Schirmer's: 85.8% mild, TBUT: 65% moderate). Similarly, most previous studies also reported a predominance of mild dry eye (53.32% by Venugopal[58] and 58.06% by Manjula et al.[73]). However, Jayashree et al.[72] reported a predominance of severe dry eye.

At postoperative 1 month, the incidence of dry eye as per Schirmer's test, TBUT, and OSDI was 16.7%, 19.2% and 20.8%, respectively. Compared to 1-week follow-up, there was a significant change at 1 month. As far as pattern of change in different dry eye parameters was concerned, we observed that mean Schirmer's test result was 27.22±4.40 preoperatively and 12.91±2.95 and 24.61±6.32 mm at postoperative 1 week and 1 month, respectively. At the same time points, mean TBUT was 13.50±1.89, 9.64±2.20, and 13.16±2.45 seconds, respectively, and the proportion of patients with lissamine green staining scores of 2 or higher was 34.2%, 97.5%, and 44.2%, respectively. In general, as compared to preoperative assessment, all of the values peaked at 1 week and then tended to decline by the end of 1 month. However, none of these parameters returned to baseline even at 1-month follow-up. These findings indicate that the peak impact of cataract surgery in terms of dry eye was during the first week and tended to decline thereafter.

Similar to our findings, Kasetsuwan et al.[20] also observed that severity of dry eye peaked 7 days after cataract surgery as measured by OSDI questionnaire and clinical tests which showed

rapid and gradual improvements within 1 and 3 months post-surgery. This was similar to observations made by Sahu et al.,[13] who found a deterioration in the Schirmer's test I, tear meniscus height, TBUT, and lissamine green staining of the cornea and conjunctiva following phacoemulsification surgery which started improving after 1 month. They reported that despite the improvements observed at 1 month, as observed in the present study, preoperative values were not achieved until 2 months after surgery. The majority of researchers observe the impact of cataract surgery to be a transient one and recoverable within 3 to 6 months.[59,60,61,64,71]

The findings of the present study indicated that there is a high incidence of dry eye following cataract surgery. This may be due to corneal nerve transection, which results in impaired epithelial wound healing, increased permeability, decreased epithelial metabolic activity, and loss of cytoskeletal structures leading to decreased corneal sensitivity with subsequent reduction in tear production, as found by Sutu et al.[25] Elevation of inflammatory response leading to recruitment of neutrophils and macrophages and production of free radicals, proteolytic enzymes, and cyclooxygenase is also considered to be a key factor in the development of dry eye. Topical anesthetics and pre- and postoperative preservative-containing eye drops also contribute to the inflammatory reaction.

Conclusion

The findings of the present study showed that incidence of dry eye after cataract surgery was quite high, irrespective and nearly independent of variables such as demographic and anthropometric profile, type of surgical procedure, microscope exposure time and amount of energy used. The trends showed that this dryness was transient in nature and tended toward normalization at the end of 1 month. Due to the limited follow-up time of the study, we could not ascertain when all the patients returned to normal. Further studies with longer duration of follow-up targeted to assess time taken to attain normal status are recommended. Moreover, long-term residual dry eye following cataract surgery also needs to be investigated.

Thus, dry eye is seen to be a common complaint post-cataract surgery that significantly affects patient satisfaction despite excellent visual recovery and needs to be addressed. In light of the high incidence of dry eye following cataract surgery, we recommend the use of an appropriate lubricating agent during postoperative recovery for 2 to 3 months after cataract surgery in order to avoid dry eye-related complications following surgery and provide symptomatic relief to patients.

Ethics

Ethics Committee Approval: The study was conducted after ethical approval by the institutional ethics committee in accordance with international agreements and the Declaration of Helsinki.

Informed Consent: Informed and written consent was obtained from all the subjects included in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.G., A.G., N.T., P.R., Concept: P.G., A.G., N.T., P.R., Design: P.G., A.G., N.T., P.R., Data Collection or Processing: P.G., A.G., N.T., P.R., Analysis or Interpretation: P.G., A.G., N.T., P.R., Literature Search: P.G., A.G., N.T., P.R., Writing: P.G., A.G., N.T., P.R.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.49204
Turk J Ophthalmol 2020;50:143-150

Original Article

The Role of Heredity and the Prevalence of Strabismus in Families with Accommodative, Partial Accommodative, and Infantile Esotropia

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Abstract

Objectives: To investigate the prevalence of strabismus in families of a proband with accommodative, partial accommodative, or infantile esotropia, and to evaluate the mode of inheritance and the role of consanguineous marriages in this prevalence.

Materials and Methods: Families of probands with comitant strabismus were invited to participate in the study. The family members of 139 subjects with accommodative, 55 with partial accommodative, and 21 with infantile esotropia agreed to participate. Detailed family trees were constructed. The first- and second-degree relatives were invited for a complete ophthalmological examination, and 518 individuals from 168 families were evaluated. The role of consanguinity, the presence of tropia, phoria (≥8 PD), microtropia, and hypermetropia (≥3.00 D) among first- and second-degree relatives were analyzed.

Results: A non-Mendelian pattern was found in 49 families (23%), an autosomal dominant pattern in 39 families (18%), and an autosomal recessive pattern in 6 families (3%). The prevalence of consanguineous marriages among parents of probands was 18.1%, 22.6%, and 14.3% in the accommodative, partial accommodative, and infantile esotropia groups, respectively (p=0.652). The prevalence of strabismus in first-degree relatives was 58.9%, 45.5%, and 38.1%, respectively (p=0.07). The prevalence of microtropia in probands' siblings was significantly higher in the accommodative esotropia group (p=0.034).

Conclusion: Sporadic cases and non-Mendelian inheritance were more frequent than autosomal recessive inheritance. Autosomal recessive inheritance was found not to be frequent in consanguineous marriages. The prevalence of strabismus and microtropia was significantly higher in families of esotropia cases than in the general population.

Keywords: Strabismus, genetics, esotropia, inheritance

Introduction

Comitant strabismus is a multifactorial disease with genetic and environmental components, in which the influence of environmental factors appears dependent on genetic susceptibility.[1,2,3] The increased risk of strabismus among those with a family history of the condition has been known since the time of Hippocrates (470-360 BC), 2400 years ago.[4,5] Although the strabismus rate in the general population is 2%-6%, several

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Received: 22.09.2019 **Accepted:** 27.11.2019

Cite this article as: Çorak Eroğlu F, Oto S, Şahin Fİ, Terzi Y, Kaya ÖÖ, Tekindal MA. The Role of Heredity and the Prevalence of Strabismus in Families with Accommodative, Partial Accommodative, and Infantile Esotropia. Turk J Ophthalmol. 2020;50:143-150

studies found that this rate varies from 13%-65% among families of affected individuals.[1,6,7,8,9,10] Parikh et al.[11] reported that having a first-degree relative with strabismus led to a 3-5-fold increase in the risk of developing the same condition, while investigation of a cohort of 7100 strabismus patients in 12 studies revealed that 30.6% of strabismic probands had a close relative with strabismus.[6]

Numerous modes of inheritance have been suggested for comitant strabismus, but none has been proven.[9,12,13,14] Maumenee et al.[7] suggested an autosomal recessive inheritance pattern for 173 pedigrees with infantile esotropia (IET), involving a total of 1589 family members. However, computer segregation analysis by the authors was most compatible with the presence of codominant genes. They therefore proposed that the disease best fitted a model of either multifactorial inheritance or codominant genes with incomplete penetrance.

Previous studies have assessed inheritance in comitant strabismus by performing genome-wide linkage scans and revealing a number of susceptibility loci.[11,15,16] The present study evaluated the prevalence of strabismus in families with IET, partial accommodative esotropia (PAET), and accommodative esotropia (AET), with the aim of determining the mode of inheritance and the role of consanguinity in the heritability of different types of esotropia. We also investigated the frequency of coexisting visual impairments and the presence of hypermetropia of ≥+3.00 diopter (D) within these families.

Materials and Methods

Participants

This study was approved by the Başkent University Institutional Review Board and Ethics Committee (project no: KA 09/246) and was supported by Başkent University Research Fund (Ankara/Turkey). Written informed consent was obtained from all patients.

Two different strategies were applied to collect patient data. The first was a retrospective cross-sectional review of the medical records of all patients diagnosed with comitant esotropia at Başkent University Department of Ophthalmology between 1998 and 2010. A total of 215 families of probands agreed to participate in the study: 139 had a proband with AET, 55 with PAET, and 21 with IET. The following exclusion criteria were applied after detailed questioning: prematurity, organic amblyopia, presence of a neurodevelopmental disorder, residence outside the city, and failure to communicate with all members of a given family. A total of 518 individuals from 168 families then underwent ophthalmological examination. These included 116 AET families, 39 PAET families, and 13 IET families.

The second part of the study was conducted prospectively at Başkent University Department of Ophthalmology between June 2010 and August 2011.

Ophthalmic examination

All 518 individuals underwent full ophthalmic examination by the same ophthalmologist (F.C.E.). The presence of deviation was determined using a prism cover test performed at distance and near fixation, with and without correction. The Worth four-dot test at distance, Randot stereopsis test at near, and 4-prism base-out test at distance were performed to evaluate binocular function. All tropias, microtropias, phorias ≥ +3.00 PD, hypermetropias >+3.00 D, and anisometropia were acknowledged as important clinical findings. Anisometropia was defined as unequal refractive error (with a difference in refractive error between the eyes of 2 D or more).

Data Analysis

The parents of probands were interviewed to identify relatives with a history of strabismus, and detailed family trees were constructed. Each set of parents answered questions about the presence of consanguinity, high refractive errors, amblyopia, night blindness, and any other known eye disease among family members. Family trees were interpreted by members of the Department of Genetics and analyzed using Cyrilic 3 pedigree software (AP Benson, London, UK) to determine the mode of inheritance. Data were collected for 3 main aspects: the frequency of consanguinity among parents of probands; the frequency of strabismus among first-, second-, and third-degree relatives; and the frequency of hypermetropia ≥+3.00 D and anisometropia among first-degree relatives.

Statistical Analysis

Categorical variables were statistically evaluated using Pearson's χ^2 test and the likelihood ratio χ^2 test to reveal relationships between the variables; odds ratios were calculated for all risk factors identified. The likelihood ratio test was used because some cells of the contingency tables included values of zero or small frequencies. Data analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL). A p-value less than 0.05 was considered statistically significant.

Results

Demographic properties of the study group are summarized in Table 1. Based on pedigree analysis, no definite mode of inheritance could be assigned to 121 families (56.3%), so the strabismic individuals in these families were considered sporadic cases. A non-Mendelian trait was found in 49 families (23%), an autosomal dominant pattern in 39 families (18%), and an autosomal recessive pattern in 6 families (3%). A sample of autosomal recessive inheritance pedigree pattern with affected 3 generations is shown in Figure 1. First-cousin marriage among parents of the proband was found in 20 subjects (16.5%) in the AET group, 11 (20.0%) in the PAET group, and 1 (4.8%) in the IET group. A history of second-cousin marriage was reported for 3 subjects (2.6%) in the AET group, 2 (2.6%) in the PAET group, and 2 (9.5%) in the IET group. There was no significant relationship between either the frequency (p=0.457) or degree (p=0.125) of cross-cousin (parents are opposite gender siblings) marriage among any of the esotropia subtypes studied. The distribution of consanguinity and established inheritance patterns for various sub-types of esotropia is shown in Figure 2. An autosomal recessive inheritance pattern was detected in 6 families, all of which reported consanguineous marriages;

Table 1. Demographic characteristics of probands and family members who underwent ophthalmic examination

Type of esotropia	Proband			Mother		Father	Siblings				Relatives			
	n				Mean age (years)	n	Mean age (years)	n			Mean age (years)	n			Mean age (years)
	Male	Female	Total	n				Male	Female	Total		Male	Female	Total	
AET	59	57	116	116	8.12±5.3	116	31.1±12.9	55	69	114	9.4±3.8	8	4	12	16.7±6.2
PAET	15	24	39	39	7.1±4.2	39	29.6±11.5	20	17	37	7.9±4.1	2	4	6	13.4±5.9
IET	8	5	13	13	4.9±3.7	13	30.6±14.2	5	7	12	5.7±2.6	2	-	2	13.5

AET: Accommodative esotropia, PAET: Partial accommodative esotropia, IET: Infantile esotropia

however, most consanguineous families displayed a sporadic mode of inheritance. There was no significant relationship between any esotropia subtype and the inheritance pattern suggested by pedigree analysis (p=0.682).

Examination of the pedigrees showed that the prevalence of strabismus in any first-degree relative of the proband was 54% for the group overall, 59% for the AET group, 45.5% for the PAET group, and 38.1% for the IET group. No significant difference was found between the three groups (p=0.077). The likelihood of having one parent with strabismus was 30.6% for the group overall, 35.3% for AET, 20% for PAET, and 28.6% for the IET group (p=0.113). Table 2 presents the prevalence and type of strabismus found parents and probands by ophthalmic examination. Based on ophthalmic examination, no correlation was found between the esotropia subtypes of probands and the prevalence of strabismus in their mothers (p=0.462). Notably, the fathers of 31 probands (26.7%) in the AET group and 5 (12.8%)

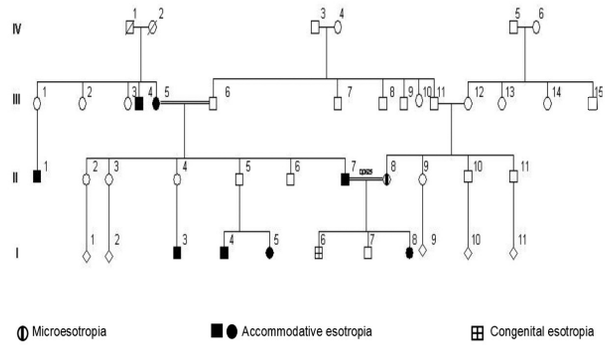

Figure 1. Autosomal recessive inheritance pedigree pattern with 3 affected generations

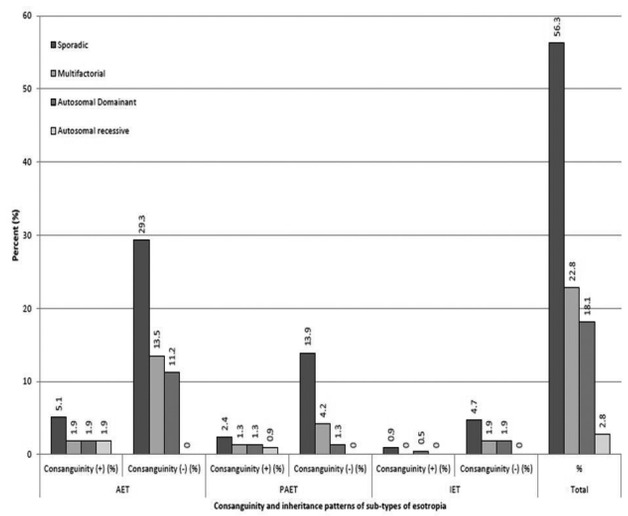

Figure 2. Distribution of consanguinity and inheritance patterns in esotropia subtypes
ET: Esotropia, AET: Accommodative esotropia, PAET: Partial accommodative esotropia, IET: Infantile esotropia,
(+): Presence of consanguinity, (-): Absence of consanguinity

in the PAET group had strabismus, while none of the fathers in the IET group was strabismic. The prevalence of strabismus in fathers was significantly higher in the AET group (p=0.027) compared with other groups. The OR for the increased likelihood of strabismus in AET compared with PAET proband fathers was 2.87 (95% confidence interval [CI]: 1.054-7.820).

Microtropia was the most prevalent deviation seen in mothers among all groups. However there was no significant relationship between the proband esotropia subtype and the type of strabismus in the mother (p=0.974) or the frequency of an esotropia subtype (p=0.914) and microtropia (p=0.852) found in the mother. Similarly, no significant relationship was observed between the esotropia subtype of the proband and the types of tropia (p=0.240) or subtypes of esotropia (p=0.219) observed in the examined fathers. Nonetheless, the frequency of microtropia was significantly higher among the fathers of probands with AET (p=0.046) compared with other groups.

Table 2. Strabismus prevalence and types of strabismus found in parents by physical examination

Type of esotropia		Type of deviation														Total
		AET		IET		XT		MicroET		MicroXT		E		X		
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	
AET	Mother	4	3.4	1	0.9	3	2.6	16	13.7	1	0.9	3	2.6	1	0.9	29/116
	Father	5	4.3	1	0.9	3	2.6	17	14.7	-	-	5	4.3	-	-	31/116
PAET	Mother	1	2.6	-	-	-	-	5	12.8	-	-	-	-	-	-	6/39
	Father	1	2.6	2	5.2	1	2.7	1	2.7	-	-	-	-	-	-	5/39
IET	Mother	-	-	-	-	-	-	3	23.1	-	-	-	-	-	-	3/13
	Father	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/13
Total	Mother	5		1		3		24		1		3		1		38/168
	Father	6		3		4		18		-		5		-		36/168

AET: Accommodative esotropia, PAET: Partial accommodative esotropia, IET: Infantile esotropia, XT: Exotropia, MicroET: Microesotropia, MicroXT: Microexotropia, E: Esophoria, X: Exophoria

Table 3. Characteristics and risk factors assessed in family and population studies

Source	Characteristics of population	Number of the pedigrees (% Incidence)	Included relatives	Inheritance	Significant risk factors
Maumenee et al.[7]	Congenital ET	173 (34.6%)	Third-degree	Autosomal inheritance	-
Richter[12]	ET and XT	697 (29.6%)	Third-degree	Multifactorial etiology	-
Chimonidou et al.[13]	Comitant strabismus	170 (all affected siblings)	First-degree	-	-
Shaaban et al.[16]	ET and XT	55 (100%, each family had to have at least 2 affected members with comitant strabismus)	All available	Non-Mendelian inheritance	-
Chaudhuri et al.[19]	ET and XT	39 (1.7%)	All available	Vertical transmission (maternal side of family)	Family history
Seeley et al.[20]	Familial and sporadic AET	33 familial AET (24.24%)	All available	Autosomal recessive (familial AET)	-
Birch et al.[21]	AET	95 (22% first-, 77% first- and second-degree, 91% any relatives)	All available	-	Family history, Anisometropia
Taira et al.[22]	IET, AET & PAET, IXT	101 (22%) IET, 83 (25%) AET & PAET, 143 (32%) IXT	All available	-	Family history, Anisometropia,
Hu[23]	XT	425 (9% first-, 2.2% second-, and 1.1% third-degree relatives)	Third-degree	-	Family history
Abrahamsson et al.[24]	Population-based	1571 (all had positive family history)	All available	-	Family history
Ziakas et al.[25]	IET, AET, XT	26 (14.9%) in IET, 49 (67.3%) in AET, 6 (4%) in XT	Third-degree	-	Family history (AET group)
Ferreira et al.[26]	Horizontal and vertical deviation	107 (46%)	All available	Autosomal dominant	Family history

AET: Accommodative esotropia, PAET: Partial accommodative esotropia, ET: Esotropia, XT: Exotropia, IXT: Intermittent exotropia

Figure 3 presents the types of strabismus found in affected siblings. The siblings of subjects in the AET group were significantly more likely to have AET (p=0.047) or microtropia (p=0.034) than the other groups. Siblings of those patients with AET were 3.0-fold (95% CI 1.102-7.671) more likely to develop strabismus relative to siblings of those with PAET. The number of affected siblings for each proband was also investigated. In the AET group, 29 probands had a total of 34 affected siblings. One proband had 2 affected siblings and 2 probands had 3 affected siblings. In the PAET group, 6 probands had a total of 8 affected siblings, and 1 proband had 3 affected siblings. In the IET group, 2 probands had 1 affected sibling.

Twenty-five first-degree relatives (1 mother, 5 fathers, 19 siblings) associated with 20 probands in the AET group had ≥3.00 D hypermetropia. In the PAET group, 2 probands had 1 first-degree relative with ≥3.00 D hypermetropia, and in the IET group, the mother of 1 proband had ≥+3.00 D hypermetropia. There was no significant relationship between the frequency of ≥+3.00 D hypermetropia among first-degree relatives and any particular esotropia subtype (p=0.113). Also, we found 9 myopic (4 mothers, 2 fathers, 3 siblings), 7 hypermetropic (2 mothers, 4 siblings), and 2 astigmatic (1 mother and 1 sibling) anisometropia in the AET group. In the PAET group, 3 myopic (2 mothers, 1 sibling) and 1 hypermetropic (1 mother) anisometropia, and in the IET group, the sibling of the 1 proband had hypermetropic anisometropia. Anisometropia was more frequent in mothers of AET and PAET groups but there was no significant relationship between the frequency of anisometropia among first-degree relatives and any particular esotropia subtype (p=0.324).

We also investigated coexisting ocular pathologies found in family members. In the AET group, 2 relatives had degenerative myopia, 1 relative had iridocyclitis, 3 relatives had keratoconus, and 2 relatives had primary open-angle glaucoma. In the PAET group, 1 relative had iridocyclitis and 1 relative had keratoconus. In the IET group, none of examined relatives displayed any comorbidity.

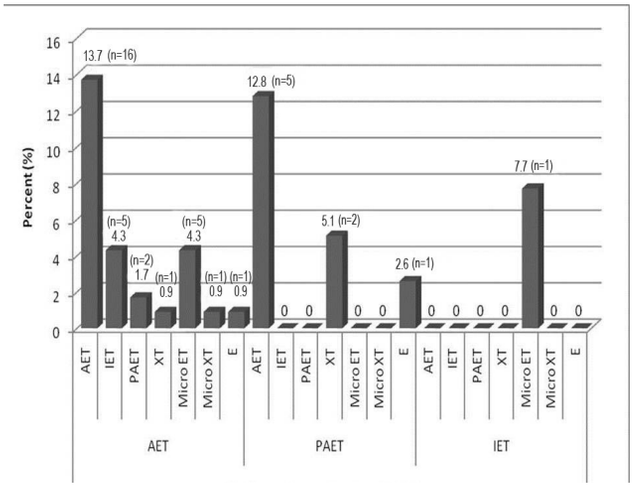

Figure 3. Types of strabismus found in siblings by examination Siblings of subjects in the AET group (p=0.012) were significantly more likely to have AET (p=0.047) or microtropia (p=0.034) than those in other groups

AET: Accommodative esotropia, IET: Infantile esotropia, PAET: Partial accommodative esotropia, XT: Exotropia, MicroET: Microesotropia, MicroXT: Microexotropia, E: Esophoria

Based on the pedigree analysis of 215 strabismus cases included in the study, 43 probands (20.5%) had at least 1 second-degree relative who was strabismic; 54 (25.1%) had 1 third-degree relative with strabismus. There was no significant correlation between any given esotropia subtype and the frequency of strabismus observed among second- (p=0.193) or third-degree relatives (p=0.065).

Discussion

The present study analyzed the roles of heredity and consanguinity in the development of strabismus by studying the frequency of various types of strabismic deviations among the families of the probands. In cases with cross-cousin marriages, multifactorial patterns of inheritance were more frequent than recessive modes of inheritance. Strabismus and microtropia were also significantly more prevalent among first-degree relatives and other family members compared with the general population.

For each esotropia subgroup, most cases (53.2% in the AET group, 63.6% in the PAET group, and 57.1% in the IET group) were sporadic. The pattern of inheritance was not compatible with a Mendelian trait, so the etiology was assumed to be polygenic or multifactorial. An autosomal dominant origin was found in 18.1% of cases. Although the frequency of consanguinity in AET, PAET, and IET groups was 16.5%, 23.6%, and 14.3%, respectively, an autosomal recessive mode of inheritance was only observed in 2.8% of all cases. Each of the autosomal recessive cases observed was associated with a cross-cousin marriage, but the families that included the offspring of a cross-cousin marriage exhibited mainly sporadic or multifactorial inheritance patterns. Articles reporting risk factors including study type, risk factors assessed, inheritance type, and significant findings are summarized in Table 3.[7,12,13,16,19,20,21,22,23,24,25,26] Maconachie et al.[17] made a systematic review of the literature relating to the risk factors and inheritance of comitant strabismus, and reported that most of the studies proposed a polygenic inheritance where genetic and environmental factors are involved. Family studies highlighted difficulties in assessing inheritance patterns for comitant strabismus because the patterns were not compatible with simple Mendelian models.

Bagheri et al.[18] previously investigated the role of consanguinity as a risk factor for developing comitant strabismus. Their study included 461 patients categorized into 4 groups as exotropia (XT), IET, non-accommodative acquired esotropia, and accommodative acquired esotropia. These patients were compared with a control group of 421 healthy children. The rate of first-cousin marriage was 37.7% in the patient group and 23.5% in the control group. Following the calculation of inbreeding coefficients, the authors suggested that patients with non-accommodative acquired esotropia had the highest mean of inbreeding coefficient and recessive form of inheritance had an important role in the etiology of comitant strabismus.

Chaudhuri et al.[19] prospectively evaluated consecutive families with 2 or more affected subjects with comitant horizontal strabismus. These included 18 families with esotropia and 18 families with XT. They found vertical transmission in 76.5% of families with XT and 54.54% of families with esotropia with significant familial concordance, the transmission was from the maternal side of the family.

A study by Richter[12] of 697 probands with either eso- or XT and their available relatives suggested that a multifactorial etiology underlied the inheritance pattern of strabismus. Shaaban et al.[16] analyzed 55 Japanese families in which at least 2 family members had either eso- or exodeviations. The authors concluded that the mode of inheritance was not compatible with conventional Mendelian inheritance. The results of our study are consistent with these two studies because most of our patients also demonstrate a non-Mendelian inheritance pattern.

Seeley et al.[20] examined 48 patients from 33 families with familial AET, and compared 112 family members of these patients with a gender- and age-matched group of 20 AET patients with no known family history. The authors identified a pattern of inheritance in 8 families, of which 75% was autosomal recessive. Comparing the clinical characteristics of familial and non-familial AET patients revealed no difference in terms of refraction, stereopsis, or the likelihood of subsequent strabismus surgery.

Our pedigree analyses showed that 116 probands (54.0%) were related to at least 1 other strabismic individual. The positive rate of family history was 59% in the AET group, 45.5% in the PAET group, and 38.1% in the IET group. We found 1-2 affected family members in 35.1% of families, 3-4 affected members in 15.3% of families, and 5 or more affected members in 3.2% of families. When parents who underwent complete ophthalmic examinations were considered, 40.5% of probands in the AET group, 25.6% in the PAET group, and 23.1% in the IET group had an affected parent.

Birch et al.[21] investigated 95 consecutive patients with esotropia, aged 18-60 months and obtained related data from a total of 2828 blood relatives. Overall, 22% of the study group was found to have 1 affected first-degree relative, 77% had first- and/or second-degree relatives, and 91% had at least 1 affected relative. By contrast, in our patient cohort, the familial occurrence rate of strabismus in first-degree relatives was 46%, while 56% had at least 1 affected relative. Therefore, the prevalence of strabismus in first-degree relatives in our study group was twice that observed by Birch et al.[21], which might reflect the significant consanguinity rate in our study group.

Taira et al.[22] studied a total of 327 Japanese strabismus patients, 101 with IET, 83 with AET or PAET, and 143 with intermittent XT. Each subject was evaluated for background factors such as family history, abnormalities during pregnancy, and any issues associated with delivery. A positive family history was detected in 22% of subjects in the IET group, 25% in AET and PAET groups, and 32% in the intermittent XT group. The positive rate of family history was similar for each type of comitant strabismus.

Mass screening for genetic eye diseases has been performed on more than 700000 people across numerous districts in China to investigate the prevalence and mode of inheritance of major genetic eye diseases. More than 5000 pedigrees with genetic eye diseases were evaluated. Among these, Hu[23] investigated the mode of inheritance of XT in 425 individuals. The familial occurrence rate in first-, second-, and third-degree relatives was 9%, 2.2%, and 1.1%, respectively. Moreover, the prevalence of XT was 0.58% and the heritability was calculated as 81.3%.

In Sweden, Abrahamsson et al.[24] followed 1571 children with a reported family history of strabismus for 6 years from the age of 1 year. They found that a positive family history of strabismus led to a 3-fold increase in the risk of developing strabismus. In cases with 2 strabismic parents, the risk was increased to 7-fold. Ziakas et al.[25] conducted a study on 96 probands with IET, AET, anisometropic esotropia, and XT. A complete 3-generation pedigree was established for each subject. From a total of 2074 family members, 67.3% of 49 cases in the AET group had at least 1 first-degree relative affected with strabismus, although the subtype was not specified; this percentage was significantly higher than in the other three groups.

In our study, the likelihood that a subject had a strabismic sibling was 29.3% in the AET group, 23.1% in the PAET group, and 30.8% in the IET group. Similarly, Richter[12] found that the incidence of strabismus or strabismus-associated ocular anomalies among siblings of an affected proband was 20% if both parents were unaffected, and 30%-40% if one or both parents were affected. Chimonidou et al.[13] examined 345 affected brothers and sisters having comitant strabismus who originated from 170 families. The frequency of congenital strabismus (strabismus within the first year of life) was 42.9% (n=148). Out of 148 patients with congenital strabismus, 42% had a sibling affected at a more advanced age, while the remaining patients were brothers and sisters who developed strabismus at the same age. In 96.5% of siblings, strabismus was concordant. Ferreira et al.[26] ophthalmically evaluated 110 strabismic probands from 107 families and 329 associated relatives, observing a high prevalence of strabismus within each family, although the type of deviation varied between individuals. Almost half (46%) of the families with more than 1 affected individual included both exotropes and esotropes, suggesting an autosomal dominant inheritance pattern.

The frequency of microtropia among proband mothers was 14.7% in the AET group, 12.8% in the PAET group, and 14.7% in the IET group of the present study. This compared with frequencies of 14.7% in the AET group but only 2.7% in the PAET group among proband fathers. The higher prevalence of microtropia in mothers compared with probands fathers may be related with the high prevalence of anisometropia found in proband mothers. Close association between microtropia and anisometropia has been supported by previous studies.[4,8] Cantolino and von Noorden[4] found close associations between microtropia and large-angle strabismus in other family members.

They suggested that because of the high incidence of binocular vision abnormalities observed in family members of microtropia patients, microtropia was not a segregating phenotype but was rather caused by multifactorial inheritance. Scott et al.[8] reported a 7.7% prevalence of primary monofixation syndrome among family members of IET patients, which is higher than the 1% observed for the general population. They suggested that primary monofixation syndrome represents the partial expression of a genotype that codes for esotropia.

In our study, the incidence of hypermetropia ≥+3.00 D was similar for all strabismic subtypes. The frequency of hypermetropia ≥+3.00 D among first-degree relatives was 16.3% in the AET group, 5.2% in the PAET group, and 7.7% in the IET group. Hypermetropia ≥+3.00 D was not found in IET or PAET siblings, but was observed in 11.2% of AET siblings. The frequency of hypermetropia ≥ +3.00 D among first-degree relatives with strabismus differed significantly among groups, at 36.7% for the AET group, 13.3% for the PAET group, and 25% for the IET group. Shah et al.[27] prospectively examined 81 probands with AET and their 115 siblings for the prevalence of amblyogenic risk factors, and found that 14.8% had strabismus and 23.5% had hypermetropia ≥+3.50 D.

Study Limitations

Our study group consists only of a Turkish population without ethnic heterogeneity and having a considerable rate of consanguinity. This increases the statistical power of our investigation of the role of recessive inheritance in strabismus. Additional studies of families with multiple affected members should be conducted to identify the genetic mechanism underlying comitant strabismus.

Conclusion

Although the gene(s) responsible for comitant strabismus remain to be identified, the genetic etiology of this condition is indisputable. The results of our study support the concept that a positive family history significantly increases the risk of a strabismic deviation, which was shown to be independent of refractive error heritability; this was especially true for AET. We also found that the autosomal recessive mode of inheritance was not a frequent pattern of inheritance, even in the presence of consanguinity.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board and Ethics Committee (project no: KA 09/246) and supported by Başkent University Research Fund.

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and intenally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., F.Ç.E., Concept: S.O., Design: S.O., F.İ.Ş., Data Collection or Processing: F.Ç.E., S.O., Analysis or Interpretation: S.O., F.Ç.E., F.İ.Ş., Literature Search: P.G., A.G., N.T., P.R., Writing: F.İ.Ş., Y.T., Ö.Ö.K., M.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.95871
Turk J Ophthalmol 2020;50:151-155

Original Article

Effects of Upper Eyelid Blepharoplasty on Contrast Sensitivity in Dermatochalasis Patients

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Abstract

Objectives: To evaluate the impact of upper eyelid blepharoplasty on contrast sensitivity in dermatochalasis patients.

Materials and Methods: Best corrected visual acuity, ophthalmologic examination, eyelid examination, lash ptosis, contrast sensitivity using sine-wave contrast sensitivity chart, keratometric parameters, and corneal aberrations of 34 eyes of 34 patients who underwent upper eyelid blepharoplasty due to dermatochalasis in our clinic between the years 2014 and 2018 were evaluated preoperatively and at postoperative 3 months.

Results: Twenty-three (68%) of the patients were females and 11 (32%) were males. Mean age was 63.1±7 (52-81) years. Mean best corrected visual acuity was 0.036±0.06 (0-0.15) logMAR preoperatively and postoperatively ($p>0.05$). Contrast sensitivity values of the patients at the frequencies of 1.5, 3, 6, 12, and 18 cycles per degree were 44.38±19.5, 59.03±27.2, 41.44±34.1, 15.15±19.3, and 5.15±4.26 preoperatively and 44.80±20.9, 76.85±33.4, 63.21±46.4, 28.21±31.1, and 10.5±9.5 postoperatively, respectively. The difference between contrast sensitivity values was statistically significant at the frequencies of 3, 6, 12, and 18 cpd ($p=0.005$, $=0.001$, <0.001, and <0.001, respectively). Although lash ptosis of the patients improved significantly after the surgery, there was no correlation between lash ptosis improvement and change in contrast sensitivity ($p>0.05$). Keratometric values and corneal high order aberrations did not change significantly after the surgery ($p>0.05$).

Conclusion: Contrast sensitivity significantly increases after upper eyelid blepharoplasty, especially at higher spatial frequencies which are known to deteriorate due to age-related changes in the lens and retina in older adults. Our results show that blepharoplasty may have additional functional indications for elderly dermatochalasis patients in terms of improving the functions such as performing daily tasks and reading.

Keywords: Blepharoplasty, contrast sensitivity, dermatochalasis, high order aberration, keratometry, pseudoptosis

Introduction

Dermatochalasis is an age-related condition characterized by the development of a fold of excess skin over the upper eyelid with loss of skin elasticity. It is sometimes accompanied by herniation of orbital adipose tissue through the orbital septum, which also weakens with age.[1] The mechanical pressure created by the accumulation of excess adipose and skin over the upper eyelid leads to a feeling of heaviness and narrowing of the peripheral visual field, constituting an indication for surgical treatment.[2,3]

The increase in the visual field after upper eyelid blepharoplasty is known to provide a functional benefit to patients. In addition, Rogers et al.[4] also observed that these patients reported a subjective increase in vision postoperatively. Although the authors did not observe an objective change in refraction tests, they detected improvement in the patients' contrast sensitivity test results. Similar results were also obtained

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Received: 10.03.2019 **Accepted:** 14.11.2019

Cite this article as: Nalcı H, Hoşal MB, Gündüz ÖU. Effects of Upper Eyelid Blepharoplasty on Contrast Sensitivity in Dermatochalasis Patients. Turk J Ophthalmol. 2020;50:151-155

by An et al.[5] and Fowler et al.[6] The exact reason for the postoperative increase in contrast sensitivity is unclear. Proposed explanations include changes in higher-order aberrations (HOA), elimination of the hooding effect created by the eyelids and eyelashes, or changes in corneal topography and keratometry.[5,6,7,8]

The aim of this study was to observe changes in contrast sensitivity in patients who underwent upper eyelid blepharoplasty due to dermatochalasis and to investigate the potential causes of these changes.

Materials and Methods

Patients diagnosed with dermatochalasis between 2014 and 2018 in the oculoplasty unit of the Ankara University Faculty of Medicine, Department of Ophthalmology were examined. Surgery was indicated for patients with a narrowed upper visual field in automated perimetry and for those reporting complaints of visual field narrowing even if they were unable to comply with the test. Patients with an accompanying eyelid condition or history of previous eyelid surgery and those with brow ptosis, dry eye, or any lens, optic nerve, or retinal pathologies were excluded from the study. The study was carried out in accordance with the Declaration of Helsinki and approval was obtained from the Ethics Committee of Ankara University Faculty of Medicine.

All operations were performed by a single surgeon (B. H.). During the procedure, the excess skin tissue overhanging the upper eyelid was excised; adipose tissue excision was not performed in any of the patients. All patients' best corrected visual acuity (measured with Snellen chart and presented in logMAR equivalents), ocular surface examination findings, tear film break-up times, Schirmer's test results, and upper eyelid examination findings were recorded preoperatively and at postoperative 3 months. Upper eyelid lash ptosis was graded by a single physician through clinical examination and photograph analysis. Grading was classified as none (0), mild (1), moderate (2), or severe (3) based on evaluation of lash position relative to the lid margin in primary and lateral positions (Table 1).[5] Keratometric parameters and corneal HOAs were recorded using a Scheimpflug system (Pentacam, Oculus, GmBH, Germany). Contrast sensitivity was measured with a sine-wave contrast test (Stereo Optical Co., Inc., USA) preoperatively and at postoperative 3 months. Using this chart, contrast sensitivity was evaluated at 5 spatial frequencies: 1.5, 3, 6, 12, and 18 cycles per degree (cpd). After correcting refractive errors, the chart was placed at a standard distance (3 meters) in an environment with standard photopic illumination and the patients were asked to indicate the orientation of the stripes in the circles on the chart as tilted left, tilted right, or vertical. The last degree at which the patients responded correct was marked on the contrast sensitivity curve. Descriptive data were expressed as mean ± standard deviation, median, and minimum-maximum values. After testing the normality of the data distribution, differences between pre- and postoperative results were evaluated using Wilcoxon test. The relationship between postoperative changes in independent variables was evaluated with Spearman's correlation coefficient. A p value of <0.05 was regarded as statistically significant.

Table 1. Upper eyelid lash ptosis grading criteria

No lash ptosis (Grade 0)	Position of the lashes relative to the upper lid margin is 0° or above the horizontal.
Mild lash ptosis (Grade 1)	Position of the lashes relative to the upper lid margin is 0° to 30° below the horizontal.
Moderate lash ptosis (Grade 2)	Position of the lashes relative to the upper lid margin is 31° to 45° below the horizontal.
Severe lash ptosis (Grade 3)	Position of the lashes relative to the upper lid margin is more than 45° below the horizontal.

Results

Thirty-four patients were included in the study, 23 (68%) women and 11 (32%) men. The average age was 63.1±7 (51-81) years. The mean best corrected visual acuity both pre- and postoperatively was 0.036±0.06 (0-0.15) logMAR. Mean contrast sensitivity percentage values at the frequencies of 1.5, 3, 6, 12, and 18 cpd were 44.38±19.5, 59.03±27.2, 41.44±34.1, 15.15±19.3, and 5.15±4.26 preoperatively and 44.80±20.9, 76.85±33.4, 63.21±46.4, 28.21±31.1, and 10.5±9.5 at postoperative 3 months, respectively. The difference between pre- and postoperative contrast sensitivity measurements was statistically significant at frequencies of 3, 6, 12, and 18 cpd (Wilcoxon p<0.05) (Figure 1). The median preoperative lash ptosis grade was moderate (Grade 2). Postoperatively, lash ptosis improved by at least 1 grade in 20 patients, and the postoperative median lash ptosis grade was mild (Grade 1). The difference between pre- and postoperative eyelash ptosis grade was statistically significant (Wilcoxon p<0.001). The relationship between postoperative change in lash ptosis and change in contrast sensitivity was evaluated with Spearman's correlation coefficient and no significant relationship was found at any frequency (1.5 cycles per degree [cpd]: rho=0.216, p=0.24; 3 cpd: rho=-0.98, p=0.6; 6 cpd: rho=-0.107, p=0.56; 12 cpd: rho=-0.042, p=0.83, 18 cpd: rho=0.098, p=0.6).

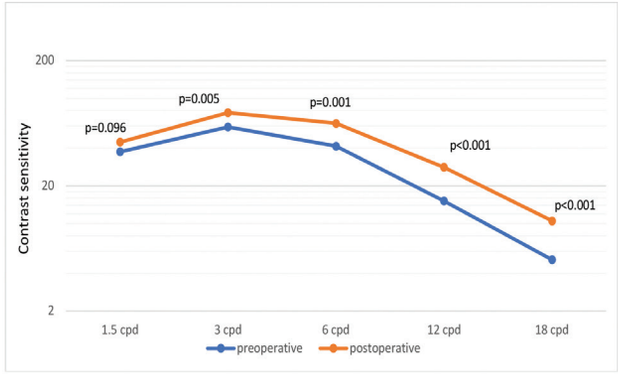

Figure 1. Pre- and postoperative contrast sensitivity values
cpd: cycles per degree

No significant differences were observed between preoperative and postoperative keratometric values, degrees of astigmatism, and corneal HOAs (p>0.05) (Table 2).

Discussion

Spatial contrast refers to the light/dark transition in the edge or corner of an object or pattern. Contrast sensitivity is a measure of the minimum contrast needed to distinguish a pattern. Visual acuity, on the other hand, measures how large an object must be in order to be seen, and the shapes used in these tests are presented at very high contrast levels. Contrast sensitivity defines the limits of visual perception at different spatial frequencies, and is the factor that determines the visual function of patients having equal visual acuity under conditions with reduced contrast between an object and its background, such as in low or bright light or fog.[9,10] Similar to previous literature findings, our results demonstrated a statistically significant increase in patients' contrast sensitivity after upper eyelid blepharoplasty. These results are also consistent with studies in which patients with dermatochalasis reported subjective improvement in contrast sensitivity-related symptoms, such as increased image brightness and comfort in reading and driving, after surgery.[4,5]

In the present study, contrast sensitivity was measured using a sine-wave grating chart, which enabled the evaluation of patients' contrast sensitivity levels at different spatial frequencies. Loss of sensitivity at high frequencies is known to occur in older adults due to age-related changes such as loss of lens transparency and degeneration of rod photoreceptors in the retina.[11,12,13] While the mean contrast sensitivity of our patients was found to be below normal limits, especially at frequencies of 6 and 18 cpd, it returned to within normal range postoperatively. Contrast sensitivity has been shown to be associated with visual functions such as vision, reading, and driving in low-light conditions and has been identified as a significant indicator of functional vision.[10] Therefore, dermatochalasis surgery may have the capacity to partially mitigate the impairment in quality of daily life associated with age-related deterioration of functional vision.

Various mechanisms have been proposed to explain the postoperative increase in contrast sensitivity and visual function. The first is changes in corneal keratometry. There are publications demonstrating changes in corneal astigmatism after levator resection for the treatment of ptosis. This indicates that modifying upper lid position can change corneal refractive power.[14,15] However, studies on the effects of upper eyelid blepharoplasty on keratometric values present varying results. Brown et al.[14] reported a mean change of 0.5 D in the astigmatism of these patients. According to Zinkernagel et al.[15], significant keratometric changes occured after upper eyelid blepharoplasty in patients with severe dermatochalasis who required adipose tissue excision. Şimşek et al.[16] and Altın Ekin et al.[17] observed statistically significant changes in astigmatism after surgery, but reported that this difference did not influence visual acuity levels. Doğan et al.[18] reported that upper eyelid blepharoplasty did not affect keratometric values. Our patients also showed no significant postoperative change in corneal keratometric parameters, and the mean change in astigmatism was 0.06 D. This may be because the operations performed in our clinic did not include adipose tissue excision and there was not a significant change in the pressure exerted by the upper eyelid on the cornea.

Table 2. Pre- and postoperative corneal keratometry and corneal aberration values

	Preoperative (n=34)	**Postoperative (n=34)**	**p value (Wilcoxon)**
Cornea keratometry values (D)			
K1	43.14±1.6	43.25±1.6	0.79
K2	43.95±1.8	44.00±1.8	0.25
Astigmatism	0.82±0.58	0.88±0.56	0.1
Corneal higher-grade aberrations			
Primary horizontal (Z_3^1)	-0.149±0.357	-0.007±0.334	0.8
Primary coma (Z_3^{-1})	0.085±0.989	0.179±0.720	0.18
Horizontal trefoil (Z_3^3)	-0.071±0.599	-0.052±0.561	0.61
Vertical trefoil (Z_3^{-3})	-0.039±0.535	-0.074±0.520	0.38
Primary spherical aberration (Z_4^0)	1.289±0.545	1.236±0.589	0.59
Secondary astigmatism (Z_4^2)	-0.034±0.221	-0.008±0.206	0.51
Oblique secondary astigmatism (Z_4^{-2})	0.006±0.171	0.021±0.200	0.38
Quatrefoil (Z_4^4)	-0.008±0.242	0.013±0.217	0.47
Oblique quatrefoil (Z_4^{-4})	-0.142±0.474	-0.140±0.329	0.27
Secondary horizontal coma (Z_5^1)	0.019±0.111	0.028±0.099	0.43
Secondary vertical coma (Z_5^{-1})	-0.043±0.155	-0.030±0.091	0.09
Secondary spherical aberration (Z_6^0)	-0.024±0.061	0.02±0.076	0.12

Another mechanism proposed as the reason for the increase in contrast sensitivity is the postoperative elimination of the diffraction effect caused by ptotic eyelashes. Kim et al.[7] suggested that the increase in contrast sensitivity after surgery may have been due to the reduction in lash ptosis that they observed. However, they did not statistically evaluate the relationship between lash ptosis and contrast sensitivity changes in their study. In the present study, we also observed lash ptosis improvement of at least one grade in over half of the patients after surgery, but no relationship was detected between the change in lash ptosis and change in contrast sensitivity. Based on these results, reduced lash ptosis alone cannot explain the increase in contrast sensitivity. In addition to the lash effect, allowing more light to enter the eye by eliminating the hooding effect caused by the overhanging skin fold is another proposed mechanism.[4,5]

Change in HOAs is yet another proposed mechanism for the improvement in contrast sensitivity.[7,19] Corneal HOAs are refractive disorders that stem from irregularities in the corneal layer and impair the quality of the retinal image.[20] Dry eye[21], advanced age[22], degenerative diseases such as keratoconus[23], and corneal surgeries that alter corneal curvature[24,25] have an effect on corneal aberrations.[20,21,22,23,24,25] There is little information in the literature about the impact of upper lid and lash position on corneal HOAs. Han et al.[26] showed that excessive skin tissue over the cornea may lead to changes in ocular surface curvature and corneal aberrations, and that lash ptosis may cause an increase in ocular aberrations. Kim et al.[7] observed a decrease in ocular aberrations following dermatochalasis surgery and associated this finding with the improvement in lash ptosis. However, there are few studies on the effect of surgery on ocular aberrations and their relationship with contrast sensitivity. We detected no significant postoperative changes in corneal HOA measurements in this study. In another study published in 2019 by Altin Ekin et al.[17], it was reported that a statistically significant change was detected in corneal HOA values based on measurements made 1 month after upper eyelid blepharoplasty. The discrepancy between their results and ours may arise from a difference in the patients' dermatochalasis grades and the effects of the excess skin over the upper lid on the corneal curvature, or from the difference in the timing of postoperative HOA measurement.

Study Limitations

In addition, the small number of cases, one of the limitations of our study, may have had an effect on statistical significance. Studies including large patient numbers and evaluating corneal and total ocular aberrations and their relationship with both lash ptosis and contrast sensitivity will better clarify these mechanisms.

Conclusion

The results of our study show that there may be an additional, functional indication for upper eyelid blepharoplasty in older patients with dermatochalasis in order to facilitate daily life and activities such as reading. The increase in contrast sensitivity in our patients may be a result of removing the excess skin and lashes that cause hooding and diffraction in the visual axis, but further studies with more patients are needed to determine the relationship between them.

Ethics

Ethics Committee Approval: The study was carried out in accordance with the Declaration of Helsinki and approval was obtained from the Ethics Committee of Ankara University Faculty of Medicine.

Informed Consent: Written informed consent was obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.H., Concept: H.N., M.B.H., Design: H.N., M.B.H., Ö.U.G., Data Collection or Processing: H.N., Analysis or Interpretation: H.N., M.B.H., Ö.U.G., Literature Search: H.N., Writing: H.N., B.H., Ö.U.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.78370
Turk J Ophthalmol 2020;50:156-162

Original Article

Early Results of Stereotactic Radiosurgery in Uveal Melanoma and Risk Factors for Radiation Retinopathy

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Abstract

Objectives: To report treatment results and complications of stereotactic radiosurgery in uveal malignant melanoma and to identify risk factors for development of radiation retinopathy.

Materials and Methods: This was a retrospective study of 36 patients diagnosed with uveal melanoma between 2014 and 2019. Best corrected visual acuity, funduscopic findings, basal tumor diameter and tumor thickness were recorded at baseline and at follow-up visits at 3-month intervals. The response of tumors to stereotactic radiosurgery and complications were determined.

Results: The mean basal diameter of tumor was 10.2 (range: 4.0-19.4, standard deviation [SD]: ±3.3) mm x 9.7 (range: 4.5-18.0, SD: ±3.3), tumor thickness was 5.1 (range: 2.0-11.0, ±2.4) mm at baseline. The mean follow-up period was 17.2 (range: 6-48, SD: ±10.43) months. The mean visual acuity was 0.5 (SD: ±0.3) logMAR before treatment and 0.6 (SD: ±0.3) logMAR after the mean follow-up period. The most common complications after stereotactic radiosurgery were cataract (38.9%) and radiation retinopathy (27.7%). There was a statistically significant relation between radiation retinopathy development and tumor distance from the optic disc (p=0.04). The rate of eye salvage was 83.3% in this study.

Conclusion: Our short-term results show stereotactic radiosurgery was an effective and sustained treatment modality among the other eye conservation therapies.

Keywords: Uveal melanoma, stereotactic radiosurgery, radiation retinopathy

Introduction

Uveal melanoma is the most common primary intraocular tumor in adults. Uveal melanoma usually originates from the choroid (85.0%), followed by the ciliary body (10.0%) and iris (5.0%).[1] In recent years, globe-preserving surgeries have taken the place of enucleation in the treatment of uveal melanoma. In an arm of the Collaborative Ocular Melanoma Study (COMS), the outcomes of patients in the medium tumor group who underwent iodine-125 plaque brachytherapy and enucleation were compared and no significant difference in long-term survival was detected between plaque brachytherapy and enucleation. Melanoma-related mortality rates in the plaque brachytherapy group were reported as 10%, 18%, and 21% at 5, 10, and 12 years, respectively, while these rates were 11%, 17%, and 17%, respectively, in the enucleation group.[3] Depending on the location and size of the tumor, globe-preserving treatment options include laser photocoagulation, transpupillary thermotherapy, radiotherapy, and tumor excision (endoresection or exoresection). Radiotherapy for uveal melanoma

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Received: 01.05.2019 **Accepted:** 14.11.2019

Cite this article as: Özcan G, Gündüz AK, Mirzayev İ, Oysul K, Uysal H. Early Results of Stereotactic Radiosurgery in Uveal Melanoma and Risk Factors for Radiation Retinopathy. Turk J Ophthalmol. 2020;50:156-162

can be delivered as brachytherapy (plaque radiotherapy) or teletherapy (proton beam radiotherapy, stereotactic radiotherapy). Ophthalmic radioactive plaque brachytherapy involves the use of γ-ray-emitting cobalt-60, palladium-103, and iodine-125, in addition to β-particle-emitting ruthenium-106.[4]

In stereotactic radiosurgery (SRS), tumor location is determined by computed tomography (CT) in order to provide the maximum radiation dose to tumor tissue and minimize radiation to healthy tissue. Devices used for SRS include Gamma Knife, linear accelerators (LINAC), and CyberKnife. Gamma Knife has been used as a successful treatment modality for the treatment of uveal melanoma for the past 15 years.[5] CyberKnife is a LINAC-based, image-guided SRS system that uses noninvasive fixation. The method is non-invasive, effective, and has a safer adverse-effect profile compared to Gamma Knife.[6,7] The main reasons we preferred CyberKnife for the treatment of uveal melanoma in our series are that stereotactic surgery causes minimal adverse effects to adjacent tissues and that CyberKnife procedures are covered by government health insurance in Turkey according to the communiqué on healthcare practices. Plaque radiotherapy is not covered by government health insurance.

Radiation retinopathy is a chronic and progressive vasculopathy that causes visual morbidity in patients who receive radiation therapy for malignancies of the globe, orbit, and head and neck region. It was first described by Stallard[8] in 1933. The primary vascular pathology manifests with endothelial cell loss and capillary bed occlusion.[9] The retinopathy that occurs subsequent to this vascular damage can be observed in the macula and the peripapillary region and/or peripheral retina.[10] The most common clinical findings include hard exudates, retinal hemorrhages, microaneurysms, telangiectasia, soft exudates, and retinal or optic disc neovascularization. The onset of radiation retinopathy occurs between 6 months and 3 years after radiation therapy.[11] Attempts have been made in the past to treat radiation retinopathy with laser photocoagulation, hyperbaric oxygen therapy, pentoxifylline therapy, and photodynamic therapy.[12,13,14] Vascular endothelial growth factor (VEGF) and other inflammatory and vasculogenic factors play a role in the pathogenesis of macular edema and neovascularization.[15] For this reason, the use of anti-VEGF agents has come to the fore in the treatment of radiation-related macular edema, neovascularization, and papillopathy.

The aim of this study was to determine the early treatment outcomes and adverse effects of SRS and identify risk factors for radiation retinopathy in patients with uveal melanoma.

Materials and Methods

Ethics committee approval required for the study was obtained from the Clinical Research Ethics Committee of the Ankara University Faculty of Medicine, and the study adhered to criteria of the Declaration of Helsinki. Thirty-six patients who were diagnosed with uveal melanoma and underwent single-fraction SRS with a single dose of 21 gray (Gy) were retrospectively analyzed. Best corrected visual acuity, intraocular pressure (IOP), affected side, tumor location and distance from the optic disc and fovea, tumor base diameter and thickness, tumor pigmentation, and presence of orange pigment and subretinal fluid were evaluated. Tumor diameter and thickness were measured using B-mode ultrasonography and the presence of subretinal fluid was recorded. Fluorescein angiography was performed on tumors in the posterior pole region. As per COMS, tumors less than 2.5 mm thick and 5-16 mm in diameter were classified as small, those 2.5-10 mm thick and less than 16 mm in diameter as medium, and those more than 10 mm thick and over 16 mm in diameter as large. Tumor classification was also done according to the American Joint Committee on Cancer (AJCC, 8th Edition) (Table 1).

The CyberKnife radiosurgery procedure started by making thermoplastic masks for patient immobilization. This was followed by T1- and T2-weighted magnetic resonance imaging (MRI) of the orbit. Immediately after standard retrobulbar anesthesia induction, contrast-enhanced CT images with a slice thickness of 1 mm were obtained. MRI and CT images were superimposed and the gross tumor volume (GTV) was delineated. Clinical target volume (CTV) was obtained by adding a 1-mm margin to the GTV. The planning target volume (PTV) was considered equal to CTV. The lens and optic nerve were marked as critical structures. The 70.0% isodose curve was planned as a single 21 Gy fraction covering 95.0% of the PTV. Dose limits for the lens and optic nerve were set to 2 Gy and 7 Gy, respectively, in cases where the tumor was sufficiently

Table 1. 8th Edition AJCC classification of posterior uvea melanoma

Tumor thickness (mm)							
>15	4	4	4	4	4	4	4
12.1-15.0	3	3	3	3	3	4	4
9.1-12.0	3	3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3	1	1	1	1	2	2	4
-	≤3	3.1-6.0	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18.0
-	Largest tumor diameter (mm)						

AJCC: American Joint Committee on Cancer

Table 1 continued

T category	T criteria
T1	Tumor size category 1
T1a	No ciliary body involvement, no extraocular spread
T1b	With ciliary body involvement
T1c	No ciliary body involvement but with extraocular extension ≤5 mm in size
T1d	With ciliary body involvement and extraocular extension ≤5 mm in size
T2	Tumor size category 2
T2a	No ciliary body involvement, no extraocular spread
T2b	With ciliary body involvement
T2c	No ciliary body involvement but with extraocular extension ≤5 mm in size
T2d	With ciliary body involvement and extraocular extension ≤5 mm in size
T3	Tumor size category 3
T3a	No ciliary body involvement, no extraocular spread
T3b	With ciliary body involvement
T3c	No ciliary body involvement but with extraocular extension ≤5 mm in size
T3d	With ciliary body involvement and extraocular extension ≤5 mm in size
T4	Tumor size category 4
T4a	No ciliary body involvement, no extraocular spread
T4b	With ciliary body involvement
T4c	No ciliary body involvement but with extraocular extension ≤5 mm in size
T4d	With ciliary body involvement and extraocular extension ≤5 mm in size
T4e	Tumor of any size with extraocular extension >5 mm
N category	N criteria
N0	No lymph node metastasis
N1	With regional lymph node metastasis or separate tumor focus in the orbit
N1a	With regional lymph node metastasis
N1b	No regional lymph node metastasis but with separate tumor focus in the orbit that is not contiguous to the eye
M category	M criteria
M0	No distant metastasis
M1	With distant metastasis
M1a	Largest diameter of the largest metastasis ≤3 mm
M1b	Largest diameter of the largest metastasis 3.1-8.0 mm
M1c	Largest diameter of the largest metastasis ≥8.1 mm

far from the lens and optic nerve. For lesions directly adjacent to the lens or optic nerve, a dose limit was not set for the lens, but it was ensured that the optic nerve received a dose below 12 Gy. The procedure was performed using the CyberKnife device (CyberKnife® MultiPlan® Treatment Planning System, Accuray Incorporated, Sunnyvale, California, USA) (Figure 1).

The patients were examined 1 week after SRS and at 3-month intervals afterwards. Visual acuity, IOP, and fundoscopic examination findings were recorded. Tumor diameter and thickness were measured by B-mode ultrasonography at each visit. Optical coherence tomography (OCT), OCT angiography (OCTA), and fundus fluorescein angiography (FFA) were performed to detect and monitor radiation retinopathy.

The obtained data were analyzed using SPSS (Statistical Package for the Social Sciences) for Windows 15 package software. Descriptive statistics were expressed as mean ± standard deviation (SD) for normally distributed variables and as median (minimum-maximum) for non-normally distributed variables; nominal variables were presented as frequency and percentage. For comparisons between two groups, a t-test was used to evaluate the significance of the differences in means and the Mann-Whitney U test was to evaluate differences in median values. For comparisons between more than two groups, differences in means were evaluated with analysis of variance and differences in median values were evaluated with the Kruskal-Wallis test. The relationship between continuous variables was investigated using Spearman's correlation coefficient if nonnormally distributed and with Pearson's correlation coefficient if normally distributed. Results with $p<0.05$ were regarded as statistically significant.

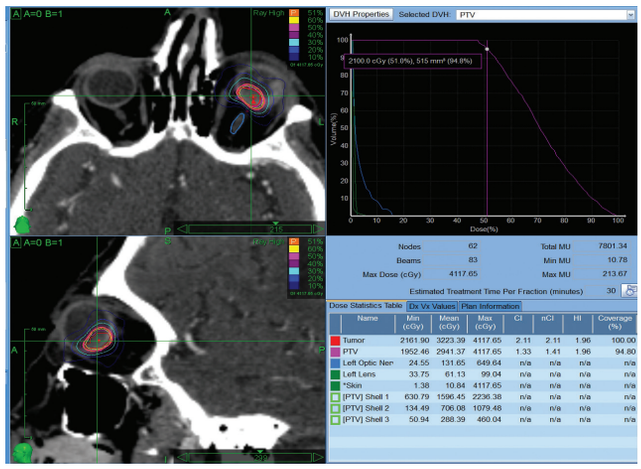

Figure 1. Planning Stereotactic Radiosurgery: Fusion of cranial MRI and cranial CT images of a patient with uveal melanoma in the left eye was performed using the Multiplan (Multiplan® Accuray Incorporated, Sunnyvale, California, USA) contouring software. Using the fused images, PTV was created by adding a 1-mm margin to the tumor. Non-isocentric, non-coplanar planning was done. Dose limits set for the optic nerve and lens were 7 Gy and 3 Gy, respectively. After planning, a 21-Gy treatment was performed with coverage of 100.0% of the tumor and 95.0% of the PTV. The CI was 1.31. The maximum dose to the optic nerve was 6.49 Gy and to the lens was 0.99 Gy

MRI: Magnetic resonance imaging, CT: Computed tomography, CI: Conformity index, PTV: Planning target volume, Gy: Gray

Results

Twenty-three (63.9%) of the patients were men and 13 (36.1%) were women. The mean age at diagnosis was 60.5 (range: 28-86, SD): ±14.8) years. In terms of tumor location, 28 tumors (77.8%) were choroidal, 7 (19.4) were ciliochoroidal, and 1 (2.8%) was iridociliochoroidal. Nine (25.0%) of the tumors were amelanotic and 25 (69.4%) had subretinal fluid. The most common tumor location was the temporal macular region. Mean distance from the optic disc was 3.9 (range: 0.0-14.0 mm, SD: ±3.4) mm and mean distance from the fovea was 3.2 (range: 0.0-9.5, SD: ±3.2) mm. The best corrected visual acuity at baseline was 0.5 (SD: ±0.3) logMAR (Table 2). On ultrasonography, uvea melanomas appeared as a dome- or mushroom-shaped, low- to mid-reflective mass. On FFA, the lesion appeared hyperfluorescent starting in the late venous phase. This hyperfluorescence increased in the late phases and appeared as leakage from the lesion surface (Figure 2).

Table 2. Characteristics of patients with uveal melanoma

Uveal melanoma	Number n=36 (%), (range, ±SD)
Gender	
Male	23 (63.9%)
Female	13 (36.1%)
Mean age (years)	60.5 (28-86, ±14.8)
Mean follow-up time (months)	17.2 (6-48, ±10.43)
Location	
Choroidal	28 (77.8%)
Ciliochoroidal	7 (19.4%)
Iridociliochoroidal	1 (2.8%)
Mean distance from papilla (mm)	3.92 (0-14.0, ±3.4)
Mean distance from fovea (mm)	3.2 (0-9.5, ±3.23)
Pigmentation	
Melanotic	27 (75.0%)
Amelanotic	9 (25.0%)
Subretinal fluid	25 (69.4%)
COMS classification	
Small	2 (5.5%)
Medium	31 (86.2%)
Large	3 (8.3%)
TNM classification	
T1aN0M0	4 (11.1%)
T2aN0M0	8 (22.3%)
T2bN0M0	2 (5.5%)
T3aN0M0	15 (41.7%)
T3bN0M0	4 (11.1%)
T4aN0M0	1 (2.8%)
T4bN0M0	2 (5.5%)
Radiation complications	
Cataract	14 (38.9%)
Radiation retinopathy	10 (27.7%)
Radiation papillopathy	3 (8.3%)
Secondary glaucoma	2 (5.6%)
Scleral thinning	1 (2.8%)
Globe salvage	30 (83.3%)

COMS: Collaborative Ocular Melanoma Study

Pre-treatment mean tumor base diameter and mean tumor thickness measured by ultrasonography were 10.2 (range: 4.0-19.4, SD: ±3.3) x 9.7 (range: 4.5-18.0, SD: ±3.3) mm and 5.1 (range: 2.0-11.0, SD: ±2.4) mm, respectively. According to the COMS classification, 31 (86.2%) of the patients had medium tumors, 3 (8.3%) had large tumors, and 2 (5.5%) had small tumors. According to the AJCC TNM classification, 4 cases (11.1%) were T1aN0M0, 8 cases (22.3%) were T2aN0M0, 2 cases (5.5%) were T2bN0M0, 15 cases (41.7%) were T3aN0M0, 4 cases (11.1%) were T3bN0M0, 1 case (2.8%) was T4aN0M0, and 2 cases (5.5%) were T4bN0M0. The mean radiation dose (MRD) applied to the tumors was 2456 cGy (SD: ± 212.6), the MRD to the disc was 164.1 cGY (SD: ± 131.2), and the MRD to the lens was 132.4 cGY (SD: ± 83.5).

The mean follow-up period was 17.2 (range: 6.0-48.0, SD: ±10.4) months. At the end of the mean follow-up, mean tumor base diameter and thickness were 10.8 (range: 4.5-20.0, SD: ±3.6) x 9.8 (range: 4.5-18.0, SD: ±3.1) mm and 5.1 (range: 2.0-11.0, SD: ±2.4) mm, respectively (p=0.001). Best corrected visual acuity at the end of mean follow-up was 0.6 (SD: ±0.3) logMAR (p=0.2). Complications that occurred after SRS included cataract, radiation retinopathy, radiation maculopathy, radiation papillopathy, glaucoma, and scleral thinning. Fourteen patients (38.9%) developed radiation-induced cataract during the follow-up period. The most common cataract type was posterior subcapsular cataract. There was a significant relationship between cataract formation and the dose to the lens during radiosurgery (p=0.04). In 60.0% of patients with cataracts, the tumor was located adjacent to the optic disc.

Ten (27.7%) of the patients developed radiation retinopathy retinopathy based on fundoscopic findings. Macular changes were confirmed with OCT. The mean time to develop radiation

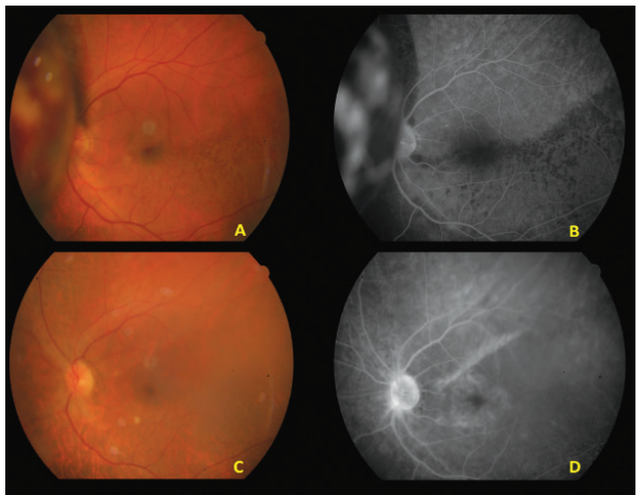

Figure 2. Fundus photograph of a patient with uveal melanoma nasal to the optic disc (A). On fundus fluorescein angiography, leakage over the mass is seen in the late venous phase (B). At 13 months after SRS, fundus photograph shows tumor regression and soft exudates inferior to the fovea (C). In the late venous phase of fluorescein angiography, leakage due to cystoid macular edema and hyperfluorescence of the optic disc due to radiation papillopathy are observed (D)

SRS: Stereotactic radiosurgery

retinopathy was 12 (SD: ±4) months. The relationship between tumor distance from the disc and the development of radiation retinopathy was found to be statistically significant (p=0.001). Development of radiation retinopathy was not significantly associated with MRD to the tumor (p=0.53), tumor thickness (p=0.69), or tumor distance from the fovea (p=0.55). Of the 10 eyes that developed radiation maculopathy, 8 were given anti-VEGF therapy. Five eyes received ranibizumab injections, 2 eyes received aflibercept injections, and 1 eye received bevacizumab injections. The mean number of injections was 8.5 (SD: ±5.7) (Figure 3). The mean visual acuity of the patients treated with intravitreal injections was 0.8 (SD: ±0.1) logMAR pre-treatment and 0.6 (SD: ±0.1) with LogMAR post-treatment (p=0.07). Three patients (8.3%) had radiation papillopathy, 2 (5.6%) had secondary glaucoma, and 1 (2.8%) had scleral thinning. Of the 5 eyes (14.0%) that showed regrowth on ultrasonography and 2 eyes (5.6%) that developed neovascular glaucoma (7 eyes in total), 5 underwent enucleation and 2 underwent endoresection. Of the patients who underwent endoresection, one had subsequent enucleation. The globe preservation rate was 83.3%.

In the patients who developed radiation maculopathy, OCT revealed intraretinal edema, epiretinal membrane (ERM), and subretinal fluid (Figure 3a-4b). OCTA of these patients demonstrated an enlarged and irregular foveal avascular zone, nonperfusion, and microaneurysms in the superficial and deep capillary plexuses (Figure 4). FFA revealed areas of nonperfusion around the tumor and cystoid macular edema (Figure 2d).

Discussion

CyberKnife is a LINAC-based, robot-controlled radiosurgery system. With the possibility of radiation rays coming from an almost infinite number of angles, it only targets tumor tissue and aims to preserve healthy radiosensitive tissue. Since its introduction, CyberKnife has become an alternative to Gamma Knife. The main drawbacks of the Gamma Knife system were the invasive immobilization via the rectus muscles, the need for long-lasting general anesthesia/sedation, and the unfavorable adverse-effect profile due to the optimal dose for one-time therapy being up to 40 Gy. Haas et al.[16] reported radiation retinopathy in 84.0% and neovascular glaucoma in 47.0% of patients after single fraction Gamma Knife treatment (50 median Gy) for choroidal melanoma. The radiation dose to the ciliary body and lens is lower with the CyberKnife method compared to Gamma Knife. However, the doses to the optic disc and macula are higher.[17]

In our study group, the globe salvage rate was 83.3%. In his pioneering paper, Muacevic et al.[18] performed 18-22 Gy SRS on 20 patients with medium and large uveal melanoma and reported that none of the 7 patients they were able to follow up for more than 6 months required enucleation due to adverse effects or tumor growth. However, their case series was small, and the follow-up period was short. In a later paper from the same group, Eibl-Lindner et al.[19] reported the results of 18-22 Gy SRS on 217 patients with medium or large uveal melanoma and reported a globe preservation rate of 86.7% at 3 years and 73% at 5 years.

In our series, the most common complications seen after SRS were cataract (38.9%) and radiation retinopathy (27.7%). In another publication from Turkey, Yazıcı et al.[20] reported a 42.0% prevalence rate of radiation retinopathy in their 181-case series. The radiation dose to the critical intraocular structures including lens, optic disc, and macula depend on tumor location as well

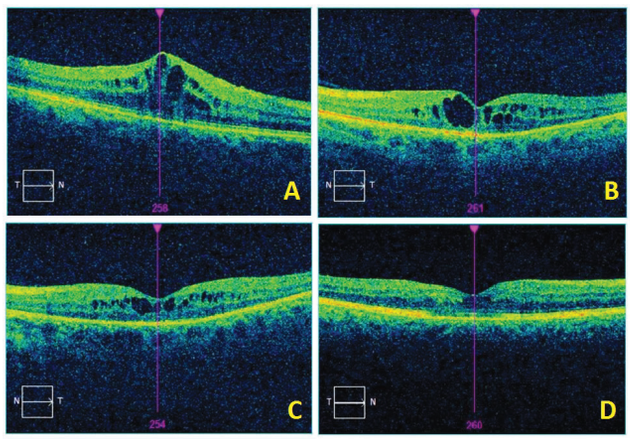

Figure 3. At 13 months after SRS, OCT reveals cystoid macular edema in a patient whose fluorescein angiography shows macular leakage (A). Regression of the macular edema was observed after 2 monthly injections of aflibercept (B). After the third dose of aflibercept, the intraretinal cysts diminished in size (C) and after the fifth dose of aflibercept, there was substantial improvement of the cystoid edema in the macula (D)

SRS: Stereotactic radiosurgery, OCT: Optical coherence tomography

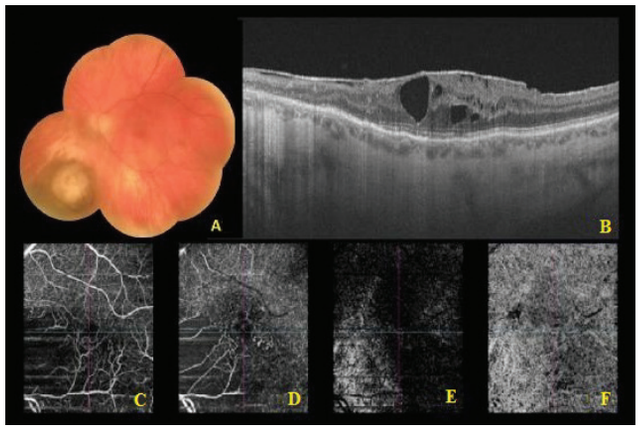

Figure 4. Color fundus photograph of a patient who underwent 21 Gy SRS and developed radiation maculopathy after 11 months. The patient received 17 doses of ranibizumab (A). Swept-source OCT image showing ERM and cystoid macular edema. Atrophy of the outer retina and RPE in the nasal fovea with associated reverse shadowing (B). OCTA images show areas of capillary dropout in the superficial (C) and deep (D) capillary plexuses, non-flow areas due to cystoid macular edema, and ERM-induced vascular traction. The choriocapillaris vasculature is visible due to RPE atrophy in the outer retina (unmasking) (E). Artifacts consisting of cystoid spaces and signal void areas due to shadowing are observed in the choriocapillaris layer (F)

SRS: Stereotactic radiosurgery, Gy: Gray, RPE: Retinal pigment epithelium, OCT: Optical coherence tomography, OCTA: Optical coherence tomography angiography, ERM: Epiretinal membrane

was the radiation method used. In our series, the rate of cataract formation was 38.9% and the tumor was in a peripapillary location in 60.0% of those patients. Radiation retinopathy was observed in 27.7% of the patients. There was a significant association between radiation retinopathy and distance of the tumor from the optic disc but not between radiation retinopathy and MRD to the tumor, tumor thickness, or distance from the fovea. Previous studies reported the distance of the tumor to the fovea as a risk factor for the development of radiation retinopathy.[21,22] In our series, the mean distance of the tumor from the fovea was similar between patients who developed radiation retinopathy and those who did not. The similar mean values and small number of cases may explain why a statistically significant relationship was not detected.

Local recurrence is known to be associated with metastasis-related mortality.[23] Recurrence was observed in 5 of the patients in our case series. Metastasis was observed in 2 of the patients who had recurrence and 1 of these patients died. Recurrence may occur due to problems with eye immobilization during SRS. Our globe salvage rate was 83.3% at a mean follow-up of 17.2 months.

As noninvasive methods, OCT and OCTA have made a significant contribution to the diagnosis and treatment of radiation maculopathy. OCT reveals macular thickening in the early stages of radiation maculopathy, followed by the development of cystoid macular edema. In advanced cases, subretinal fluid and opacities with increased reflectivity consistent with subretinal exudation and hemorrhage are observed on OCT.[24]

OCTA is a non-invasive angiography method that provides cross-sectional and volumetric information about the retina. While fluorescein angiography only allows evaluation of the superficial capillary plexus, OCTA enables separate imaging of the superficial and deep capillary plexuses, outer retina, and choriocapillaris layer. In radiation maculopathy, changes are observed in all four layers.[25]

According to our early results, SRS is an effective method for local control of uveal melanoma that provides patient comfort, saves time, and has a favorable adverse-effect profile. After SRS, patients should be followed closely for the development of radiation maculopathy with frequent OCT and OCTA imaging, and anti-VEGF therapy should be initiated at the onset of radiation maculopathy to improve visual prognosis. Laser photocoagulation can also be performed for retinal nonperfusion after wide-angle fluorescein angiography when necessary.

The main limitations of our study are that it is a retrospective study, it included a small number of cases, and the follow-up period was short. The safety of this treatment should be supported through studies with larger case series and longer follow-up periods.

Ethics

Ethics Committee Approval: Approval required for the study was obtained from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (decision no: 04-287-19).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K.G., K.O., Concept: G.Ö., A.K.G., İ.M., Design: G.Ö., A.K.G., İ.M., Data Collection or Processing: G.Ö., A.K.G., Analysis or Interpretation: G.Ö., A.K.G., H.U., Literature Search: G.Ö., Writing: G.Ö., A.K.G., K.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.91962
Turk J Ophthalmol 2020;50:163-168

Original Article

Relationship Between Final Visual Acuity and Optical Coherence Tomography Findings in Patients with Diabetic Macular Edema Undergoing Anti-VEGF Therapy

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Abstract

Objectives: To identify the prevalence of findings in optical coherence tomography (OCT) sections before intravitreal anti-VEGF treatment in patients with diabetic macular edema (DME), and to evaluate the relationship between these findings and final visual acuity and number of injections.

Materials and Methods: This retrospective study included 296 eyes of 191 patients (104 male, 87 female) who started intravitreal ranibizumab treatment after being diagnosed with DME in the retina unit between January 2013 and April 2017 were included the study. Spectral domain OCT findings at the time of presentation such as presence of serous macular detachment (SD), vitreomacular traction (VMT), and epiretinal membrane (ERM) were recorded. In addition, the regularity of the ellipsoid zone (EZ) and inner retinal layers was also studied.

Results: The mean central retinal thickness measured in SD-OCT was 449±81 µm before treatment and 350±96 µm after treatment ($p<0.001$). SD was detected in 155 eyes (52.4%), ERM in 67 eyes (22.6%), and VMT in 9 eyes (3%). Thirty eyes (10.1%) had disorganization of the retinal inner layers (DRIL) and 54 eyes (18.2%) had EZ deterioration. The presence of ERM, EZ irregularity, and DRIL were associated with significantly lower final visual acuity ($p<0.0001$), while there was no relationship between pre-treatment SD and final visual acuity ($p=0.11$). Injection number was higher in eyes with SD and ERM compared to those without, but this difference was statistically significant only in the presence of SD ($p=0.01$ and $p=0.59$, respectively). There was no difference in injection number according to EZ irregularity or presence of DRIL.

Conclusion: The coexistence of SD with DME was associated with increased need for treatment but not with final visual acuity. EZ irregularities, DRIL, and ERM are findings that negatively affect visual acuity.

Keywords: Diabetic macular edema, optical coherence tomography, anti-VEGF treatment

Introduction

Diabetic retinopathy (DR) is an important complication of diabetes and is closely associated with disease duration. DR is among the leading causes of acquired vision loss in adults worldwide. Diabetic macular edema (DME) is a serious and characteristic complication of DM-related maculopathy and is the most common cause of vision loss in these patients.[1,2] DME can emerge at any stage of DR, and its prevalence is expected to increase with that of diabetes, as is the case with DR. The global

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Received: 21.08.2019 **Accepted:** 27.11.2019

Cite this article as: Eraslan S, Yıldırım Ö, Dursun Ö, Dinç E, Orekici Temel G. Relationship Between Final Visual Acuity and Optical Coherence Tomography Findings in Patients with Diabetic Macular Edema Undergoing Anti-VEGF Therapy. Turk J Ophthalmol. 2020;50:163-168

prevalence was 8.3% in 2013 and is projected to increased to 10.1% by 2035.[3] Two different studies conducted in Turkey reported the prevalence of DME as 14.2% and 15.3%.[4,5]

Optical coherence tomography (OCT) is a noninvasive, noncontact imaging method that allows *in vivo,* quantitative imaging of the human retina with high-resolution sections. It is the only method that provides cross-sectional images of the anatomic and topographic structure and pathologies of the retinal layers.[5,6] OCT has become an important diagnostic tool due to the information it provides about vitreoretinal relationships and the internal structure of the retina in the assessment and monitoring of DR. The use of OCT has not only made it possible to objectively evaluate DME, but also to make new descriptions such as serous macular detachment (SD). In addition, OCT has advanced our understanding of the importance of vitreoretinal interface pathologies in the pathogenesis of DME and their impact on treatment response. Thanks to newly described OCT findings, personalized information can be obtained about disease severity, treatment response, and prognosis. In addition to all of these, in the current era of anti-VEGF therapy, drug effectiveness is assessed using OCT, which has further increased the importance of OCT in the treatment monitoring of macular edema.

The present study aims to evaluate the relationship between pre-treatment OCT findings and final visual acuity and number of injections in patients who presented with complaints of low visual acuity due to DME and underwent anti-VEGF therapy.

Materials and Methods

The study was conducted after obtaining approval from the Mersin University Clinical Research Ethics Committee (decision number 2017/284). The study included 296 eyes of 191 patients (104 men and 87 women) who presented to the ophthalmology department of the Mersin University Faculty of Medicine with complaints of decreased vision between January 2013 and April 2017, were diagnosed as having DME in the retina unit, and were started on intravitreal ranibizumab therapy. Patients whose records included detailed medical history, complete examination findings, and OCT sections suitable for evaluation, had no history of previous intravitreal therapy or retinal surgery, and attended regular follow-up appointments were included in the study. Patients whose records were incomplete, whose OCT images could not be obtained due to media opacity, who had a history of previous intravitreal therapy or retinal surgery, or did not attend regular follow-up appointments were excluded from the study. The visual acuity, examination findings, and OCT data of all patients who met the inclusion criteria were screened and recorded.

OCT images (Cirrus 4000 HD-OCT, Zeiss Meditec) of all patients were evaluated in terms of the presence of vitreomacular traction (VMT), epiretinal membrane (ERM), SD, disorganization of the retinal inner layers (DRIL), and integrity of the ellipsoid zone (EZ). The relationship between OCT findings and the number of injections and final visual acuity were statistically evaluated.

Statistical Analysis

Conformity of the data to normal distribution was evaluated using Shapiro-Wilk test. Descriptive statistics were expressed as mean and standard deviation for normally distributed data and as median and percentage values for nonnormally distributed data. Categorical parameters were expressed as numbers and percentages. Differences between two groups were evaluated using Student's t-test for parameters that showed normal distribution and Mann-Whitney U test for parameters that did not. Kruskal-Wallis test was used to evaluate differences between more than two groups. A paired-samples t-test was used to analyze pre- to post-treatment changes, chi-square test was used to analyze relationships between categorical parameters, and correlation analysis was used to evaluate relationships between continuous parameters. The data were analyzed using SPSS 11.5 package software. $P<0.05$ was set as the threshold for statistical significance.

Results

The mean age of the patients included in the study was 60.96±8.58 years and the mean disease duration was 15.49±7.78 years. The patients' mean follow-up time was 19.61±9.31 months and they received a mean of 5.92±2.77 injections during this time. Best corrected visual acuity was 0.3±0.22 before intravitreal injection and 0.36±0.26 after injection ($p<0.001$). Similarly, central retinal thickness was 449±81 µm before treatment and 350±96 µm after treatment ($p<0.001$). The most common OCT finding in the eyes included in the study was SD, which was detected in 52.4% of the eyes (Figure 1). Other than these findings, ERM was present in 22.6% of the eyes (Figure 2), DRIL in 10.1% (Figure 3), and VMT in 3% (Figure 4). In addition, EZ irregularity was observed in 18.2% of the eyes included in the study (Table 1).

Although eyes with SD and ERM received more injections compared to eyes without, this difference was only statistically significant for eyes with SD ($p=0.01$ and $p=0.59$, respectively). In contrast, EZ irregularity and DRIL were not significantly

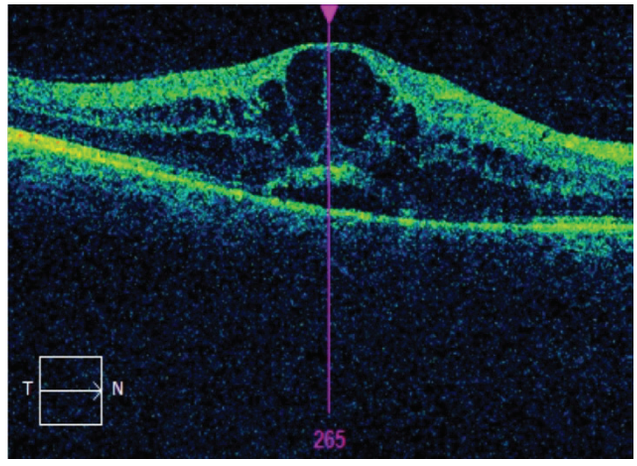

Figure 1. Optical coherence tomography shows serous macular detachment in the right eye of a patient with cystoid macular edema

associated with number of injections (p=0.84 and p=0.4, respectively) (Table 2). When the relationship between OCT findings and final visual acuity was evaluated, there was no statistical relationship between final visual acuity and presence of SD, whereas presence of ERM was associated with significantly lower final visual acuity (p=0.11 and p<0.0001, respectively).

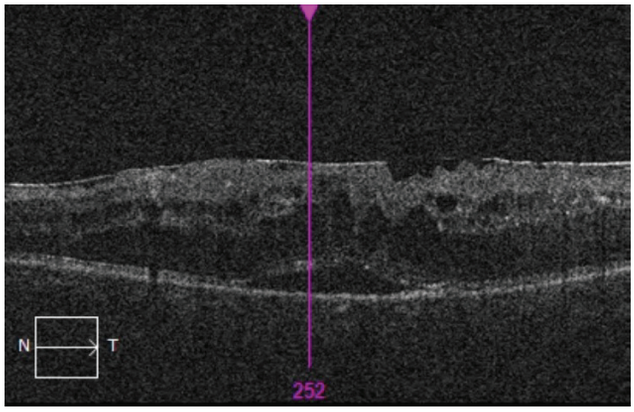

Figure 2. Optical coherence tomography demonstrates coexistence of epiretinal membrane and serous macular edema in a patient with diabetic macular edema

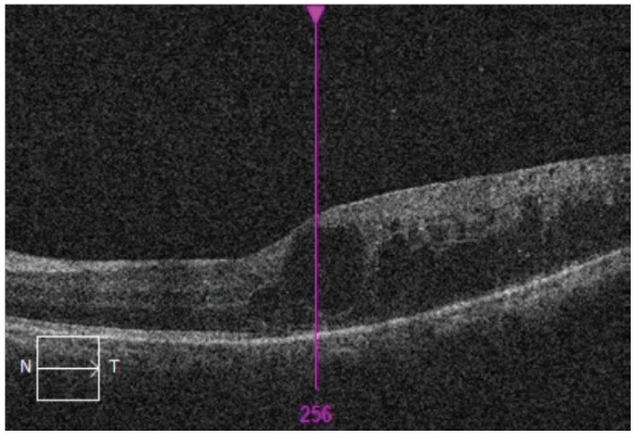

Figure 3. OCT reveals DRIL and irregular ellipsoid zone in the left eye of a patient with cystoid macular edema. Although the macular edema completely regressed over a 36-month follow-up period, there was no improvement in visual acuity
OCT: Optical coherence tomography, DRIL: Disorganization of retinal inner layers

EZ irregularity and DRIL were also associated with significantly lower final visual acuity (p<0.0001 for both) (Table 3).

Discussion

With the widespread use of OCT in the diagnosis and monitoring of retinal diseases, we have gained a better understanding of the importance of the vitreomacular interface. In addition, new pathologies have been identified in relation to retinal diseases and researchers have started to investigate the relationship between these pathologies and visual outcomes. Similar developments have occurred for DME patients, as OCT

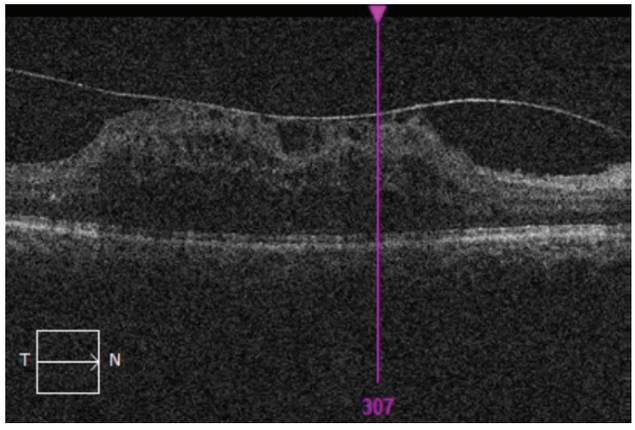

Figure 4. Extensive vitreomacular traction is observed in a patient with diabetic macular edema

Table 1. Distribution of pre-treatment OCT findings		
n=296	**Present**	**Absent**
SD	155 (52.4%)	141 (47.6%)
ERM	67 (22.6%)	229 (77.4%)
VMT	9 (3%)	287 (97%)
DRIL	30 (10.1%)	266 (89.9%)
EZ Irregularity	54 (18.2%)	242 (81.8%)

OCT: Optical coherence tomography, SD: Serous macular detachment, ERM: Epiretinal membrane, VMT: Vitreomacular traction, DRIL: Disorganization of retinal inner layers, EZ: Ellipsoid zone

Table 2. Number of injections in patients with and without serous macular detachment, epiretinal membrane, DRIL, and irregular ellipzoid zone								
	SD		**ERM**		**DRIL**		**EZ Irregularity**	
	+	**-**	**+**	**-**	**+**	**-**	**+**	**-**
Median number of injections	6	5	6	5	5.5	5	6	5

DRIL: Disorganization of retinal inner layers, SD: Serous macular detachment, ERM: Epiretinal membrane, EZ: Ellipsoid zone, +: Present, -: Absent

Table 3. Relationship between OCT findings and final visual acuity								
	SD		**ERM**		**DRIL**		**EZ Irregularity**	
	+	**-**	**+**	**-**	**+**	**-**	**+**	**-**
Median visual acuity	0.3	0.4	0.2	0.4	0.1	0.35	0.1	0.4

OCT: Optical coherence tomography, SD: Serous macular detachment, ERM: Epiretinal membrane, DRIL: Disorganization of retinal inner layers, EZ: Ellipsoid zone, +: Present, -: Absent

has enabled identification of various pathologies such as the presence SD, DRIL, EZ irregularity, and hyperreflective dots in these patients and these findings have started to shed light on both the pathogenesis and prognosis of the disease.

In OCT studies of patients with DME, the prevalence of SD has been found to range from 11.4% to 51.9%.[8,9,10,11,12] In the present study, the most common OCT finding observed in patients was SD, which was present in approximately half of the patients. This result is consistent with the literature, as the results of more recent studies demonstrate a higher prevalence of SD compared to earlier studies. This phenomenon parallels advances in OCT technology, which have made it possible to obtain higher quality images and more clearly visualize pathologies that were previously overlooked. The mechanism underlying the development of SD is not fully known, but a study by Turgut et al.[13] suggested that there may be a relationship between serum $HbA1_c$ levels and the development of SD and that SD may occur due to impaired retinal pigment epithelium functions in patients with poor metabolic control.

Ozdemir et al.[14] first showed that SD observed in patients with DME may regress after intravitreal triamcinolone treatment and that an increase in visual acuity may be achieved. In another study, Maalej et al.[15] suggested that the presence of SD was associated with low visual acuity. However, Murakami et al.[16] asserted that the presence of SD in DME patients was not associated with low visual acuity. Seo et al.[17] proposed a different view, stating that visual prognosis is related to the initial deterioration in the photoreceptor layer and that this occurs more commonly in the presence of SD. All these studies show that the impact of SD on visual prognosis in patients with DME is controversial. In the present study, the presence of SD was not associated with visual outcomes. However, the more interesting result is that DME patients with SD received more injections compared to patients without SD. In a study conducted by Koytak et al.[18] evaluating patients treated with intravitreal bevacizumab, it was found that the decrease in central retinal thickness was greater in the cystoid macular edema group and SD group, but that there was no effect on visual prognosis. Kim et al.[19] emphasized that although eyes with SD responded better to intravitreal bevacizumab injections, they also required the administration of repeated doses. The high number of injections received by patients with SD may be due to the fact that these patients respond well to treatment but need repeated injections. In addition, the presence of SD may also be associated with edema severity. This is supported by the results obtained in the present study.

In OCT studies of DME patients, the prevalence of ERM has been found to vary between 10.92% and 34.5%.[10,20,21,22] The prevalence of ERM in the DME patients in the present study was 22.6%, consistent with the literature. However, these patients should be monitored long-term for the development of ERM. Kulikov et al.[23] compared the visual acuity outcomes of DME patients with and without ERM and determined that the patients with ERM had poorer visual acuity and showed a more limited response to treatment compared to those without ERM. Lai et al.[24] also stated that treatment response was limited in DME patients with ERM but that visual acuity at 3 months was not affected. The main limitation of their study was the short follow-up period; in a study by Wong et al.[25] with longer follow-up period, the presence of ERM was shown to adversely affect visual acuity. The mean follow-up time in the present study was longer than in all of these three studies, and it was found that the presence of ERM was associated with worse final visual acuity but did not affect the number of injections. This result is not surprising, as it is clear that the presence of ERM will have a negative impact on the anatomical structure of that region.

Another new concept related to patients with DME that has emerged in recent years due to developments in OCT technology is DRIL. DRIL is defined as the inability to distinguish any of the borders separating the retinal inner layers (ganglion cell layer-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer). DRIL was detected in 10.1% of the eyes included in the present study. Studies show that the presence of extensive DRIL is associated with poor visual outcomes and that this is associated with capillary perfusion disorder.[25,26,27,28,29] Nicholson et al.[27] stated that the presence of DRIL was an indicator of macular capillary nonperfusion. According to their study, DRIL had 84.4% sensitivity and 100% specificity in the detection of macular capillary non-perfusion. Considering that fundus fluorescein angiography is an invasive method, the evaluation of DRIL may enable macular ischemia to be detected without performing an invasive procedure. DRIL may regress over time and this is associated with improvements in vision. In other words, the regression of DRIL actually indicates anatomical recovery and a return to a more normal morphology.[27] DRIL is a good indicator of whether an eye's vision will increase or decrease with treatment, and thus is a good guide for predicting visual prognosis. The findings obtained from the present study are also consistent with the literature, and the presence of DRIL has been shown to adversely affect visual prognosis. If DRIL is considered an anatomic defect, this anatomic defect will inevitably affect vision. Interestingly though, a significant relationship was not established between the presence of DRIL and number of injections.

Another concept emphasized in DME patients is EZ integrity. This layer, previously referred to as the IS/OS band, was believed to be associated with the photoreceptor inner segments, and the second hyperreflective band seen on OCT was named the EZ as a result of the consensus reached in international terminology.[30] Both the EZ and the external limiting membrane are an important indicators of photoreceptor integrity and are used as indicators in predicting the visual prognosis of patients with DME. In a study by Iacono et al.,[31] the integrity of both the EZ and the ELM were shown to be closely related with final visual acuity. A similar result was also reported by Mori et al.[32] In addition, EZ integrity has been shown to be a good indicator of treatment response.[33,34] EZ irregularity was observed in 18.2% of the eyes in the present study, and the visual acuity outcomes of these patients were significantly poorer compared to patients without EZ irregularity. However, a significant relationship was

not observed between EZ irregularity and injection number. This result is consistent with studies in the literature. Similar to the presence of DRIL, anatomic disruption in the central macula adversely affects visual acuity and is reflected in the visual acuity achieved after treatment.

Conclusion

In the present study, it was found that OCT findings obtained from patients with DME may be related to injection number and to visual prognosis in particular. In light of these findings, informing patients before the treatment about visual prognosis will be greatly beneficial for both the physician and the patient and will prevent unexpected surprises. Conducting this and similar studies with new devices that can yield more detailed images will provide better opportunities both to identify new pathologies and to evaluate the effects of these pathologies on visual outcomes compared to currently available technology.

Ethics

Ethics Committee Approval: Mersin University Clinical Research Ethics Committee (decision number 2017/284).

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Ö.Y., E.D., Concept: S.E., Ö.Y., E.D., Design: S.E., Ö.Y., E.D., Data Collection or Processing: S.E., E.D., Analysis or Interpretation: S.E., Ö.Y., E.D., Ö.D., G.O.T., Literature Search: S.E., Ö.D., E.D., Writing: S.E., Ö.Y., E.D., Ö.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2019.60308
Turk J Ophthalmol 2020;50:169-182

Review

Behçet's Uveitis: Current Diagnostic and Therapeutic Approach

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Abstract

Behçet's disease is a chronic, multisystem inflammatory disorder characterized by relapsing inflammation. Although its etiopathogenesis has not yet been clarified, both the adaptive and innate immune systems, genetic predisposition, and environmental factors have all been implicated. It is more frequent and more severe in males in the third and fourth decades of life. The eye is the most frequently involved organ in the course of the disease. Ocular involvement (Behçet's uveitis) is characterized by bilateral recurrent non-granulomatous panuveitis and occlusive retinal vasculitis. Recurrent inflammatory episodes in the posterior segment may lead to permanent vision loss due to irreversible retinal damage and complications such as macular scarring, macular atrophy, and optic atrophy. Early and aggressive immunomodulatory treatment and the use of biologic agents when needed are crucial for preventing recurrences and improving visual prognosis.

Keywords: Behçet's uveitis, imaging, treatment, biologics, prognosis

Introduction

First identified by Turkish Dermatology Professor Hulusi Behçet in 1937, Behçet's disease (BD) is a chronic, multisystemic vasculitis of unknown etiology that involves various organs and tissues and is characterized by inflammatory episodes.[1,2] The skin, eyes, gastrointestinal tract, and central nervous system are among the affected organs, tissues, and systems. Ocular involvement is the most common vital organ involvement and has poor prognosis, potentially culminating in blindness despite many advances in diagnosis and treatment.

Epidemiology and Demographic Features

The disease is more common in the Mediterranean region and in Far East and Middle East countries. This geographical region falls between the 30° and 45° northern latitudes, a region that also includes the historic "Silk Road" trade route connecting the East and West and the highest HLA-B51 antigen distribution.[3,4] The country with the highest incidence of BD worldwide is Turkey.[4] The highest reported prevalence is in İstanbul, at 420/100,000 population.[5] It is much less prevalent in Europe and the United States.[4,6] Even along the Mediterranean coasts of Europe, where BD is more common compared to Northern Europe, it is much rarer than in Turkey, with a reported prevalence of 2.4-7.5/100,000.[6]

BD mostly affects the younger population between the ages of 25 and 35 years.[1,4,7] The incidence in childhood is geographically variable and ranges from 4% to 26%.[8] Although the initial symptoms may appear in childhood, BD is rarely diagnosed

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Received: 19.08.2019 **Accepted:** 17.12.2019

Cite this article as: Çakar Özdal P. Behçet Üveiti: Tanı ve Tedavide Güncel Yaklaşım. Turk J Ophthalmol. 2020;50:169-182

before the age of 16.[1,7] The onset of uveitis associated with BD in children also generally occurs in late childhood.[4,7] Likewise, the incidence of both BD and its ocular manifestations decreases with age.[4] Disease activity is also observed to decrease in the older age group.[9] According to a multicenter national database study on the epidemiology of uveitis conducted in Turkey, Behçet's uveitis (BU) is the leading cause of non-infectious uveitis, accounting for 24.9% of cases. BU is responsible for 9.3% of pediatric uveitis cases and 9.7% of uveitis cases in older adults (>60 years).[10] In our series, this rate was 16.5% for pediatric uveitis, while BD was not observed among patients diagnosed with uveitis at an advanced age.[11,12]

Although BD is more common among males, there are regional variations in the male/female ratio. In publications from Western Europe, this ratio is quite low and sometimes even higher among females, whereas in publications from Turkey, males outnumber females by at least two fold.[4,11,13,14] Panuveitis and resulting poor visual prognosis are also more common in males.[1,4,14]

Etiopathogenesis

Despite better recognition of the disease and numerous studies investigating its underlying causes, there is lingering uncertainty regarding its etiopathogenesis. Disorders of both the innate and adaptive immune systems have been implicated. Environmental factors are believed to play a triggering role in individuals with immunogenetic susceptibility, leading to an increased and abnormal immune response that results in the development of systemic vasculitis.[15,16] The most well-known genetic link is its association with HLA-B51.[17,18] Gül et al.[19] reported that ocular involvement was more common in HLA-B51-positive patients, but there was no relationship with severity of the involvement. It was reported that HLA-A*2601 was significantly more frequent among BU patients in Japan, especially in patients without HLA*B5101, and that HLA-A*2601 was therefore another risk factor for BU in the Japanese.[20] Other causes implicated in the pathogenesis of the disease include abnormal cellular responses, T-cell-mediated immune responses, abnormal response to bacterial antigens, increased Th1 cytokine production, disorders of the complement system, upregulation of endothelial cell surface molecules, hemodynamics, and coagulation factor abnormalities.[21] Environmental factors also play an important role. The lower prevalence of the disease among Turks living in Germany is significant evidence of this.[22] Japan has seen decrements in both the incidence and severity of the disease in recent years. Such changes in a genetically homogeneous country with low immigration rates also suggest the impact of environmental factors. The main reasons for this change in the Japanese population are an increase in atopic/allergic diseases, which are shown to be inversely associated with BD, and a reduction in infectious diseases. Improvement in oral hygiene in particular is the most important factor.[23] In Turkey, the lower socio-economic status and education level and higher unemployment rate among BD patients compared to patients with ankylosing spondylitis or inflammatory bowel disease further supports the importance of environmental factors.[24]

Systemic Involvement and Diagnosis of Behçet's Disease

The underlying pathology is an occlusive, necrotizing vasculitis that can involve arteries and veins of all sizes in all organs and systems. For this reason, the disease is characterized by recurrent inflammatory episodes in affected organs and systems.[25] The earliest and most common finding is recurrent oral aphthae, which are painful, non-scarring lesions with well-defined borders. In contrast, genital ulcers heal with scarring. Erythema nodosum, papulopustular lesions, acneiform lesions, and increased dermal hypersensitivity reaction to trauma (pathergy) are the most common skin lesions. Other known involvements include superficial thrombophlebitis, deep vein thrombosis, arthritis, epididymitis, and gastrointestinal tract and central nervous system manifestations.[1,4,21]

Diagnosis is based on a constellation of various clinical signs; there is no specific diagnostic test. Positive pathergy test or HLA-B51 positivity alone are not diagnostic findings. There are various recommended diagnostic criteria.[1] Of these, oral aphthae that recur at least 3 times a year are necessary for the diagnosis of BD according to the criteria established by the International Study Group for Behçet's Disease. In addition to this, at least two of the following findings are required: Recurrent genital ulcers, cutaneous lesions, uveitis, or a positive pathergy test.[26] The eye is the most commonly involved organ, with a rate as high as 90% depending on which clinic is performing the study.[27] Although ocular involvement generally occurs within 2 to 4 years of disease onset, it can be the first sign of the disease in up to 20% of cases.[9,19] Moreover, ocular involvement is often the complaint that prompts the patient to seek medical care and thus leads to a diagnosis. Therefore, good knowledge of the ocular manifestations of BD is of diagnostic value.

Ocular Involvement in Behçet's Disease

Ocular involvement is characterized by bilateral, recurrent, non-granulomatous panuveitis and retinal vasculitis. Isolated anterior uveitis and unilateral involvement are rare.[13] Posterior segment involvement has been reported in 50-93% of cases. Recurrent episodes of posterior uveitis can result in severe retinal damage and permanent vision loss.[1,13,14,28] Therefore, recognition of posterior segment involvement also has prognostic value.

BU is characterized by exacerbations and remissions. Sudden, severe attacks followed by spontaneous, gradual remission periods are important findings suggestive of BU.

The prevalence of isolated anterior uveitis is approximately 10%. Anterior chamber reaction is accompanied by dust-like keratic precipitates called endothelial dusting. The eye may appear quiet and white despite a severe anterior chamber reaction and even hypopyon, or there may be anterior segment involvement accompanied by conjunctival hyperemia and ciliary injection. Hypopyon has been reported in 5-30% of cases. However, as hypopyon can regress spontaneously, the actual rate may be higher than reported. The anterior chamber reaction is typically not accompanied by fibrinous exudation, and the inflammatory cells are able to move freely. For this reason, the hypopyon that occurs in BU shifts readily with

gravity. The presence of hypopyon is also an indicator of severe posterior segment involvement. These features are essential for distinguishing BU-related hypopyon from ankylosing spondylitis hypopyon, which is sticky with fibrinous reaction and only affects the anterior segment (Figure 1).[1,13,21]

The main posterior segment findings are diffuse vitritis with or without vitreous haze, retinal vasculitis, occlusion of major or peripheral retinal veins and less commonly the arterioles, superficial/deep retinal infiltrates, optic disc inflammation, and cystoid macular edema (CME).[14,21] Diffuse vitritis is an unvarying sign of posterior segment involvement. Vitreous haze is a sign of active inflammation that is most pronounced at the beginning of an attack and gradually diminishes. Sometimes the vitreous haze is so dense that it obscures the posterior segment (Figure 2). As vitreous inflammation regresses, inflammatory precipitates (vitreous pearls) form in a string like a pearl necklace in the inferior peripheral retina (Figure 3).[1,13,21] This finding is pathognomonic and is an indication that the attack started about 1 week ago and is now regressing. Unlike the snowball opacities in the pars planitis, these are smaller, show an organized arrangement, are mostly located in the inferotemporal retina, and regress spontaneously without scarring.[1]

Retinal vasculitis is another characteristic finding that involves white perivenous sheathing that is often diffuse but can also be segmental.[13,29] Veins (periphlebitis) are affected more than arteries (periarteriolitis). Periarteriolitis is not seen in isolation; it is always accompanied by periphlebitis. Capillaritis is also a common finding that leads to diffuse capillary leakage and is best observed with fluorescein angiography (FA). The characteristic feature of periphlebitis associated with BU is that it is occlusive, leaky, and recurrent. It can affect vessels in any location and of every size. Occlusive vasculitis may lead to retinal hemorrhage and exudations, and even the formation of branch retinal vein occlusion or more rarely, central retinal vein occlusion (Figures 4, 5). After the active inflammation has subsided, findings including armor-like gliotic sheathing of the internal vascular wall, ghost vessels (Figure 6), and retinal ischemia demonstrated by FA may be observed.[1] Retinal neovascularization (NVE) and

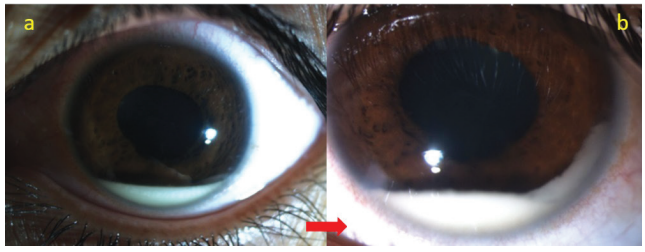

Figure 1. Soft hypopyon (a) that moves freely (b) with head movements (red arrow) is seen in a patient with Behçet's uveitis. Note that the eye is white despite hypopyon

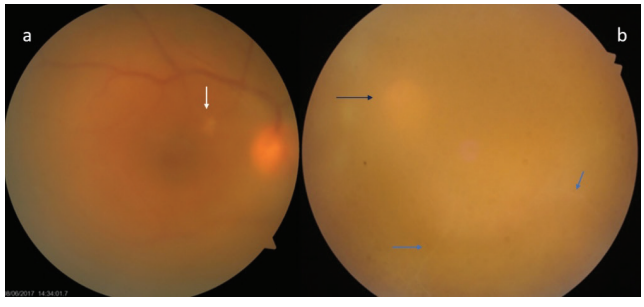

Figure 2. Diffuse vitritis and vitreous haze are observed in two different Behçet's uveitis patients. In the first patient (a), the optic disc is hyperemic and there is a small retinitis focus (white arrow) at the posterior pole. In the other patient (b), the vitreous haze is very dense and the optic disc (black arrow) and ghost vessels below (blue arrows) are barely discernible

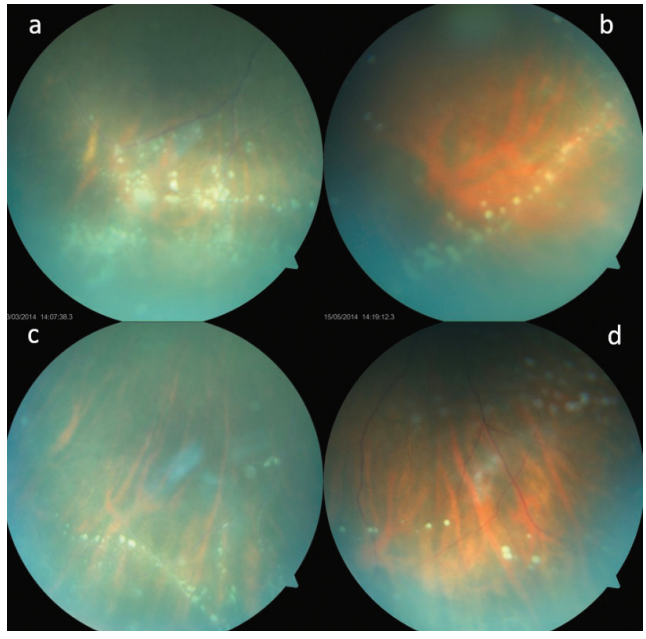

Figure 3. In different patients (a,b,c,d), precipitates (vitreous pearls) are seen in the inferior periphery of the retina, indicating a regressing acute inflammatory episode

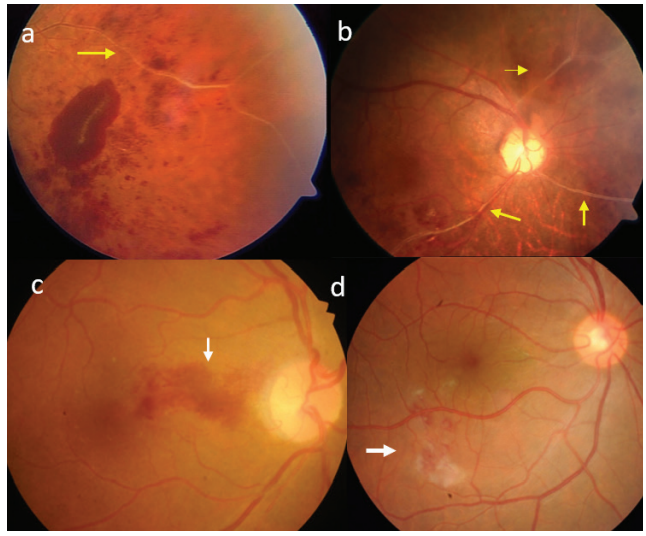

Figure 4. Different patients exhibit perivenous white sheathing (a, b, yellow arrows), hemorrhagic occlusive vasculitis at the posterior pole and associated hemorrhage in the papillomacular bundle (c, white arrow), and hemorrhage and exudates in the inferior macular region (d, white arrow)

less commonly neovascularization of the disc (NVD) may also occur as a complication of retinal ischemia (Figures 7, 8).[1] The underlying cause of NVD is not ischemia but uncontrolled inflammation, and its treatment should be targeted accordingly. Tutkun et al.[30] reported that ischemia was present in only 13% of cases who developed NVD due to BU. Sometimes retinal vasculitis is not observed clinically, but manifests as subclinical chronic vasculitis demonstrated by FA. Optic disc staining and retinal capillary leakage observed on FA during a clinically calm period between attacks are key signs of persistent subclinical inflammation (Figure 9).[28,31]

Superficial and deep retinal infiltrates are the most common findings of posterior segment involvement of BU. Superficial infiltrates heal within a few days without scarring. Even without accompanying retinal vasculitis, the presence of even one of these infiltrates is considered an indicator of posterior segment involvement (Figure 10). Deep retinal infiltrates take longer to heal and may leave a scar. The wedge-shaped defect in the retinal nerve fiber layer (RNFL) left as retinal infiltrates in the posterior pole regress, and visual field loss and RNFL thinning on optical coherence tomography (OCT) in the region corresponding to this defect have been identified as characteristic findings for patients with BU (Figure 11).[32]

The main anterior segment complications of BU include cataract, posterior synechiae, and glaucoma. Posterior segment complications are more numerous and many have the potential to cause permanent vision loss. These include macular edema, optic atrophy, retinal atrophy, macular scarring, epiretinal membrane, retinal detachment, retinal tears, NVE, NVD, macular holes, and even phthisis bulbi. Macular complications and optic atrophy are the leading causes of permanent vision loss.[1,10,11] The clinical

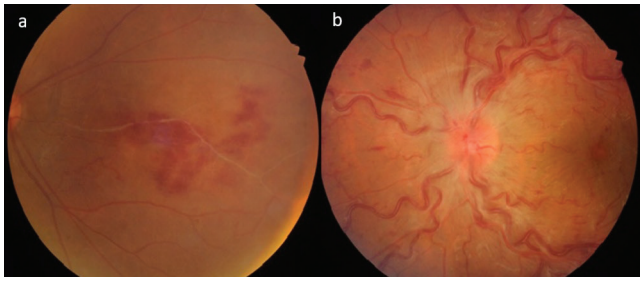

Figure 5. Branch retinal vein occlusion (a) and central retinal vein occlusion (b) due to occlusive retinal vasculitis in two different Behçet's patients

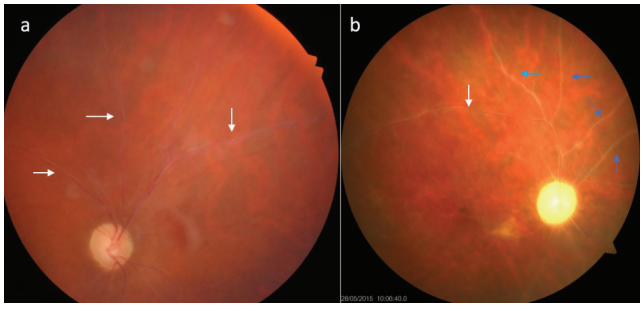

Figure 6. Gliotic sheathing (white arrows) of the retinal vessels and ghost vessels (blue arrows) are observed in two different Behçet's patients (a, b)

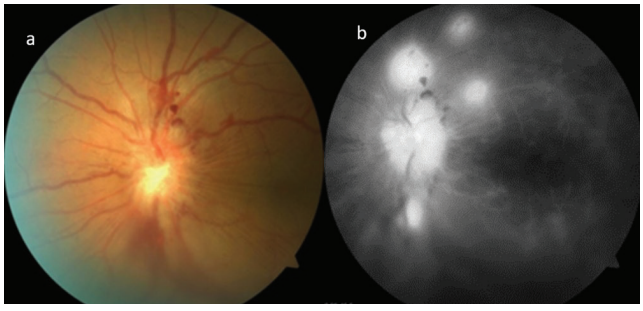

Figure 7. Color fundus photographs (a) and fluorescein angiography images (b) of a Behçet's patient who developed optic disc neovascularization. There is extensive vascular and capillary leakage

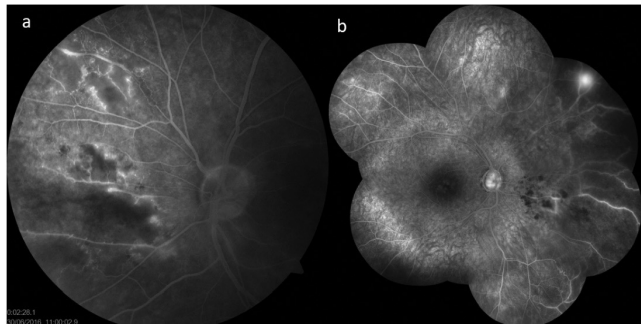

Figure 8. Fluorescein angiography images of two different Behçet's uveitis patients with occlusive retinal vasculitis. The first (a) shows nasal optic disc ischemia and collateral formation in some areas; a composite image from the other patient (b) shows diffuse ischemia in the nasal periphery and retinal neovascularization

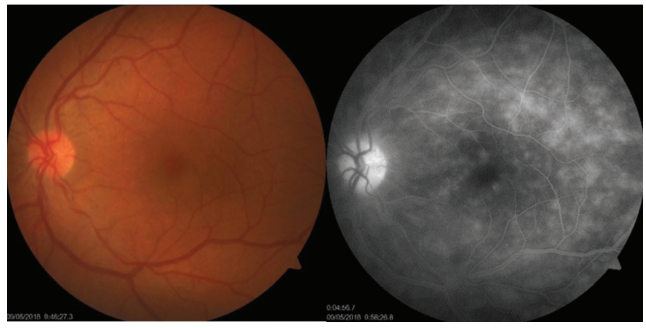

Figure 9. Fluorescein angiography of a Behçet's patient with no clinically apparent retinal vasculitis on color fundus photograph shows optic disc staining, macular edema, and diffuse capillary and vascular leakage

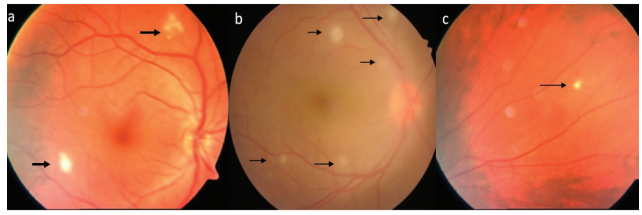

Figure 10. Superficial retinal infiltrates (arrows) are observed in different patients (a, b, c). Even a single one (c) is regarded as posterior segment involvement

picture in the most advanced stage of the disease (end-stage, terminal disease) is characterized by optic atrophy, ghost vessels, varying degrees of pigmentation, diffuse retinal atrophy, gliosis, macular scarring, and a transparent vitreous (Figure 12).[1] This clinical presentation can sometimes be confused with retinitis pigmentosa. Even patients with end-stage disease can sometimes have new activations (Figure 13).

Imaging in Behçet's Uveitis

Color fundus photography is a method we often use to visualize and monitor BU lesions. Demonstrating vitreous haze, retinal infiltrates, and the spontaneous regression of the vitreous precipitates observed in the inferior peripheral retina is particularly helpful in distinguishing from other possible causes.[31] Despite all of the advances in imaging methods, FA is still the gold standard for detection and monitoring of the occlusive and leaky vasculitis caused by BU.[31,33] The most important FA findings of active BU include dilation and increased tortuosity of the retinal veins, vascular leakage, and leakage from the optic disc, macular, and retinal capillaries. Fern-like capillary leakage is the most characteristic FA finding of BU as well as an important indicator of activity (Figure 14). This finding shows that inflammation is active even if the uveitis appears calm clinically and indicates that the current treatment is inadequate. The extent and occlusivity of retinal vascular involvement, capillary non-perfusion areas, collateral vascular formations, and neovascularization are best visualized with FA.[31,33] The need for laser photocoagulation (LPC) is also determined based on FA findings. As mentioned above, most NVD exhibit diffuse capillary leakage rather than ischemia as an indicator of persistent inflammation. Therefore, the treatment is not LPC, but rather strengthening the anti-inflammatory therapy.[30] FA findings also have prognostic value. In various studies, FA findings such as NVD, macular window defect, macular ischemia, macular leakage, posterior and diffuse retinal vasculitis, excessive retinal vascular leakage, optic disc hyperfluorescence, peripheral capillary

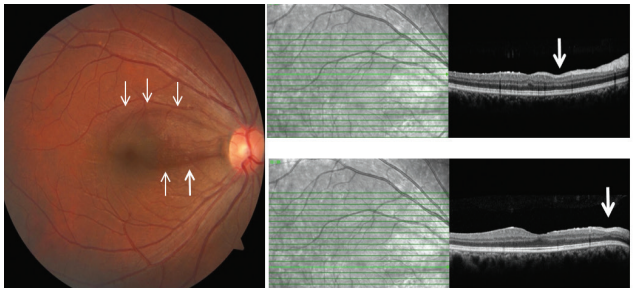

Figure 11. Color fundus photograph of a Behçet's uveitis patient shows a wedge-shaped localized retinal nerve fiber layer loss (arrows) in the superior macula and the papillomacular bundle and thinning (arrow) on SD-OCT sections corresponding to the area of loss

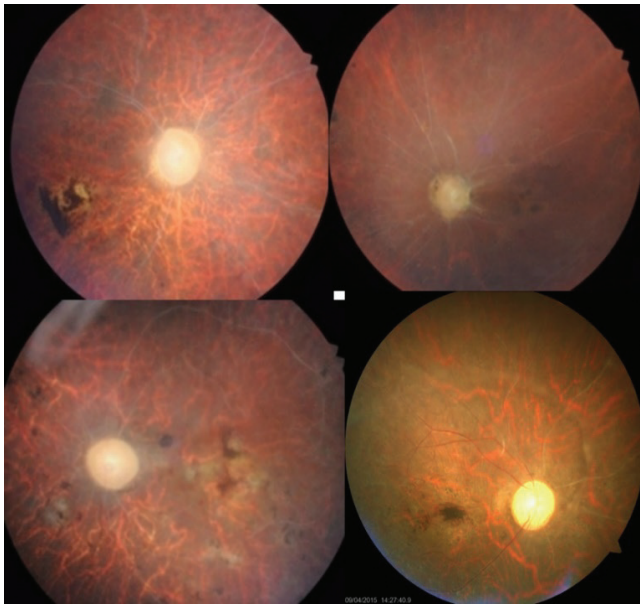

Figure 12. The appearance of the fundus in different patients with end-stage disease. Optic atrophy, macular scarring, retinal atrophy, ghost vessels, and areas of retinal pigmentation can be seen

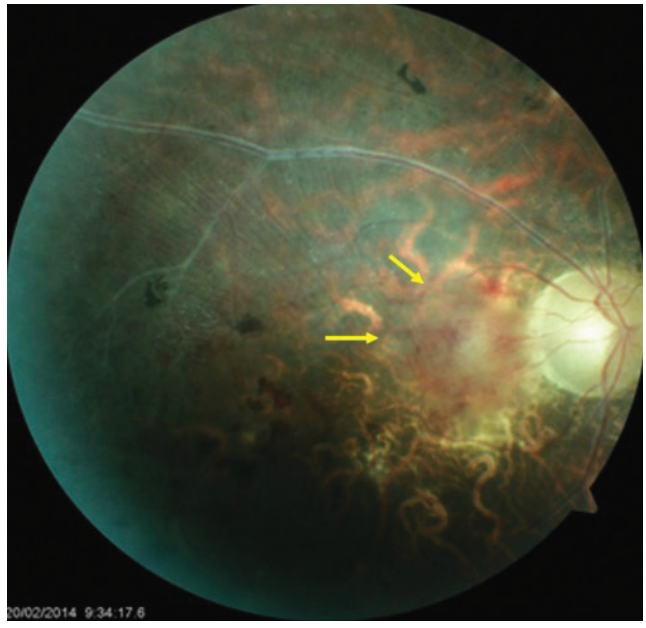

Figure 13. Active vasculitis in the papillomacular bundle (yellow arrows) is observed in an end-stage eye with retinal and macular atrophy, gliotic sheathing, pigmentation, and optic atrophy

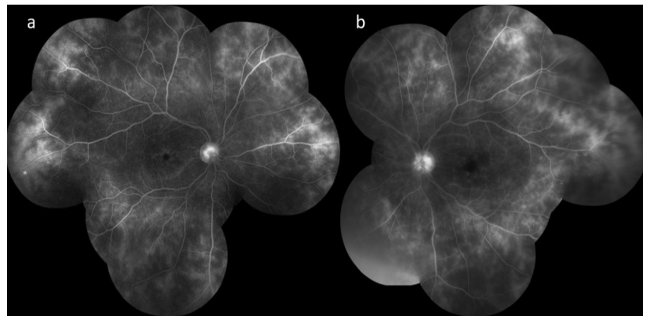

Figure 14. Bilateral (a,b) optic disc staining, cystoid macular edema, vascular leakage, and fern-shaped capillary leakage are noted on fluorescein angiography in a Behçet's patient

non-perfusion, CME, and arterial narrowing have been associated with poor visual prognosis.[34,35,36,37] For this reason, the focus shifted to angiographic classification and staging of Behçet's retinal vasculitis and monitoring activation accordingly.[35,38,39] Keino et al.[40,41] reported that after 1 year of infliximab (IFX) therapy, there were decreases in both ocular inflammatory episodes and retinal vascular leakage and disc leakage. When the same authors evaluated the effect of IFX over a 4-year period, they demonstrated that mean retinal vascular and disc leakage scores decreased further after each year of treatment.[41]

With conventional fundus cameras, images limited to 30°-60° can be obtained and the entire retina cannot be visualized simultaneously. The ultra-wide-field imaging system (OptosPLC, Scotland, UK) makes it possible to obtain fundus photographs and autofluorescence and angiography images of a 200° field.[31] Studies comparing clinical examination with conventional and ultra-wide-field imaging have shown that wide-field imaging contributes significantly both to detection of disease activity and treatment decision-making.[42,43,44] A recent study by Jones et al.[43] compared standard 7-zone FA with an ultra-wide-field imaging system in a series of 106 cases of retinal vasculitis. It was reported that 43.4% of lesions detected with wide-field imaging could not be visualized with standard FA and that a large portion of treatment modifications were made based on the lesions detected by wide-field imaging.[43] Peripheral retinal vascular involvement due to Behçet's retinal vasculitis and the associated leakage, ischemia, and neovascularization are quite difficult to demonstrate with standard FA. Therefore, visualizing the peripheral retina with ultra-wide-field imaging contributes significantly to the diagnosis, monitoring, and treatment of Behçet's vasculitis (Figure 15).[31] In fact, the use of wide-field imaging in 20 Behçet's patients with active retinal vasculitis revealed additional findings requiring treatment changes in 80% of the patients. It is notable that peripheral retinal non-perfusion was observed in 66.7% of the eyes. Based on wide-field imaging findings, immunomodulatory therapy was modified in 65% of the patients and LPC was performed on 10.5% of eyes.[44]

As BD is a systemic vasculitis, involvement of the choroidal vasculature is also expected. The method that best shows the choroidal vascular structure is indocyanine green angiography (ICGA). The ICGA findings seen in BU have been demonstrated in various studies.[45,46,47] These findings are not specific to BU, but include filling delay/defect of the choriocapillaris, hyperfluorescence of stromal vessels, staining of the choroidal vascular walls, hyperfluorescent spots, hyperfluorescent plaques, and hyperfluorescence in the optic disc and diffuse hyperfluorescence in the choroid in the middle or late phase of ICGA. [45,46,47] It has been shown that these findings are not significantly associated with systemic findings of BD. Likewise, it is believed that there is no remarkable relationship between FA and ICGA findings, that ICGA does not provide additional information regarding disease activity and treatment monitoring, and therefore is unnecessary in the routine follow-up of BU. ICGA is used more for differential diagnosis than diagnosis.[31]

There are not many studies regarding the use of fundus autofluorescence (FAF) imaging in BU. In a study conducted with ultra-wide-field FAF, it was reported that active retinal vasculitis may lead to retinal pigment epithelium (RPE) changes in the peripheral retina, with 82.3% of patients showing such changes.[44] Our view is that FAF does not make an additional contribution in the follow-up of BU.[31]

OCT is a method that non-invasively shows posterior pole lesions and macular complications and is frequently used in the follow-up of BU. Although FA is the best method for evaluating the general uveitis activity, OCT is superior in demonstrating macular edema and identifying its pattern. Only OCT can show whether the fluid is diffuse, cystoid, or located subretinally.[48] With the introduction of OCT, it has been shown that BU can cause not only CME, but also serous macular detachment.[49] Vitreoretinal interface disorders are also best demonstrated by OCT. The incidence of interface disorders was shown to be associated with uveitis duration.[50] Complications such as epiretinal membrane, vitreomacular adhesion, vitreomacular traction, lamellar or full-thickness macular holes, macular atrophy, and macular scarring are best visualized with OCT. Spectral domain (SD)-OCT also enables evaluation of the outer retinal layers (Figure 16). The integrity of the ellipsoid zone (inner segment [IS]/outer segment [OS] band) and interdigitation zone is closely associated with visual function and prognosis in eyes with uveitic macular edema. The foveal thinning and ellipsoid zone irregularity shown on OCT reflect irreversible damage to the macula caused by BU and are an indicator of poor visual prognosis.[31] In a recent study, Kang et al.[51] examined whether central macular thickness (CMT) and macular volume values measured with SD-OCT were associated

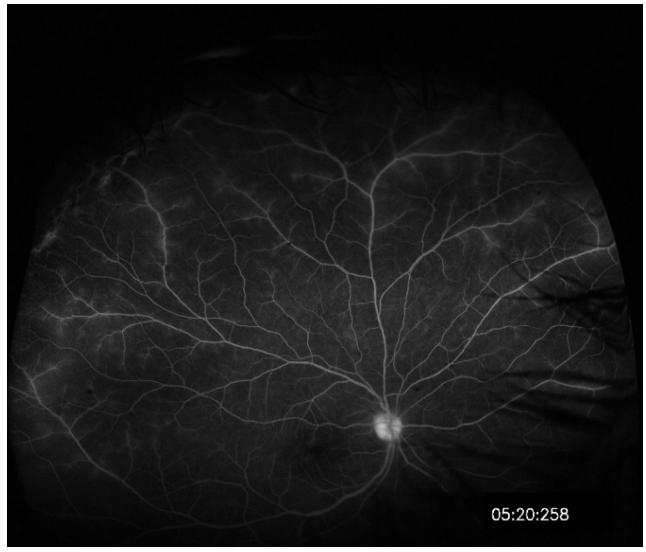

Figure 15. Fluorescein angiography with ultra-wide-field imaging shows vascular leakage in the superior and temporal periphery in addition to the optic disc and macular leakage. Shadowing caused by the lashes is present in the inferior and nasal regions

with the uveitis severity in BU patients without macular edema. Mean CMT and macular volume were significantly higher in patients with posterior involvement and decreased with treatment. They reported that OCT is a useful adjunctive method in BU follow-up, especially for identifying posterior segment involvement, that it would reduce unnecessary FA imaging, and that it is also useful for treatment monitoring. However, as the authors also acknowledged, OCT cannot replace FA in the follow-up of BU because it does not demonstrate the current state of the retinal vasculature. In addition, since macular thickening may occur independent of disease activity in eyes with permanent vascular damage, follow-up with OCT alone is misleading in chronic cases.[51]

Nevertheless, the use of OCT has improved our understanding of the structure of BU lesions and the damage they cause. Transient superficial white infiltrates are the most common lesions seen in BU exacerbations. SD-OCT sections obtained from over these retinal infiltrates show focal retinal thickening, blurring of the inner retinal layers, as well as increased hyperreflectivity and optical shadowing (Figure 17). Unlike in retinochoroiditis, there is no choroidal thickening below the retinal infiltrates and the RPE contour is not disrupted. These infiltrates disappear quickly without leaving a clinically apparent scar. However, SD-OCT sections have shown that internal retinal atrophy develops in this region and that the superficial retinal infiltrates at the posterior pole leave localized non-glaucomatous defects in the RNFL (Figure 11).[31,32,33,52] Papillomacular or arcuate RNFL defects, which can be demonstrated very well with SD-OCT, also lead to localized visual field defects.[32,52] These localized RNFL defects are a diagnostic finding indicative of posterior pole involvement in early BU but cannot be observed in end-stage disease due to diffuse retinal and optic atrophy.[31] In Behçet's neuroretinitis, the localized vitreous inflammation that appears like a hat over the optic disc infiltration and its regression can also be observed non-invasively on SD-OCT (Figure 18).[31]

Numerous enhanced depth imaging (EDI)-OCT studies have been conducted in BU patients and they have yielded conflicting results. One study demonstrated that subfoveal choroidal thickness is greater during the acute stage compared to the remission period and is associated with clinical inflammation scores, while another study showed that thickness was not related to uveitis severity or duration.[31] There are even studies indicating that the choroid is thinner in patients with active posterior uveitis or that choroidal thickness does not differ between patients experiencing acute episodes and those who are in remission. It has been suggested these differences in results stem from the inhomogeneity of the patient populations, differences in activity and remission criteria, and varying disease durations. The fact that choroidal thickness shows individual variations also contributes to these conflicting results. For this reason, automated central foveal thickness measurement by OCT is still a more useful method for evaluating the inflammatory activity of BU.[31] A fairly recent study by Onal et al.[53] quantitatively evaluated choroidal structural changes in patients with active BU. It was shown that there was enlargement of the choroidal stroma in the patient group compared to the control group, but that this did not lead to an increase in choroidal thickness or make a difference in terms of subfoveal choroidal thickness. In contrast, the authors stated that central foveal thickness measurement is a useful and non-invasive method for evaluating inflammatory activity in early BU. In their study, central foveal thickness was shown to be significantly associated with visual acuity, BU ocular episode score, and total FA and ICGA scores.[53] The studies of both Onal et al.[53] and Kang et al.[51] show that CMT measurement is an easily applicable method for assessing activity in patients with early BU, who do not have macular edema or macular and optic atrophy.

Optical coherence tomography angiography (OCTA) is a newer imaging method that demonstrates retinal and choroidal vascular morphology. There are few studies on its use in cases of BU.[54,55,56] In their first study, Khairallah et al.[54] reported

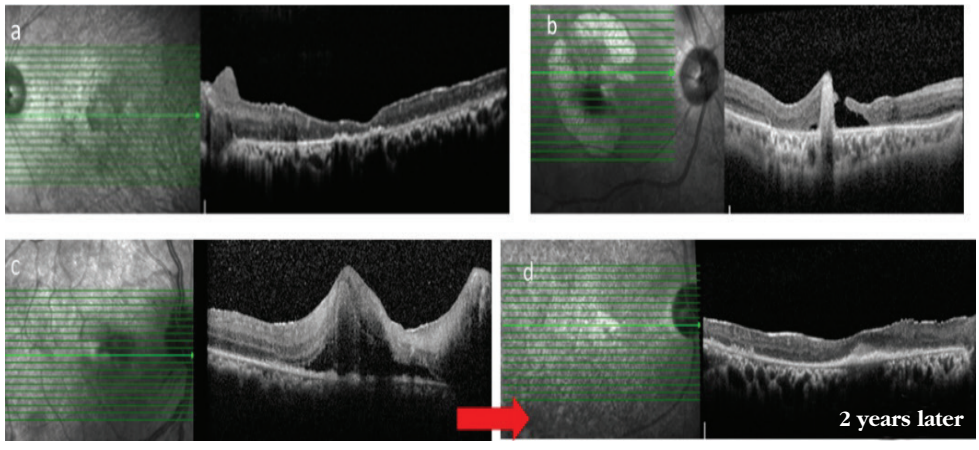

Figure 16. Macular atrophy in a patient with advanced Behçet's uveitis (a), macular atrophy and hole in another patient (b), a patient who presented with active retinitis involving the macula and associated macular edema (c), and the same patient 2 years later, exhibiting disorganization and atrophy of the retinal layers and subfoveal fibrosis (d)

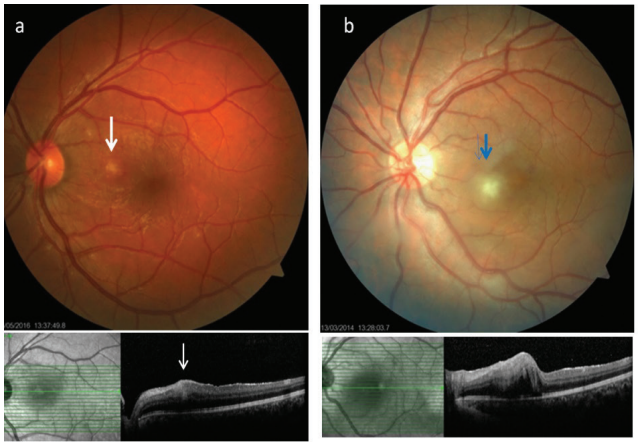

Figure 17. The superficial retinal infiltrates (a, white arrow; b, blue arrow) associated with Behçet's uveitis led to focal retinal thickening and blurring and increased hyperreflectivity in the inner retinal layers in particular, while the contour of the retinal pigment epithelium was not disrupted

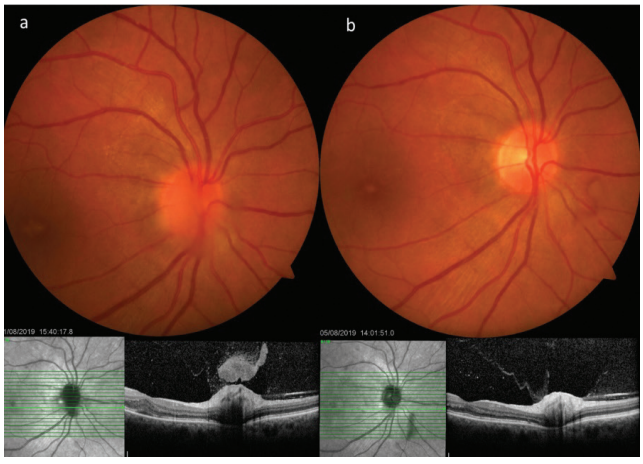

Figure 18. A patient with Behçet's neuroretinitis exhibits optic disc infiltration accompanied by vitreous inflammation that looks like a hat over the disc on SD-OCT, as well as subfoveal fluid and cystic edema (a). Four days after intravenous methylprednisolone therapy, substantial regression of the optic disc infiltration, overlying vitreous inflammation, and macular edema are observed (b)

that the foveal avascular zone was larger and capillary vessel density was lower in the BU group compared to the control group, and that OCTA was superior to FA in demonstrating perifoveal microvascular changes. It was also shown that impaired capillary perfusion and capillary network anomalies were more pronounced in the deep capillary plexus compared to the superficial capillary plexus.[54] Subsequent studies have also supported these findings.[55,56]

Treatment of Behçet's Uveitis

The path to preventing recurrent episodes of uveitis and the resulting ocular complications, and thus improving visual prognosis, lies in effective treatment. There are several goals in the treatment of BU. Quickly suppressing acute episodes to prevent tissue damage and restore potential vision is the primary goal, but is not sufficient. Additional goals include suppressing chronic subclinical inflammation to prevent possible complications, preventing recurrences, and maintaining achieved remission, thereby preserving vision.[57]

At present, corticosteroid (CS) monotherapy has no place in the treatment of BU, and posterior segment involvement definitely requires the use of immunosuppressive or immunomodulating agents.[58] However, CSs are still used for the treatment of acute inflammatory episodes. When a rapid response is desired, the most commonly used treatment protocol consists of 1 g/day intravenous (IV) pulse methylprednisolone for 3 days, followed by high-dose oral prednisone (1 mg/kg/day) which is tapered gradually and reduced to the maintenance dose (≤7.5 mg) after active inflammation has been suppressed.[21,59] Starting with a high oral dose (1-1.5 mg/kg) is another option. Immunosuppressive agent(s) should be started simultaneously and used in conjunction with CSs until they take effect. Periocular or intravitreal CSs can be used as an adjunctive therapy in cases where systemic CSs cannot be used or an adequate response is not achieved, and especially in patients with a unilateral panuveitis episode and/or refractory CME.[60,61] It should not be forgotten that BD is a systemic disease and should therefore be treated systemically. When treatment must be intensified or switching to a biologic agent is necessary, CS injections should be kept in mind as a convenient and time-saving adjunctive therapy.[57,61] Markomichelakis et al.[62] reported that a single-dose IFX infusion was faster acting than IV or intravitreal CS in the suppression of acute episodes. Therefore, it is a good option for this purpose, but its use as a first-line treatment agent is not currently feasible in Turkey.

In cases of isolated anterior uveitis, treatment with potent CS drops at high initial frequency and tapered to discontinue after 6-8 weeks and mydriatic and/or cycloplegic agents started at 2-3 times a day and discontinued at 2-3 weeks is sufficient.[21]

For posterior segment involvement, the most commonly used conventional treatment agents are antimetabolites (azathioprine [AZA], mycophenolate mofetil, methotrexate), T-cell inhibitors (cyclosporine-A [CSA], tacrolimus), and alkylating agents (cyclophosphamide, chlorambucil). Of these, only AZA and CSA were shown to be effective in randomized controlled trials.[63,64,65,66] These trials have also been supported by many clinical studies.[67,68,69,70] Despite the introduction of many new molecules, AZA and CSA are still the most commonly used agents, either alone or in combination. They are also known to be more effective when used in combination.[71] Complete blood count and liver function tests should be followed for AZA, while complete blood count, kidney function, blood pressure, and development of gingival hyperplasia and hirsutism should be followed when treating with CSA. Another important point to consider about CSA is that it should not be used by patients with neurological involvement.[72] Although no study has investigated the use of mycophenolate mofetil to treat BU specifically, there are studies showing that this drug is effective in uveitis patients, which also included those with BU.[73] Although alkylating

agents are still used for some extraocular involvements of BD (acute deep vein thrombosis, arterial involvement), they are not preferred in cases of ocular involvement due to serious adverse effects, such as development of malignancy, and the current availability of biologic agents. Although colchicine is effective for the mucocutaneous symptoms of BD, its efficacy against ocular involvement has not been demonstrated.[21,74]

More potent and faster acting agents are needed for patients who are non-responsive to conventional treatment, those who have frequent recurrences, and those who present with severe posterior segment involvement and vision loss. Currently, biologic agents are used for this purpose. In 2018, EULAR (European League Against Rheumatism) updated its 2008 recommendations for the treatment of BD.[74,75] The updated EULAR recommendations also broadened the areas of use of biologic agents in the treatment of BU. While they formerly recommended starting BU patients with posterior segment involvement on AZA and CS therapy and adding CSA or IFX or switching to interferon-alpha (IFN-α) for non-responders, they now recommend initiating AZA, CSA, INF-alpha, or monoclonal anti-tumor necrosis factor (TNF) therapy for the treatment of posterior segment involvement. It is emphasized once more that CSs should not be used alone, but rather in combination with AZA or other immunosuppressants. It is also stressed that high-dose CSs, IFX, or IFN-α-2a should be used to treat patients presenting with first-time or recurrent vision-threatening acute uveitis. In other words, the use of biologic agents as first-line therapy is recommended in selected patients. Intravitreal CS injection is recommended as an adjunct to systemic treatment in patients with unilateral episodes.[75] Expert recommendations for the use of anti-TNF agents to treat ocular inflammatory diseases published by Levy-Clarke et al.[76] also recommended IFX and adalimumab (ADA) as first-line treatment for BU only, and second-line therapy for all other causes.

The human-mouse chimeric monoclonal antibody IFX and the completely human protein-based ADA are the anti-TNF agents most commonly used in the treatment of BU. Published studies show that both agents effectively treat refractory BU through the rapid and potent suppression of ocular inflammation. They are known to reduce both the frequency and severity of uveitis episodes. Anti-TNFs reduce the optic disc and vascular leakage observed on FA, enable substantial CS cessation, and are generally well tolerated.[40,41,77,78,79,80,81,82,83] When conventional therapy and IFX were compared with respect to the treatment of Behçet's retinal vasculitis, it was shown that with IFX, the mean remission period was longer (17 months vs 5 months), the average number of episodes in 24 months was lower (1.2 vs 6.3), visual outcomes were better (the prevalence of optic atrophy was 30% with IFX and 60% with conventional therapy), and there were fewer ocular and systemic complications.[84]

If IFX and ADA were compared, the conclusions would be that both effectively suppress uveitis, that IFX has a fast-acting and potent anti-inflammatory effect equivalent to that of IV pulse methylprednisolone but should be combined with an antimetabolite due to its high immunogenicity (autoantibody formation, loss of effect, infusion reaction), whereas ADA is more effective at inducing sustained remission and is safer and more appropriate as monotherapy due to its lower risk of immunogenicity. Another difference is how they are used. IFX is administered IV in hospital conditions, while ADA is administered subcutaneously.[76,85,86] The first study to compare these 2 anti-TNF agents in BU patients resistant to conventional therapy was published in 2019 and confirmed that both agents were effective.[87] However, it was also reported that after 1 year of treatment, patients using ADA had better outcomes, and in particular showed significantly greater improvement in visual acuity and treatment continuation rate.[87] Another fact that should be regarded as being in favor of ADA is that it is the only biologic agent tested in randomized controlled trials and approved for the treatment of non-infectious uveitis.[88,89]

Another biologic agent that is often used to treat Behçet's uveitis and whose efficacy has been demonstrated in many studies is IFN-α-2a. It provides complete or partial improvement of inflammation at rates of up to 98% and improves or stabilizes vision when used to treat BU. It takes effect within 2 to 4 weeks. It has been reported that due to its antiangiogenic activity, it also leads to reperfusion of occluded vessels and regression of neovascularization.[30,90,91,92,93,94,95,96,97,98] There is no standard usage. Some recommend starting at a high dose and then tapering after a response is achieved, while others prefer to start with a low dose and increase the dose according to the response achieved. Due to its potential myelosuppressive effect, it should not be used together with other immunosuppressants. The main adverse effects include the influenza-like symptoms experienced by nearly all patients, especially at the beginning of treatment, as well as alopecia, elevated liver enzymes, thyroiditis, autoantibody formation, weight loss, and depression.[21,97] The most important advantage of IFN-α-2a is that it can provide long-lasting remission that persists even after treatment is discontinued, and that the same effectiveness can be attained if treatment must be reinitiated.[95,96]

When Ozgüler et al.[97] compared studies in which IFN-α and IFX were used to treat BU, they reported that IFX took effect more rapidly (24 hours) and improved visual acuity in more cases (76% vs 46%), but that rates of sustained remission (71% vs 44%) and CS cessation (66% vs 33%) were higher with IFN. Rates of complete or partial remission and drug discontinuation due to adverse effects were similar.[97] Yalçindağ and Köse[98] conducted the only study comparing IFN-α and IFX in BU patients resistant to conventional therapy and reported that there was no difference between the agents in terms of anti-inflammatory activity or visual acuity improvement, while there were more adverse effects with IFN.

In cases where an adequate response is not achieved even with biologic agents, instead of using high-dose CS, the current biologic agent should be increased in dose and/or frequency

or treatment should be switched to an alternative biologic. Tocilizumab, an anti-interleukin-6 (IL-6) receptor antibody, was used to treat 5 BU patients resistant to IFN-α and anti-TNF-α therapy, and all of the patients showed both clinical and angiographic improvement as well as a significant reduction in CMT.[99] Another molecule reported to be successful in treating resistant patients is golimumab, which is also an anti-TNF-α agent. It was shown to induce rapid regression of retinal vasculitis and reduce ocular episodes in 5 patients resistant to conventional and other biologic therapies.[100] Another alternative may be the use of the IL-1 inhibitors anakinra and canakinumab. Fabiani et al.[101] reported that Behçet's patients with uveitis of long duration in particular responded better to IL-1 inhibitors. Studies on pegylated IFN-α, secukinumab, daclizumab, gevokizumab, and rituximab showed they were not sufficiently effective.[97]

We can summarize our current approach to the treatment of Behçet's uveitis as follows: Every patient with posterior segment involvement is started on conventional therapy consisting of AZA ± CSA. If the patient presents during an acute episode, we also add systemic CS, aiming to taper the dose slowly and discontinue within 3 months. As second-line treatment we use biologics, of which IFN-α is our first choice. In patients who are non-responsive to this treatment, we switch to anti-TNF agents. If there is severe, vision-threatening involvement at the time of admission, we try to switch to biologic agents without wasting too much time with conventional agents. Periocular or intravitreal CS injections are used as adjunctive therapy in patients with severe involvement whose treatment we plan to change and especially in patients with unilateral exacerbations or a condition that precludes systemic CS use.

Before initiating a systemic conventional or biologic therapy, all patients should be evaluated in terms of complete blood count, liver and kidney function tests, systemic comorbidities, infectious diseases like hepatitis and tuberculosis (TB), history of malignancy, mental state, pregnancy/breastfeeding, and immunization history. Patients should be screened for risk of TB and demyelinating disease before using an anti-TNF agent.[102] Among the rheumatoid diseases, BD poses the highest risk for TB. Anti-TNF agents increase this risk. The risk with IFX is reported to be 2 fold higher than with ADA.[103] For patients with an induration >5 mm on tuberculin skin test and/or positive QuantiFERON test, it is recommended to start isoniazid prophylaxis 1 month before anti-TNF therapy and continue for 9 months. In Turkey, the Ministry of Health issued a guide for the management of TB in patients using anti-TNF.[104] Anti-TNFs should not be used by patients with a history of demyelinating disease, and those with a family history should be informed of the risk.[85]

As mentioned above, FA is the gold standard in treatment monitoring. However, the laser flare meter, which objectively assesses the presence of inflammation by measuring the amount of protein in the anterior chamber, is also an important tool in the follow-up of BU. Tuğal-Tutkun et al.[105] demonstrated that there was a significant relationship between laser flare meter measurements and anterior chamber cells, vitreous haze score, and fundus lesions in BU patients. It was also shown in patients in clinical remission that anterior chamber flare score and FA leakage score were significantly associated and that those with flare measurements over 6 photons/ms were more likely to have recurrence. Therefore, laser flare meter measurements can be used in patient follow-up as an adjunctive method that demonstrates the presence of chronic refractory vasculitis and reduces the need for FA.

There is still no definitive answer to the question of when to discontinue treatment. Clinical improvement of uveitis does not mean that the disease is inactive. Treatment effectiveness should be evaluated based on clinical symptoms together with FA findings (Figure 19). There must be no signs of retinal vascular and capillary leakage on FA to say that complete remission has been achieved. Generally, we use the immunosuppressive/biologic agent for at least 2 years, and if clinical and angiographic remission are observed we continue treatment while reducing the drug dose and/or lengthening the infusion/injection intervals for another year with periodic FA examination, and finally discontinue treatment. Patients should be followed closely even treatment discontinuation.

Prognosis of Behçet's Uveitis

Despite reports that the course of BD has become milder in recent years due to advances in treatment, changing environmental factors, and increased awareness regarding the disease, it still has a high potential for blindness.[106] The most important determinant of visual prognosis is cumulative damage

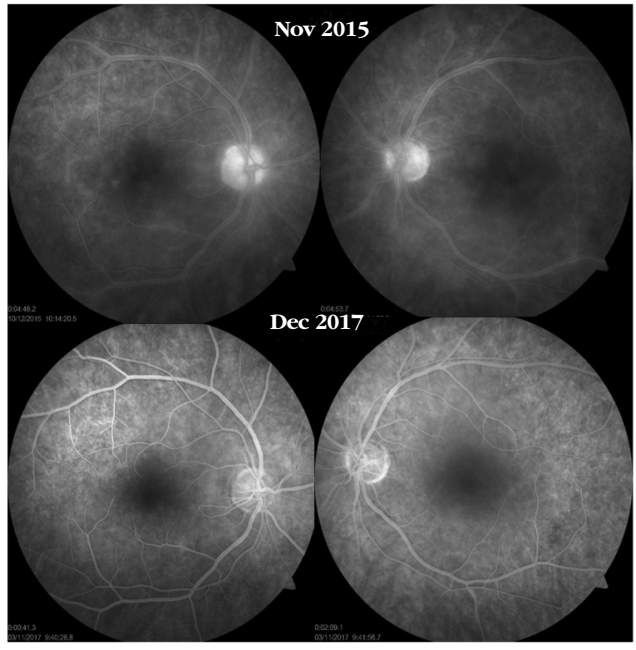

Figure 19. A Behçet's uveitis patient with bilateral optic disc staining, macular edema, and vascular and capillary leakage shows marked improvement approximately 2 years after interferon-alpha therapy

caused by recurrent episodes involving the posterior segment. The main factor in improving prognosis is developments in therapeutic agents and our understanding of treatment. The introduction of CSA in the 1990s and of biologic agents in the 2000s, the abandonment of CS monotherapy, earlier initiation of immunomodulatory therapy, and the use of combined treatment regimens have improved visual prognosis.[13,107,108,109]

Conclusion

BU is the leading cause of non-infectious uveitis in Turkey. It is characterized by recurrent episodes of non-granulomatous panuveitis and occlusive retinal vasculitis. As it is more common among young adults and is potentially blinding, early diagnosis and potent treatment are crucial.

Peer-review: Externally peer reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2020.53503
Turk J Ophthalmol 2020;50:183-186

Case Report

In Vivo Confocal Microscopy and Anterior Segment Optical Coherence Tomography Findings in Two Cases with Mucopolysaccharidoses

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Abstract

The mucopolysaccharidoses are a group of disorders caused by inherited defects in lysosomal enzymes resulting in widespread intracellular and extracellular accumulation of glycosaminoglycans. Due to the mucopolysaccharidoses subtype, glycosaminoglycans can be deposited in many organs and tissues including cornea. In this report, we presented *in vivo* confocal microscopy and anterior segment optical coherence tomography findings in a 39-year old man with Scheie syndrome and a 41-year old woman with Morquio syndrome (Heidelberg Retina Tomograph 3 Rostock module, Germany) and reviewed the literature. On *in vivo* confocal microscopy, there were multiple small and larger hyperreflective deposits in the epithelium, Bowman layer and anterior stroma and abnormally shaped, elongated keratocytes with hyporeflective round structures, which might be vacuoles in the anterior-mid stroma. In anterior segment optical coherence tomography images, accumulation of glycosaminoglycans deposits lead to an increased hypereflective appearance throughout the thickened cornea.

Keywords: *In vivo* confocal microscopy, mucopolysaccharidoses, Morquio syndrome, Scheie syndrome

Introduction

The mucopolysaccharidoses (MPSs) are a group of disorders caused by inherited defects in lysosomal enzymes resulting in widespread intracellular and extracellular accumulation of glycosaminoglycans (GAGs). MPSs are subdivided according to their enzyme defects and their systemic manifestations.[1]

Scheie syndrome (MPS-IS; 607016) is a rare form of MPSs with an autosomal recessive pattern. It is caused by mutations in the *IDUA* gene (4p16.3) that lead to a partial deficiency in the α-L-iduronidase enzyme and lysosomal accumulation of dermatan sulphate and heparan sulphate. In MPS-IS, ocular findings have been reported including corneal clouding, retinal pigment epithelial changes, acute angle closure glaucoma, optic nerve swelling and atrophy, and changes similar to macular edema as well as systemic findings.[2] Corneal clouding becomes visually significant after the first decade of life in MPS-IS. Diagnosis is based on the detection of increased urinary secretion of heparan and dermatan sulfate through the 1.9-dimethylmethylene blue test, the electrophoresis of GAGs, enzymatic deficiency in leukocytes or fibroblasts and genetic testing.[1,2,3] In MPS-IS, the main histopathological features are vacuoles containing fibrillogranular material in corneal epithelial cells and keratocytes, a disrupted epithelial basement membrane, slightly attenuated Bowman layer, changes in collagen fibers and keratocytes with GAG accumulation, a normal Descemet's membrane, and inconstant vacuoles in the endothelial cells.[4]

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Received: 01.09.2019 **Accepted:** 02.01.2020

Cite this article as: Karaküçük Y, Bozkurt B, Şahin M, Okudan S. *In Vivo* Confocal Microscopy and Anterior Segment Optical Coherence Tomography Findings in Two Cases with Mucopolysaccharidoses. Turk J Ophthalmol. 2020;50:183-186

Morquio syndrome (MPS-IVA; 253000) is an autosomal recessive lysosomal storage disorder caused by mutations in *GALNS* (16q24.3) and deficient N-acetylgalactosamine-6-sulphatase. This enzyme deficiency leads to progressive accumulation of keratan sulphate and chondroitin-6-sulphate in the cornea, bone, cartilage, and ligaments. In addition to systemic findings, the ocular findings in patients with MPS-IVA include cataract, optic atrophy, tapetoretinal pigmentary degeneration, and corneal clouding.[5] Corneal clouding and retinopathy, which are common in all variants of MPS, are the major causes of impaired vision. On light microscopy, the basal cells of the epithelium are swollen and the keratocytes and endothelium contain numerous intracytoplasmic bodies.[6] At the ultrastructural level, the apical portion of the basal cells is packed with small clear membrane-bound vacuoles which decrease in numbers in the wing cell and superficial cell layers.[6] Keratocytes include intracytoplasmic inclusions in the form of multilaminar bodies, fingerprint whorl patterns, fibrillogranular inclusions, small lipid vacuoles, and clear vacuoles. The endothelial cell cytoplasm also contains membrane-bound vacuoles which fuse to form large empty cytoplasmic spaces, causing the cell membranes to collapse.

In vivo confocal microscopy (IVCM) of the living human cornea offers the ability to perform real-time imaging without tissue damage and has been widely used in clinical practice to evaluate corneal and ocular surface pathologies. In the literature, there are only a few studies about the use of IVCM and anterior segment optical coherence tomography (AS-OCT) in MPSs.[7,8,9,10,11,12] Herein, we report the clinical, AS-OCT, and laser IVCM findings of 2 patients with MPS-IS and MPS-IVA. Our aim was to compare our findings with previous studies in the literature, determine whether these imaging devices can show the typical histopathological features of MPS, and demonstrate the differences between MPS-IS and MPS-4A.

Case Reports

Case 1

A 39-year-old man with a prior diagnosis of MPS-IS who had been using a dorzolamide-timolol fixed combination and brimonidine for the last 5 years presented to our clinic for refractive error and glaucoma evaluation. He had normal intellectual function, an abnormal gait, and skeletal dysmorphism. He had low levels of leukocyte α-L-iduronidase enzyme activity. His visual acuity was 4/20 in the right eye (OD) with correction of +8.50/+1.00x130 diopter (D) and 4/20 in the left eye (OS) with +8.50/+1.25x5 D. Biomicroscopic examination showed multiple corneal opacities in the corneal stroma and severe corneal clouding (Figure 1a). Intraocular pressure (IOP) measured with a Goldmann applanation tonometer was 24 mmHg in both eyes (OU). The fundus could not be examined due to severe corneal haze. Laser IVCM (Heidelberg Retina Tomograph 3 Rostock module, Heidelberg Engineering GmbH, Heidelberg, Germany) showed multiple small hyperreflective deposits in the epithelium (Figure 1b), larger opacities (up to 80 µm in length) in the epithelium, Bowman layer and anterior stroma (Figure 1c,d), hyperreflective corneal stroma with round hyporeflective structures inside (Figure 1e,f). The posterior stroma and the endothelium could not be assessed due to stromal hyperreflectivity. On AS-OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) examination, thick corneas (central corneal thickness [CT] 658 µm OD and 664 µm OS, peripheral CT 950 µm) with increased hyperreflectivity in the stroma were observed (Figure 1g). Iridocorneal measurements could not be taken. Anterior chamber depth measured by a corneal topography device with a Scheimpflug camera (Sirius, CSO, Italy) were 3.55 mm OD and 3.43 mm OS.

Case 2

A 41-year-old woman with a diagnosis of MPS-IVA had been followed-up for glaucoma and using timolol maleate-brimonidine fixed combination for the last 3 years. She had low levels of leukocyte N-acetylgalactosamine-6-sulphatase

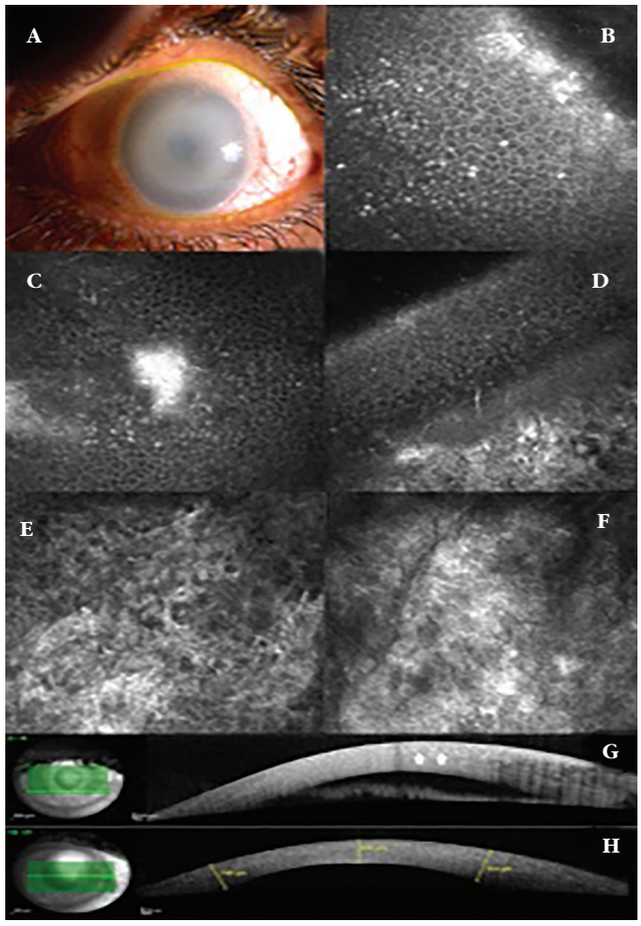

Figure 1. Slit-lamp biomicroscopy of a patient with mucopolysaccharidose-IS demonstrating severe corneal clouding obscuring iris details (a). *In vivo* confocal microscopy images showing multiple small hyperreflective deposits in the epithelium (b), larger opacities in the epithelium, Bowman layer, and anterior stroma extending up to 80 µm in length (c,d), and hyperreflective anterior and mid stroma (e,f). Anterior segment optical coherence tomography images showing thickened corneas with increased hyperreflectivity in the stroma, especially in a granular pattern in the anterior stroma (arrow) (g,h)

enzyme activity, severe skeletal deformities and gait disturbance, but no intellectual impairment. Bilateral best-corrected visual acuity was 16/20 with a correction of +0.50/+1.00x135 D OD and +1.00x105 D OS. IOP was 22 mmHg OU. Slit-lamp biomicroscopic examination revealed moderate corneal clouding and diffuse stromal opacities (Figure 2a). The fundus examination could hardly be done, but the optic discs seemed normal with a cup/disc (C/D) ratio of 0.4. IVCM revealed hyperreflective basal epithelial cells, dot-like and larger opacities (up to 25-30 µm in length) in the Bowman layer and the anterior stroma (Figure 2b) and around the subepithelial nerve plexus (Figure 2c). Abnormally shaped, elongated keratocytes and hyporeflective dark, round structures outlined by white borders (which might be vacuoles), lacunae, and microdots were observed in the anterior-mid stroma (Figure 2d-e). The endothelial layer, although not very clear, seemed normal (Figure 2f). In AS-OCT images, diffuse hyperreflectivity in the corneal stroma and thick corneas were noted (CCT 634 µm OD and 629 µm OS) (Figure 2g). Iridocorneal angle measurements, which could be taken only from patient 2, revealed that the angle opening distance at 500 µm from the scleral spur (AOD 500) was 210 µm on the temporal side and 251 µm on the nasal side. The temporal and nasal iridocorneal angles were 21.7° and 25.9°, respectively. Anterior chamber depth measured by a corneal topography device with a Scheimpflug camera were 3.53 mm OD and 3.67 mm OS.

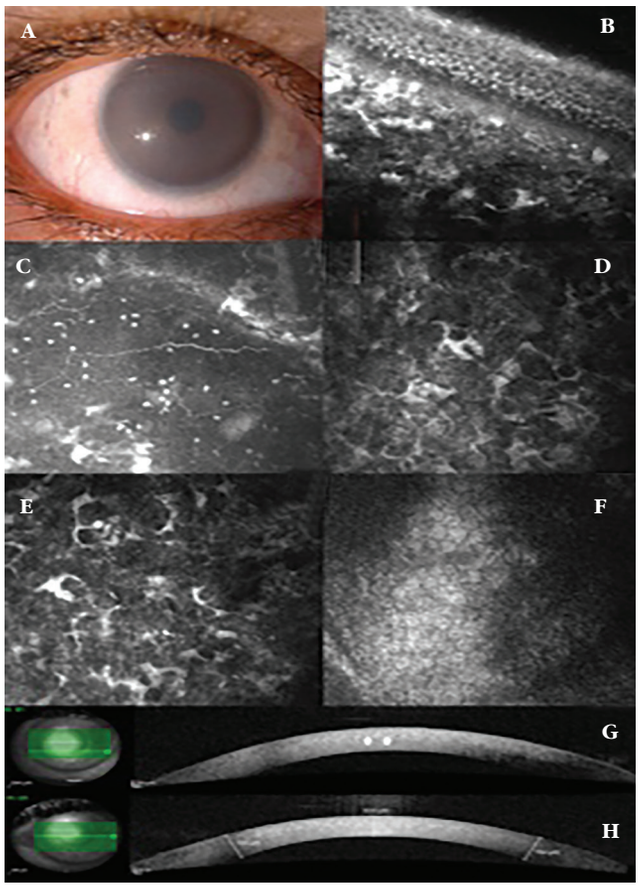

Figure 2. Slit-lamp biomicroscopy of a patient with mucopolysaccharidose-IVA demonstrating moderate corneal clouding (a). *In vivo* confocal microscopy imaging revealed hyperreflective basal epithelial cells, dot-like and larger opacities extending 25-30 µm in length in the Bowman layer and anterior stroma (b) and around the subepithelial nerve plexus (c). Abnormally shaped, elongated keratocytes and dark, round structures outlined by white borders, which might be vacuoles, lacunae, and microdots were observed in the anterior-mid stroma (d,e), while the endothelial layer, although not very clear, seemed normal (f). Anterior segment optical coherence tomography images, showing thickened corneas with diffuse hyperreflectivity in the stroma, especially in a granular pattern in the anterior stroma (arrow) (g,h)

Discussion

In AS-OCT imaging, the internal structure of the corneas of both patients showed increased hyperreflectivity. The thickness measurements of the cornea were high, around 650 µm in the center and 950 µm in the periphery. Ahmed et al.[7] reported a narrower and more compact anterior segment and angle configuration in MPS VI than in MPS I via Visante AS-OCT. MPSs type I and type VI had a greater tendency to corneal clouding, and cornea was thicker compared to type II. They also reported that corneal thickening in the periphery and narrowing of the iridocorneal angle might be the mechanisms of raised IOP in patients with MPS I and VI. Aragona et al.[9] showed diffuse hyperreflective structures throughout the thickened cornea in a patient with MPS-IS using OCT. In our patient with MPS-IVA, temporal and nasal AOD 500 were much lower than cut-off values for narrow angles (320 µm and 340 µm, respectively).

Grupcheva et al.[8] were the first to report findings using a real-time, slit-scanning IVCM to examine a 13-year-old boy with MPS-IS. There were bright cells in the basal epithelium and the keratocytes exhibited markedly altered morphology, often being round or elliptical in shape, with clearly demarcated, hyporeflective centers. The sub-basal nerve plexus contained corneal nerves similar in thickness and density to those in a normal cornea, although the nerve fibers were irregular and somewhat difficult to distinguish, possibly due to underlying fibrosis. Endothelial cell count was normal for the age group, but the cells exhibited mild polymegethism. Aragona et al.[9] described the IVCM, OCT, and histological findings of 2 corneas from a 25-year-old man with MPS-IS. Laser IVCM showed diffuse or granular hyperreflectivity in the basal epithelial cells. The keratocytes were highly reflective, causing a web-shaped stromal appearance, while the endothelial cells were barely visible. Our MPS-IS patient was a 39-year-old man who had severe corneal clouding, low visual acuity, and glaucoma. Laser IVCM revealed hyperreflective deposits in the basal epithelium, Bowman layer, and anterior stroma, which were more demonstrative than the previous studies.[8,9] This might be explained by the older age of our patient and continuous accumulation of GAG over years. In advanced cases, deposits and fibrosis lead to increased hyperreflectivity, which obscures the detailed examination of the cellular structures in the stroma and endothelium by IVCM. In our case, we could not detect typical keratocyte vacuolation and the endothelium changes.

Stewart et al.[10] reported laser confocal findings of a 7-year-old boy with MPS-IVA who had very mild diffuse, fine granular

corneal stromal appearance and good visual acuity. IVCM demonstrated a diffuse hyperreflectivity immediately posterior to the Bowman's layer and in the anterior and middle stroma. The keratocyte cytoplasm was clearly visible; it had a fine, granular appearance, and the nuclei were rounded and exhibited vacuolation, particularly in the posterior stroma. The corneal epithelium, subbasal nerves, and endothelium appeared normal.

Our MPS-IVA patient was a 41-year-old woman who had been followed-up for corneal clouding and glaucoma for the last 3 years. In IVCM imaging, there were hyperreflective basal epithelial cells, dot-like and larger opacities around the subepithelial nerve plexus, in the Bowman layer and the anterior stroma, which were not reported by Stewart et al.[10] In MPSs, GAGs accumulate progressively with age, which might explain why deposits were not observed in the corneal epithelium and around the subbasal nerves in the 7-year-old child reported by Stewart et al.[10] Also, there were abnormally shaped, elongated keratocytes and dark, round structures outlined by white borders, which were believed to be vacuoles within the keratocytes, lacunae, and microdots in the anterior-mid stroma. The endothelial layer, although not very clear, seemed normal.

IVCM and AS-OCT imaging technologies can be used to show macroscopic and microscopic corneal changes related to MPSs. In this study, using AS-OCT, we found that accumulation of GAG deposits lead to an increased hypereflective appearance throughout the thickened cornea. IVCM showed hyperreflective dot-like and larger deposits in the basal epithelium, Bowman layer, and stroma and altered morphology of keratocytes with vacuoles inside. In advanced cases with severe corneal clouding, examination of the stroma and endothelium with IVCM is not possible due to increased reflectivity in the anterior stroma.

Ethics

Informed Consent: Obtained.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B., Y.K., Concept: B.B., Y.K., S.O, Design: B.B., S.O., Data Collection or Processing: Y.K., M.Ş., Analysis or Interpretation: Y.K., B.B., Literature Search: Y.K., M.Ş., Writing: Y.K., B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2020.89814
Turk J Ophthalmol 2020;50:187-189

Case Report

A Rare Cause of Type II Neovascularization: Unilateral Retinal Pigment Epithelium Dysgenesis

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Abstract

Unilateral retinal pigment epithelium dysgenesis (URPED) is a very rare clinical condition first described in 2002. Fundus examination and imaging findings are almost pathognomonic and can facilitate diagnosis of this uncommon disease. In this article, we present a 32-year-old patient who developed type II neovascularization (NV) as a complication of URPED. After 6 months of monthly intravitreal bevacizumab injection, visual acuity increased from 20/32 to 20/20 but optic coherence tomography findings were partially improved. The aim of this report is to highlight URPED and secondary type II NV, the pathogenesis and prognosis of which are unknown but which cause visual loss especially in the younger population.

Keywords: Unilateral retinal pigment epithelium dysgenesis, type II neovascularization, bevacizumab

Introduction

Unilateral retinal pigment epithelium dysgenesis (URPED) is a very rare, unilateral condition that affects the younger population. It is typically characterized by a single leopard-spot lesion with a seashell-like scalloped appearance located in the posterior pole and extending to the optic nerve. The lesion is in the RPE layer and gets its leopard-spot appearance due to fibrotic and hyperplastic changes in its periphery and areas thinning in its center. Diagnosis is established with fundoscopic examination together with fluorescein angiography (FA) and fundus autofluorescence (FAF), which provide reverse images.[1,2] Visual prognosis depends on the presence of associated neovascularization (NV) (type 1: choroidal NV, type II: subretinal NV, type III: retinal angiomatosis proliferation).[2,3,4]

In this report, we present the treatment of a patient with type II NV secondary to URPED with intravitreal bevacizumab. Our aim was to highlight URPED and secondary NV, which is extremely rare but causes vision loss in the younger population.

Case Report

A 32-year-old man presented with blurry vision in his right eye. He had no known diseases or history of trauma. Best corrected visual acuity (BCVA) was 20/32 in the right and 20/20 in the left eye. Intraocular pressure was 14 mmHg in the right eye and 12 mmHg in the left eye; anterior segment examination results were normal. Fundus examination revealed a lesion with well-defined, scalloped margins that extending from the right peripapillary region to the macula and superior quadrant, including the superior temporal vascular arcade. The part of the lesion superior to the superior temporal arcade exhibited the leopard-spot pattern while a large subretinal scar formation was observed in the part of the lesion inferior to the superior temporal

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Received: 16.11.2019 **Accepted:** 07.02.2020

Cite this article as: Şekeryapan Gediz B. A Rare Cause of Type 2 Neovascularization: Unilateral Retinal Pigment Epithelium Dysgenesis. Turk J Ophthalmol. 2020;50:187-189

arcade, and the fovea was raised. Retinal folds were visible in the macula. The vessels superior to the optic nerve appeared thin and lacked continuity (Figure 1). On FA, the lesion was generally hyperfluorescent; the part of the lesion superior to the superior temporal arcuate had very distinct hyperfluorescent edges surrounded by dark ovals (Figure 2a). The lesion and its margins appeared hypoautofluorescent on FAF imaging (Figure 2b). The optic coherence tomography (OCT) cross-section passing through the fovea demonstrated type II NV, subretinal fluid, retinal surface irregularity, and thickening of the retina over the NV (Figure 3a). Type II NV secondary to URPED was diagnosed and intravitreal bevacizumab (IVB) (1.25 mg/0.05 mL) therapy was initiated. At 1-month follow-up, the patient's BCVA had decreased to 20/32 and there were no changes in the OCT findings. After 6 monthly IVB injections, BCVA improved to 20/20 and OCT showed regression of the subretinal fluid but persistent intraretinal fluid (Figure 3b). The patient is continuing IVB therapy.

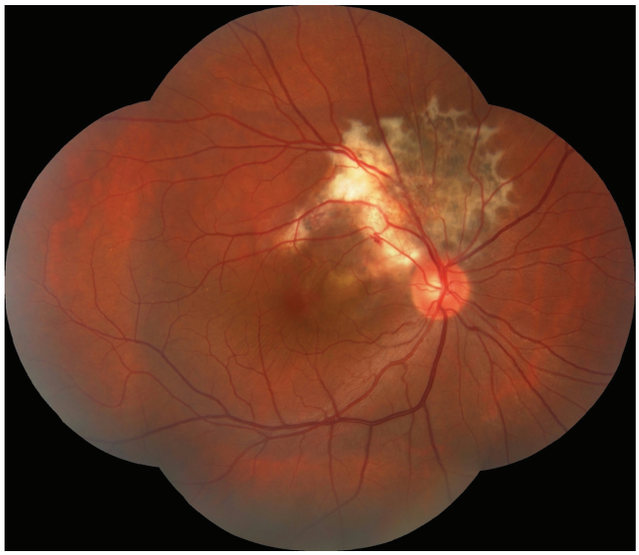

Figure 1. Color fundus photographs of the right eye show an RPE lesion with well-defined margins and a seashell-like scalloped appearance. Leopard-spot pattern is observed in the part of the lesion superior to the superior temporal arcade and a large subretinal scar formation is observed in the part of the lesion inferior to the superior temporal arcade. Retinal folds are noted in the macula and fovea is raised

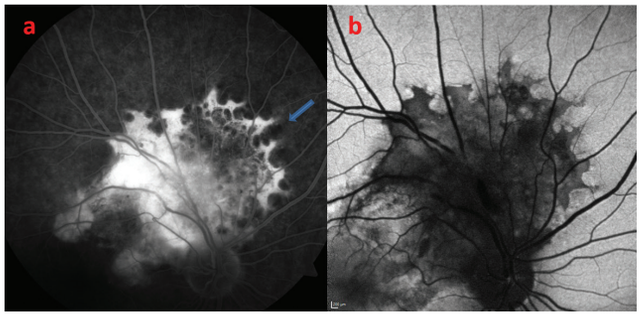

Figure 2. a) Fluorescein angiography demonstrates well-defined hyperfluorescent margins in the part of the lesion superior to superior temporal arcade, surrounded by dark ovals. b) Fundus autofluorescence shows the lesion and its margins are hypoautofluorescent, giving a reverse image of fluorescein angiography

Discussion

Dysgenesis refers to the abnormal or defective development of an organ. URPED is an extremely rare clinical condition of unknown etiopathogenesis, of which only 20 cases have been reported in the literature to date. It was first described by Cohen et al.[1] in 2002 in 4 patients with unilateral, idiopathic, leopard-spot lesions of the RPE, 2 of whom also had choroidal NV. In 2009, they named the lesion URPED and with the addition of the previous 4 patients, presented the clinical characteristics of a total of 9 cases.[2] Retinal symptoms associated with URPED include epiretinal membrane, increased retinal vascular tortuosity, and retinal folds. Shimoyama et al.[3] published a case of choroidal NV secondary to URPED in 2014 and reported that the lesion did not respond to 2 doses of subTenon's triamcinolone acetonide and 1 dose of IVB injection. In 2019, Preziosa et al.[4] reported a case of choroidal NV secondary to URPED in which they attained both functional and anatomical success after 2 doses of IVB. The type 2 NV lesion in our case responded slowly to IVB therapy and 6 months of monthly injections resulted in complete recovery of visual acuity but did not fully inactivate the lesion.

Despite its typical clinical appearance, URPED is most commonly confused with combined hamartoma of the retina and RPE. This lesion is also a rare clinical condition and is characterized by retinal thickening, epiretinal membrane, and vascular tortuosity.[5] There is one publication reporting that URPED may be an atypical form of combined hamartoma of the retina and RPE.[6] However, they can be distinguished based on FA and FAF imaging, which is pathognomonic for URPED, and clinical findings.

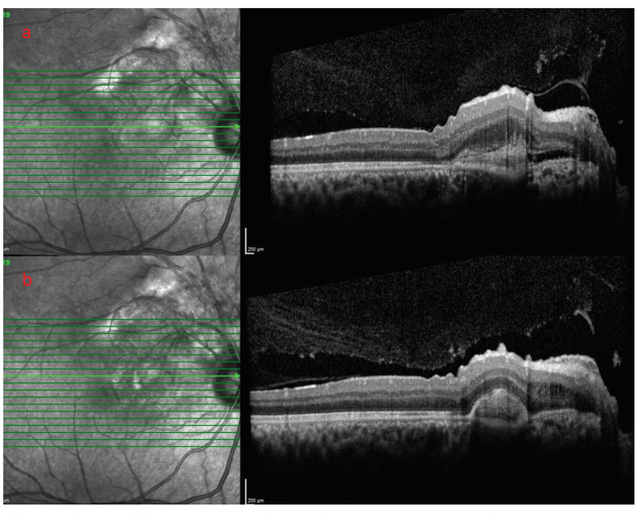

Figure 3. a) OCT cross-section of the left eye passing through fovea demonstrated type 2 NV, subretinal fluid, irregularity of the retinal surface, and thickening of the retina over the NV prior to treatment. b) OCT image of the same eye after 6 months of treatment shows regression of the subretinal fluid but persistent intraretinal fluid

Traumatic retinopathy is a clinical condition that is included in the differential diagnosis of URPED. Acute contusion necrosis, also known as commotio retinae, and resolution of hemorrhagic retinal detachment may lead to a similar appearance.[7]

Although the visual prognosis of URPED is not clear, it has been shown to slowly progress toward fovea over a period of years and cause serious vision loss.[8] Moreover, the NV that develops as a complication impacts visual prognosis in URPED patients. Although there is insufficient information in the literature to reach a definite conclusion, it should be kept in mind based on the present case that NV lesions respond slowly to IVB therapy.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2020.98415
Turk J Ophthalmol 2020;50:190-192

Case Report

Multimodal Imaging in a Case of Fovea Plana Associated with Situs Inversus of the Optic Disc

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Abstract

Fovea plana is a congenital condition characterized by anatomic absence of the foveal pit. It may be isolated or associated with congenital ocular anomalies. In this report, we present a case of fovea plana associated with situs inversus of the optic disc, optic disc hypoplasia, tilted optic disc, and prepapillary vascular loop and with best corrected visual acuity of 20/32. The aim of this report is to demonstrate the coexistence of very rare multiple optic disc anomalies and fovea plana, and also to emphasize that the use of multimodal imaging methods facilitates the identification of rare anomalies.

Keywords: Fovea plana, situs inversus of the optic disc, optic disc hypoplasia, tilted optic disc, multimodal imaging

Introduction

Fovea plana, previously called foveal hypoplasia, is a condition characterized by the anatomic absence of the foveal pit. It may be isolated or associated with diseases such as albinism, microphthalmia, and achromatopsia. Fovea plana is usually bilateral, and visual acuity varies depending on accompanying pathologies.[1] It has been reported that fovea plana may affect 3% of children, even those with normal visual acuity.[2]

Situs inversus of the optic disc is a rare congenital anomaly characterized by the abnormal course of vessels emerging from the optic disc.[3,4] It may be associated with tilted optic disc and optic disc hypoplasia.[5] In this report, we present a case of fovea plana associated with multiple optic disc anomalies consisting of situs inversus of the optic disc, optic disc hypoplasia, tilted optic disc, and prepapillary vascular loop, with multimodal imaging findings.

Case Report

A 25-year-old man presented with a long history of blurred vision. The patient had no known diseases or trauma history and his best corrected visual acuity was 20/32 with -0.50 D, -0.75 D x 180° in both eyes. Intraocular pressure was 12 mmHg in the right eye and 13 mmHg in the left eye, and anterior segment examination was normal. Fundus examination revealed that both optic discs were hypoplastic and tilted with accompanying gliotic tissue and prepapillary vascular loop;

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Received: 15.12.2019 **Accepted:** 12.02.2020

Cite this article as: Şekeryapan Gediz B, Şekeroğlu MA. Multimodal Imaging in a Case of Fovea Plana Associated with Situs Inversus of the Optic Disc. Turk J Ophthalmol. 2020;50:190-192

the vessels emerged perpendicularly, dilated, and straight from the optic disc and initially extended nasally before turning toward the temporal direction (Figure 1). Fundus fluorescein angiography revealed hypoplastic, tilted optic discs and small foveal avascular zone (Figure 2). Similar results were observed in fundus autofluorescence images (Figure 2). Optic coherence tomography (OCT) revealed absent foveal pit and continuity of the inner retinal layers through the fovea in both eyes (Figure 3). Central foveal thickness was 313 µm in the right and 312 µm in the left eye. Peripapillary retinal nerve fiber layer thickness measured with OCT was 39 µm in both eyes. OCT angiography (OCTA) demonstrated absence of the foveal avascular zone in both the superficial and deep capillary plexuses in both eyes (Figure 3). Axial length measured with A-mode ultrasound was 24.71 mm in the right and 24.72 mm in the left eye. The patient was diagnosed with fovea plana accompanied by multiple optic disc anomalies. The results of cranial magnetic resonance angiography to diagnose potential concomitant intracranial vascular pathologies were normal.

Discussion

Situs inversus of the optic disc is a congenital embryonic anomaly characterized by blood vessels initially emerging nasally from the optic disc before turning sharply temporally. It is believed to occur as a result of anomalous insertion of the optic stalk into the optic vesicle and dysversion of the optic disc.

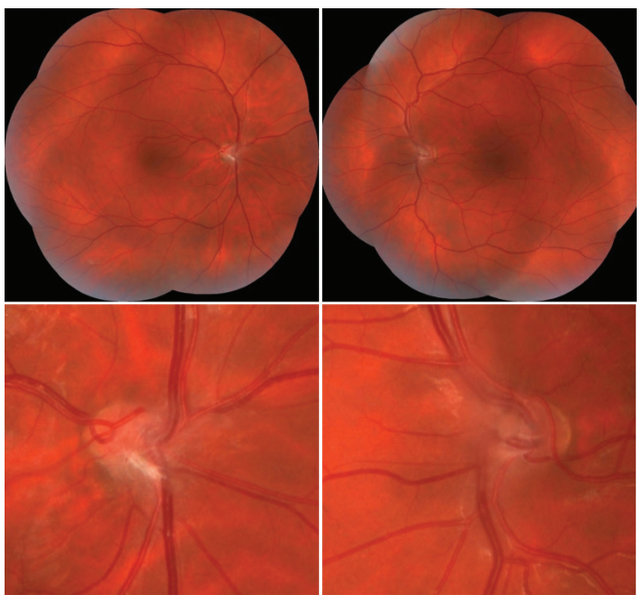

Figure 1. Colored fundus photographs of both eyes (upper panels) and magnified color photographs of both optic discs (lower panels). The colored fundus photographs show the retinal vessels emerge perpendicularly from the optic disc and are dilated, straight, and initially extend nasally before changing course to the temporal direction, especially in the left eye. The optic disc images demonstrate that both optic discs are hypoplastic and tilted, accompanied by gliotic tissue and prepapillary vascular loop, and vessels emerge nasally from the optic disc

It can be associated with other optic disc pathologies, primarily tilted optic disc.[3,4,5] It is reported to affect 5% of the normal population.[6]

As the use of OCT became common in daily practice, we gained a better understanding of the anatomic changes that take place in patients with fovea plana. Continuation of the inner retinal layers through the fovea result in increased central foveal thickness and absence of the foveal pit is in OCT cross-sections.[7] In OCTA studies of fovea plana patients, it has been reported that no foveal avascular zone is evident in the superficial or deep capillary plexus.[8] Fovea plana may be associated with conditions such as albinism, aniridia, retinopathy of prematurity, achromatopsia, microphthalmia, myopia, and incontinentia pigmenti.[1] There are reports in the literature that patients with optic disc hypoplasia have shallower foveal pit and increased central retinal thickness compared to normal eyes.[9] Small optic disc can also be observed in patients with fovea plana associated with albinism and achromatopsy.[10] Although these findings suggest a correlation between fovea and optic disc development, the etiopathogenesis of this association is not clear. In our case, fovea plana was observed with optic disc hypoplasia as well as findings of situs inversus, tilted disc, and prepapillary vascular loop. With this report, we aimed to draw attention to a very rare case of fovea plana with largely preserved visual acuity despite the coexistence of multiple optic disc anomalies. We also aimed to emphasize that the use of multimodal imaging methods facilitates the identification of rare anomalies.

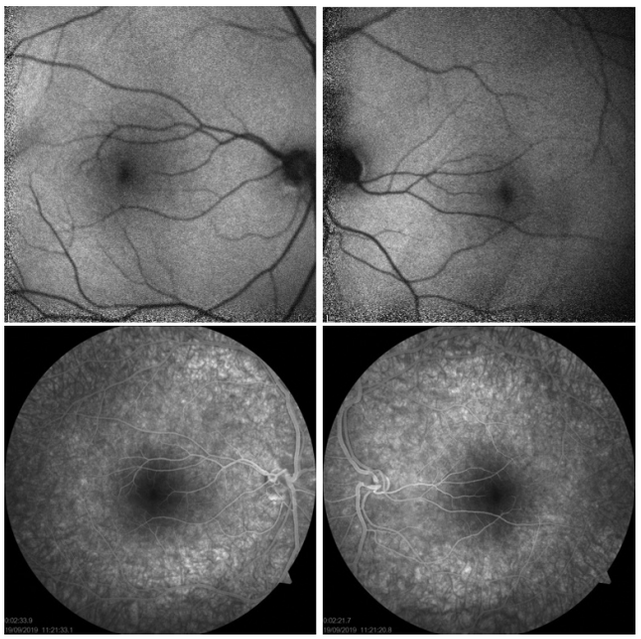

Figure 2. Fundus autofluorescence images of both eyes (upper panels) and fundus fluorescein angiography images of both eyes (lower panels). All images demonstrate hypoplastic and tilted optic discs and small foveal avascular zone

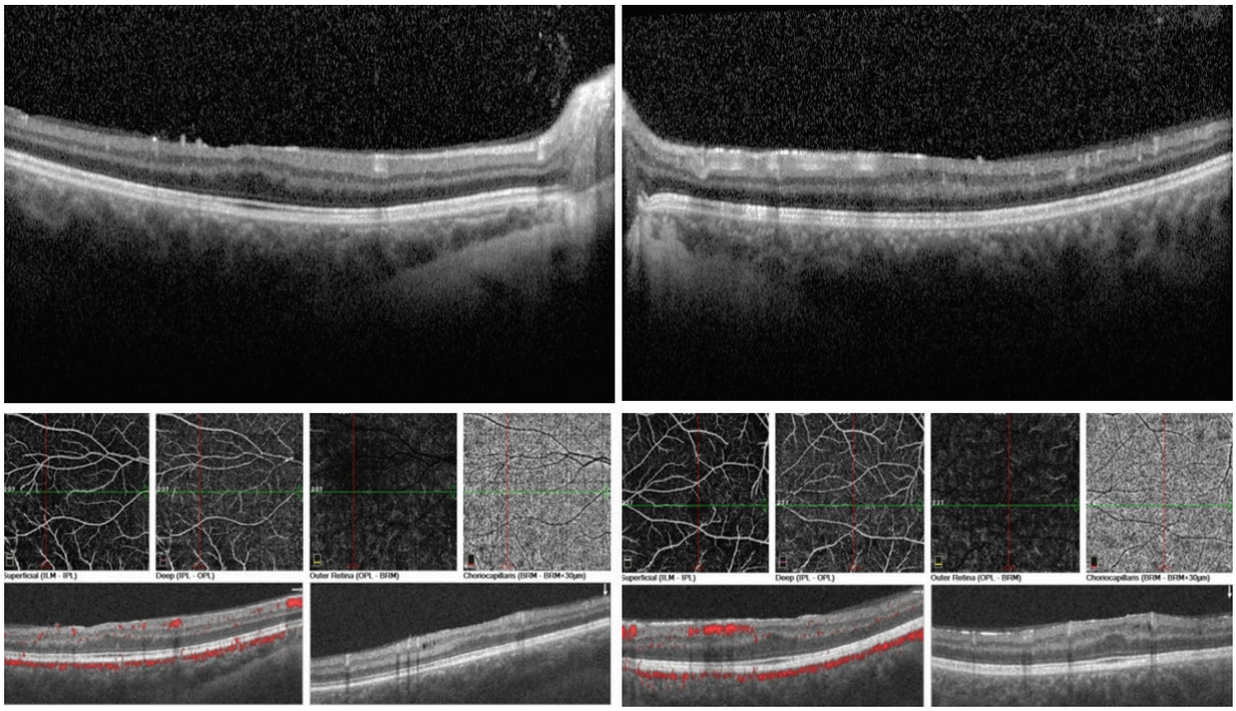

Figure 3. Optic coherence tomography images of both eyes (upper panels) and optic coherence tomography angiography images of both eyes (lower panels). Optic coherence tomography cross-sections passing through fovea demonstrate absence of the foveal pit and continuity of the internal retinal layers through the fovea. The optic coherence tomography angiography images also demonstrate absence of the foveal avascular zone in the superficial and deep capillary plexuses

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ş.G., M.A.Ş., Consept: B.Ş.G., M.A.Ş., Design: B.Ş.G., M.A.Ş., Data Collection or Processing: B.Ş.G., M.A.Ş., Analysis or Interpretation: B.Ş.G., M.A.Ş., Literature Search: B.Ş.G., M.A.Ş., Writing: A B.Ş.G., M.A.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2020.92972
Turk J Ophthalmol 2020;50:193-196

Case Report

Paracentral Acute Middle Maculopathy

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Abstract

Paracentral acute middle maculopathy (PAMM) is a variant of acute macular neuroretinopathy which is characterized by a hyperreflective band-like lesion in the inner nuclear layer and outer plexiform layer on spectral domain optical coherence tomography (SD-OCT). The etiology is believed to involve vasopressor exposure or systemic microvascular diseases that cause retinal ischemia. SD-OCT is the main imaging method in the diagnosis or evaluation of progression of PAMM, whereas multimodal imaging is useful to support the diagnosis. Herein, we present a case of PAMM in a healthy young woman using multimodal imaging methods.

Keywords: Paracentral acute middle maculopathy, acute macular neuroretinopathy, optical coherence tomography

Introduction

Paracentral acute middle maculopathy (PAMM) was first described in 2013 by Sarraf et al.[1] and was identified as a variant of acute macular neuroretinopathy. Although Bos and Deutman[2] described acute macular neuroretinopathy as red, wedge-shaped paracentral retinal lesions, since the development of spectral domain optical coherence tomography (SD-OCT) it has been determined that some acute macular neuroretinopathy lesions affect the outer retinal layers while others affect the middle and inner retinal layers. PAMM, which was described as type 1 acute macular neuroretinopathy by Sarraf et al.[1], is characterized by a band of hyperreflectivity in the inner nuclear and outer plexiform layers.[3]

Although its etiology has not been fully elucidated, causative factors may include the use of vasoconstrictors such as caffeine and epinephrine, oral contraceptive use, and microvascular diseases that affect the retina, such as diabetes, hypertension, and sickle cell anemia.[4,5]

Case Report

A 21-year-old woman presented to the retina unit of the Ege University Faculty of Medicine Ophthalmology Department with complaints of blurry vision and the appearance of a black spot in her right eye for the past 4 days. Her medical history was unremarkable. On ophthalmological examination, her best corrected visual acuity (BCVA) was 20/20 in both eyes. Bilateral intraocular pressure and anterior segment examination results were normal. Fundus examination was unremarkable in the left eye but revealed a hypopigmented lesion involving the superotemporal fovea of the right eye.

SD-OCT imaging of the right eye demonstrated a hyperreflective band lesion at the level of the inner nuclear and outer plexiform layer corresponding to the hypopigmented lesion observed in the superotemporal fovea. The outer retinal layers and retinal pigment epithelium appeared completely normal. On 30-2 visual field test, a paracentral scotoma corresponding to the hypopigmented lesion on fundus examination was observed.

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Received: 07.07.2019 **Accepted:** 13.03.2020

Cite this article as: Kıyat P, Değirmenci C, Nalçacı S, Afrashi F, Akkın C. Paracentral Acute Middle Maculopathy. Turk J Ophthalmol. 2020;50:193-196

Fundus autofluorescence imaging revealed hypoautofluorescence in the superotemporal foveal lesion and fundus fluorescein angiography revealed hypofluorescence in the same area. Substantial capillary dropout was detected in the deep capillary plexus on OCT angiography. No pathologies were detected on multifocal electroretinogram.

Hematology and genetics consultations, thrombophilia screening, hemogram and biochemical tests, carotid Doppler ultrasound, and cranio-orbital magnetic resonance imaging ordered as etiological studies revealed no abnormalities. The case was evaluated as suspected PAMM and the patient was followed without treatment.

At 4-month follow-up, the patient stated that her vision had returned to normal and the black spot had completely disappeared. Her BCVA was 20/20 bilaterally, fundus examination demonstrated regression of the hypopigmented lesion, and SD-OCT revealed minimal retinal thinning and disorganization of the outer retinal layers in the area corresponding to the lesion in the superotemporal fovea. Regression of fundus hypoautofluorescence in the lesion area was observed (Figure 1). On OCT angiography, the capillary dropout in the deep capillary plexus in the lesion area was observed to have resolved, leaving disorganization of the deep capillary plexus. On 30-2 visual field test, the paracentral scotoma detected at diagnosis had regressed (Figure 2). No recurrence was detected in subsequent follow-up examinations.

Discussion

Sarraf et al.[1] described two variants of acute macular neuroretinopathy in 2013. Type 1 acute macular neuroretinopathy, also known as PAMM, is a form that involves the inner nuclear and outer plexiform layers on SD-OCT, whereas type 2 acute neuroretinopathy is the form that involves the outer retinal layers and retinal pigment epithelium.[6]

Both type 1 and type 2 acute macular neuroretinopathy lesions manifest with paracentral scotoma, and vasopressor exposure is implicated in their etiologies. In terms of clinical presentation, they both exhibit grayish hypopigmented intraretinal parafoveal lesions. The basic imaging method to distinguish between the two types is SD-OCT, and the source of ischemia is either the intermediate or deep capillary plexus in type 1 versus the deep capillary plexus in type 2. The parafoveal location of the lesions may be due to the density of the capillary plexus in this area.

In the literature, PAMM is usually reported in men with advanced vasculopathy, while type 2 acute macular neuroretinopathy cases consist of healthy young women.[7] Unlike the cases reported in the literature, our patient was a healthy young woman with type 1 acute macular neuroretinopathy (PAMM).

SD-OCT is the main imaging method used to distinguish PAMM, which affects the inner nuclear and outer plexiform layers, from type 2 acute macular neuroretinopathy, which affects the outer retinal layers, ellipsoid zone, and retinal pigment epithelium.[8] In some cases, ophthalmoscopic retinal examination findings can be completely normal and there may be no remarkable findings on fundus fluorescein angiography. In such cases, the importance of SD-OCT for diagnosis is clear. SD-OCT can be used to visualize the inner nuclear layer thinning that can occur in chronic cases, lesion progression, or resolution.[9]

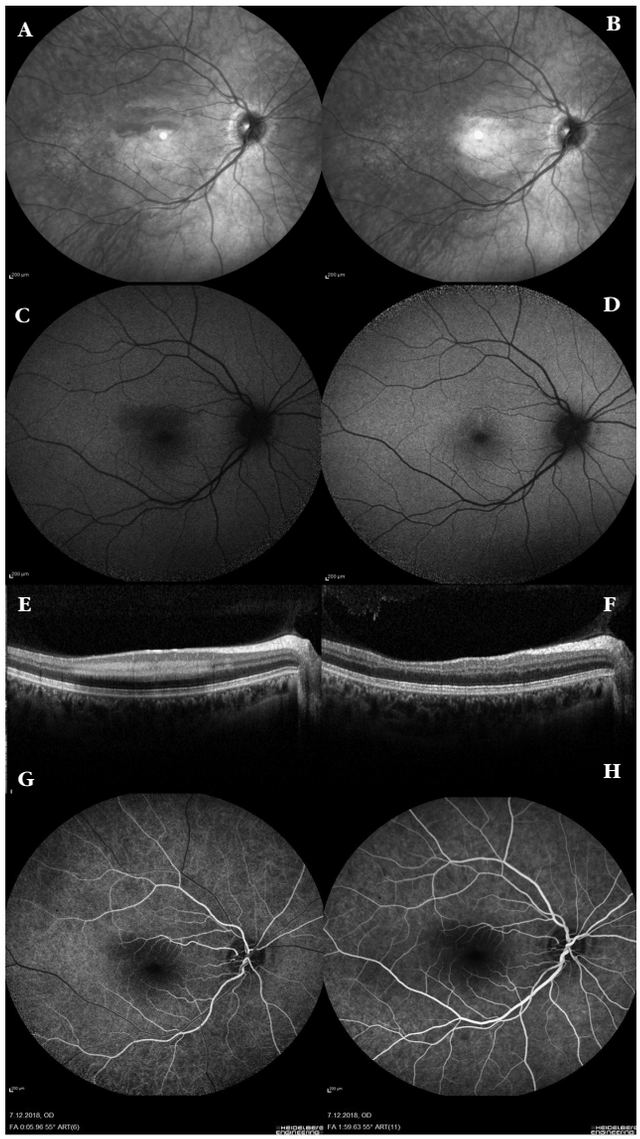

Figure 1. Fundus infrared, autofluorescence and SD-OCT and images at the time of diagnosis and at 4-month follow-up examination and FFA images at the time of diagnosis. In infrared images, hyporeflectance was detected in the superotemporal fovea lesion at the time of diagnosis (A) and was found to have regressed at 4-month follow-up (B). In fundus autofluorescence imaging, hypoautofluorescence was detected in the superotemporal fovea lesion at the time of diagnosis (C) and was found to have regressed at 4-month follow-up (D). SD-OCT performed in the right eye at time of diagnosis revealed a hyperreflective band lesion at the level of the inner nuclear and outer plexiform layer corresponding to the hypopigmented lesion observed in the superotemporal fovea (E). SD-OCT at 4-month follow-up demonstrated regression of the hyperreflective band including the inner nuclear and outer plexiform region in the superotemporal fovea, leaving retinal thinning and disorganization of the outer retinal layers in the lesion area (F). Early and late stage fundus fluorescein angiography images at the time of diagnosis (G-H).

SD-OCT: Spectral domain optical coherence tomography

Fundus fluorescein angiography imaging in our case revealed hypofluorescence in the parafoveal lesion area. Previously published cases of PAMM have generally been described as having normal fluorescence on fundus fluorescein angiography.[10,11] In cases with branch retinal artery occlusion in the etiology of PAMM, filling defect has been detected on fundus fluorescein angiography.[3] In our case, however, we observed no findings suggesting branch artery occlusion and filling defect was not detected. In their case report, Niyousha et al.[12] observed hypofluorescence in the affected retinal area on fundus fluorescein angiography of the eye with PAMM, as in our case. We attributed the hypofluorescence observed on fundus fluorescein angiography imaging of our patient to a reduction in fluorescence due to retinal thickening.

Ischemia in the intermediate and deep capillary plexuses, which supply the intermediate retinal layers, plays an essential role in the pathogenesis of PAMM.[13] Although we were unable to detect any etiological factor in our case, the presence of microvascular diseases in the etiology necessitates the evaluation of patients with PAMM lesions for microvascular diseases that may affect retina such as diabetes, hypertension, and sickle cell anemia. PAMM may be a warning sign of systemic microvascular disease.[14]

PAMM lesions have been associated with the use of sympathomimetics such as epinephrine, norepinephrine, ephedrine, and caffeine.[15] Patients diagnosed as having PAMM must also be questioned about vasopressor exposure. Sympathomimetics may cause ischemia in the retinal intermediate and deep capillary plexuses due to their vasopressor effects and may be responsible for the hyperreflective lesion in the inner nuclear and outer plexiform layers observed on SD-OCT. The inner nuclear layer thinning that occurs in some patients with chronic PAMM supports the ischemia theory. In patients whose inner nuclear layer thins in the chronic period, paracentral scotoma may be permanent.[16] In our case, the hyperreflective lesion observed on SD-OCT completely regressed and the scotoma resolved.

In conclusion, PAMM, which is defined as a variant of acute macular neuroretinopathy that affects the inner nuclear and outer plexiform layers, can be diagnosed more easily today owing to the development of SD-OCT and multimodal imaging methods. SD-OCT is a useful imaging method in the diagnosis, progression monitoring, and differential diagnosis of PAMM. The role of focal parafoveal ischemia in the retinal capillary plexus has been emphasized in the etiology of PAMM, and investigating vasopressor exposure and microvascular pathologies that may affect retina is recommended in patients diagnosed with PAMM. There is currently no treatment for PAMM lesions, but etiological research is important to identify systemic vascular risk factors.[17]

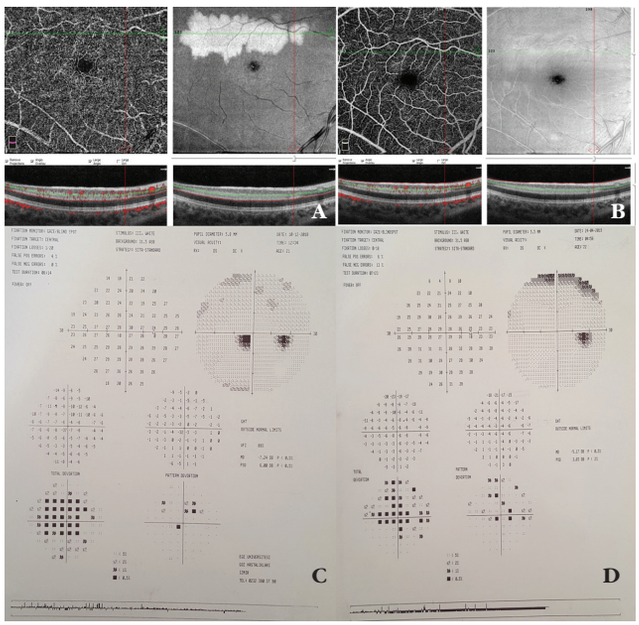

Figure 2. OCT angiography images and 30-2 visual field test at the time of diagnosis and at 4-month follow-up examination. OCT angiography at time of diagnosis demonstrated substantial capillary dropout in the deep capillary plexus (A). At 4-month follow-up, the capillary dropout was seen to have resolved, leaving disorganization in the deep capillary plexus (B). At diagnosis, 30-2 visual field test showed paracentral scotoma consistent with the hypopigmented lesion observed on fundus examination (C). On follow-up examination, the paracentral scotoma was found to have regressed (D).

OCT: Optical coherence tomography

Ethics

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.K., C.D., S.N., F.A., C.A., Concept: P.K., C.D., F.A., C.A., Design: P.K., C.D., F.A., C.A., Data Collection or Processing: P.K., C.D., S.N., Analysis or Interpretation: P.K., S.N., F.A., Literature Search: P.K., C.D., Writing: P.K., C.D., F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tjo.galenos.2020.50215
Turk J Ophthalmol 2020;50:197

Letter to the Editor

COVID-19 Pandemic and Ophthalmologists

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Dear Editor,

We would like to share our ideas on "The COVID-19 Pandemic: Clinical Information for Ophthalmologists".[1] Bozkurt et al.[1] discussed several issues related to COVID-19 and ophthalmologists. The general ophthalmologic practice during the COVID-19 pandemic is similar worldwide. In our country, Thailand, the second country to which the disease spread, the postponement of unnecessary ophthalmic procedures is set.[2] We agree that ophthalmologists are at risk to get COVID-19 infection from occupational work. Nevertheless, there is no report on COVID-19 among ophthalmologists. This might imply that we have good prevention or the ophthalmologist medical service has less risk than other types of medical care service. The use of full protective equipment is necessary and the universal precautions must be used for all patients.[3] Finally, there is limited mention that patients can also get COVID-19 from medical personnel. The holistic prevention system should be applied in ophthalmology wards.

Peer-review: Internally peer reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Received: 01.05.2020 **Accepted:** 19.05.2020

Cite this article as: Beuy J, Wiwanitkit V. COVID-19 Pandemic and Ophthalmologists. Turk J Ophthalmol. 2020;50:197

DOI: 10.4274/tjo.galenos.2020.37729
Turk J Ophthalmol 2020;50:198-199

Response to Letter to the Editor

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We thank Beuy and Wiwanitkit for their kind interest in our paper[1] and sharing their opinions about the risk of COVID-19 infection among ophthalmologists while performing their profession. The authors stated that there are no reports in the literature about COVID-19 infection among ophthalmologists and concluded that ophthalmologists protect themselves very well or the ophthalmology services carry less risk than other medical services. However, as we mentioned in our perspective, Li Wenliang, who was the first to recognize and raise the alarm about the new disease in late December, was an ophthalmologist working in Wuhan and became infected in early January after contact with a glaucoma patient and lost his life on February 7.[2,3] Other members of his family also suffered from COVID-19, but no other deaths were reported in the family. Recently, an article entitled "Symptomatic Covid-19 Eye Health Professionals in Wuhan Province of China" by Qiao et al.[4] was published online on April 18, 2020. In that study, a questionnaire was sent to healthcare professionals working in ophthalmology departments in hospitals in the Wuhan province to understand the incidence of symptomatic COVID-19 among eye professionals. The survey was sent to 28 eye professionals with symptomatic COVID-19 diagnosed through February 29, 2020 and 90 control participants randomly selected within each ophthalmology department where case(s) were identified. Among 28 eye professionals from 10 hospitals who contracted COVID-19 with pulmonary symptoms, there were 14 ophthalmologists, 12 ophthalmic nurses, and 2 ophthalmic technicians. Two participants could not answer the questionnaire; one died and another remained intubated through data collection. All 3 deaths were ophthalmologists who had worked in the same hospital. Only 5 eye health professionals with confirmed COVID-19 (17.9%) had family members with symptomatic COVID-19, which means the virus was not transmitted from family members in most of the patients. The overall incidence of symptomatic COVID-19 among eye professionals across 10 hospitals was found to be 2.52%. Extrapolated from data available from the Chinese Red Cross Foundation and Wuhan Health Commission,[5-6] the estimated COVID-19 incidence among all healthcare workers in the 10 hospitals was 2.27% (713 of 31367), which means the risk of symptomatic COVID-19 is similar among ophthalmologists and other health professionals. Based on these findings, we cannot say that the disease is uncommon among ophthalmologists or that ophthalmology practice carries less risk than other medical practices.

Qiao et al.[4] also reported that after implementing restrictions such as eye examinations and surgeries conducted only in emergency circumstances, city lockdown, use of appropriate personal protective equipment during clinical practice, and careful hand hygiene, the number of professionals infected by SARS-CoV2 decreased remarkably, similar to our recommendations for ophthalmologists.[1]

Peer-review: Internally peer reviwed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Received: 19.05.2020 **Accepted:** 19.05.2020

Cite this article as: Bozkurt B, Eğrilmez S, Şengör T, Yıldırım Ö, İrkeç M. Response to the Letter to the Editor. Turk J Ophthalmol. 2020;50:198-199

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