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E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

galenos

March
April
2019
49 Volume
Issue 2

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: April 2019
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

Osman Şevki ARSLAN,
İstanbul University Cerrahpaşa Faculty of Medicine, Department of Opthalmology, İstanbul, Turkey

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Abroad: 100 USD (Tax Incl.)

Correspondence Address

Editor-in-Chief, Murat İrkeç, MD, Professor in Ophthalmology
Hacettepe University Faculty of Medicine, Department of Ophthalmology
06100 Sıhhiye-Ankara-Turkey
Phone: +90 212 801 44 36/37 Fax: +90 212 801 44 39
E-mail: mirkec@hacettepe.edu.tr

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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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EDITORIAL

2019 Issue 2 at a Glance:

This issue of our journal includes an interesting selection of six original articles, one review, and five case reports concerning the cornea, glaucoma, and retinal diseases.

Some corneal infections are resistant to medical treatment and can lead to acute corneal perforation. The purpose of therapeutic-tectonic penetrating keratoplasty (TTPC) in patients with corneal abscess is to remove the infected tissue, reduce the infection load, and maintain globe integrity in those who develop corneal perforation. Doğan and Arslan retrospectively analyzed their outcomes of TTPC in eyes with perforated infectious corneal ulcers and showed that globe integrity was preserved in 97.6% of patients and 71% of grafts were transparent at 2 years (see pages 55-60).

Oxidative stress is known to play an important role in the pathogenesis of pseudoexfoliation syndrome (PEX) and glaucoma. In a study including 58 patients with pseudoexfoliation glaucoma (PXG), 47 patients with PEX, and 134 healthy individuals, Aydın Yaz et al. determined that serum malondialdehyde (MDA) level was highest in XFG patients and lowest in the healthy individuals, and was a significant parameter in the progression of glaucoma. They reported that superoxide dismutase (SOD) and catalase (CAT) enzyme activities were significantly lower in PEX and PXG patients compared to the control group, possibly related to deficiency of antioxidant defense mechanisms, while glutathione (GSH) level was elevated, perhaps as a compensatory response to oxidative stress. Nitric oxide (NO) concentrations were found to be lower in PXG patients, suggesting that vascular regulatory factors are involved in the transition from PEX to PXG (see pages 61-67).

Diabetic retinopathy (DR) is among the leading causes of preventable blindness. Chronic elevation of blood glucose can lead to vasodilation, vascular leakage, retinal microvascular damage, vascular endothelial growth factor (VEGF) secretion secondary to ischemia, and neovascularization. Oxytocin, synthesized by the hypothalamus, has anti-inflammatory and antioxidant effects in addition to its muscle contraction and vasoregulatory effects. Değirmenci et al. evaluated the protective effect of intravitreal and intraperitoneal oxytocin on retinopathy in a streptozocin-induced diabetes rat model and showed that at 4 weeks after treatment, the outer nuclear layer was thicker and VEGF protein expression was lower in the treatment group than in the saline group, with a more pronounced difference in the intravitreal group (see pages 68-72).

Diabetic macular edema (DME) is the leading cause of vision loss in patients with DR. Nalçacı et al. administered a single intravitreal dexamethasone implant to 20 eyes of 14 patients with DME refractory to intravitreal ranibizumab. Although they observed no improvement in best corrected visual acuity at 6 months, subfoveal thickness was reduced and there was no increase in intraocular pressure (see pages 73-77).

Kola et al. evaluated the repeatability and agreement of macular thickness measurements obtained using two different retinal scan modes, E-MM5 and MM6, of the Optovue RTVue optical coherence tomography (OCT) device in healthy eyes and reported high repeatability for macular thickness measurements. The authors attributed discrepancies in perifoveal measurements between the two scan modes to differences in their software algorithms (see pages 78-83).

Neovascular age-related macular degeneration (NVAMD) is a destructive disease characterized by neovascularization (NV) in the macula that causes exudative changes affecting all retinal layers, and is currently among the leading causes of severe, permanent vision loss in adults over the age of 55. Menteş and Yıldırım evaluated the spectral-domain OCT (SD-OCT) characteristics of 27 eyes with nonexudative AMD that later developed signs of exudation in 27 patients under follow-up and treatment for NVAMD in their fellow eye. In B-scan SD-OCT imaging, all of the eyes exhibited marked retinal pigment epithelium (RPE) irregularities and undulations due to the presence of a moderately reflective material below the RPE, but had no signs of subretinal, intraretinal, or sub-RPE fluid. In en face SD-OCT imaging, 88.8% of the eyes showed hyperreflective lesions consistent with sub-RPE type 1 NV. Fluorescein angiography revealed no signs of type 1 NV, but the presence of macular plaques was detected in 29.6% of eyes by indocyanine green angiography. The authors concluded that B-scan SD-OCT imaging is a reliable method that provides early and specific evidence of nascent preclinical type 1 NV under the RPE in eyes without exudative symptoms (see pages 84-88).

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EDITORIAL

According to 2010 data from the World Health Organization, there are an estimated 285 million people with visual impairment worldwide. Of these, 39 million are blind and 246 million have low vision. Low vision rehabilitation aims to increase the quality of life of individuals with untreatable low vision and blindness by enabling them to live independently, enjoy life, and have a gainful vocation or skill that can provide financial income. In this issue, Şahlı and İdil present a comprehensive review of modern low vision rehabilitation, including the intake, evaluation of residual visual functions, evaluation of residual functional vision, and devices used in low vision rehabilitation (telescopes, high-diopter near spectacles, magnifiers, filtering lenses, electro-optical systems, and non-optical systems) (see pages 85-98).

Relapsing polychondritis (RP) is a potentially life-threatening idiopathic inflammatory disease that can affect the ear, nose, larynx, tracheobronchial tree, and cardiovascular system. Approximately 60% of patients present with ocular involvement such as scleritis, episcleritis, keratitis, conjunctivitis, and uveitis. Hasanreisoğlu et al. diagnosed RP in a 22-year-old woman referred to their clinic due to bilateral uveitis based on accompanying auricular chondritis and successfully treated her with topical and oral steroid therapy (see pages 99-101).

Canaliculitis is a rare condition caused by infection of the canalicular system by various pathogens. It accounts for about 2% of lacrimal system diseases and generally affects middle-aged and older adults. In their case report, Eraslan Yusufoğlu and Güngör Kobat discuss the clinical examination findings and treatment of a 12-year-old girl who presented with complaints of swelling and discharge from the right lower eyelid and was diagnosed with canaliculitis. After surgical removal of the dacryoliths by punctoplasty and curettage and treatment with topical crystallized penicillin, the patient's symptoms completely resolved and had not recurred in 12 months of follow-up. Histopathologic examination of the dacryoliths revealed the infectious agent to be Actinomyces (see pages 102-105).

Bietti crystalline dystrophy (BCD) is a retinal dystrophy characterized by shiny yellow crystalline deposits in the retina and sometimes the corneal limbus with progressive chorioretinal atrophy starting in the posterior pole, shown to occur as a result of mutation in the CYP4V2 gene. İpek et al. evaluated the SD-OCT angiography and swept-source OCT angiography images of a woman with CBD who was followed for 10 years. They reported visible choroidal vessels due to RPE atrophy in the outer retinal projection and markedly reduced choriocapillaris flow in the choriocapillaris projection. The authors stated that OCT angiography was important for monitoring choroidal blood flow and changes in the choroidal vasculature in BCD (see pages 106-108).

Posterior vitreous detachment (PVD) is the detachment of the posterior vitreous cortex from the internal limiting membrane due to liquefaction of the vitreous gel and weakened vitreoretinal adhesion. Vitreomacular traction (VMT) can occur as a result of tractional interactions between the vitreous and retina during the progression of PVD. VMT can cause cysts in the inner and/or outer retinal layers, full-thickness macular hole, and schisis, or can regress spontaneously without causing any structural changes. In a case report retrospectively evaluating the SD-OCT findings of three patients who developed VMT during the course of incomplete PVD, Yıldırım et al. observed an operculum over the macula on the detached posterior hyaloid membrane, and an outer retinal microdefect at the fovea extending from the inner border of the RPE to the outer limiting membrane following the spontaneous regression of VMT. These defects were found to reduce in size over long-term follow-up, but did not completely close (see pages 109-113).

Purtscher's retinopathy is a microvascular occlusive disease first described as a result of severe head trauma and characterized by retinal findings of cotton-wool spots and hemorrhage. Onaran et al. observed extensive retinal lesions consistent with cotton-wool appearance in the posterior poles of both eyes of a 16-year-old patient who presented to the hospital with muscle weakness, fatigue, vomiting, and clouding of consciousness after using the synthetic cannabinoid Bonzai. OCT revealed subretinal fluid and macular edema in both eyes, and fundus fluorescein angiography showed hypofluorescent areas due to blockage and late leakage from the retinal vessels, leading to a diagnosis of Purtscher-like retinopathy (see pages 114-116).

We hope you read the articles in this issue of our journal with interest and pleasure.

Respectfully on behalf of the Editorial Board,
Banu Bozkurt, MD

DOI: 10.4274/tjo.galenos.2018.06937
Turk J Ophthalmol 2019;49:55-60

Original Article

Outcomes of Therapeutic and Tectonic Penetrating Keratoplasty in Eyes with Perforated Infectious Corneal Ulcer

Cezmi Doğan, Osman Şevki Arslan

İstanbul University Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To evaluate the outcomes of penetrating keratoplasty performed for therapeutic and tectonic purposes in eyes with perforated infectious corneal ulcer.

Materials and Methods: This retrospective study included 43 eyes of 43 patients who developed perforated infectious corneal ulcer of various etiological causes between June 2008 and January 2018. The patients were evaluated based on age and sex, follow-up time, presence of corneal perforation, pre- and postoperative visual acuity, postoperative graft transparency, complications, and infection recurrence.

Results: The mean age of the 43 patients was 52.9±13.8 years. The mean follow-up time was 2.7±1.3 years. Preoperatively, the visual acuity of the eyes was at the level of hand motions or counting fingers; postoperative best corrected visual acuity ranged from hand motions to 0.7. Postoperative complications included hyphema in 8 patients (18.6%), elevated intraocular pressure in 14 (32.5%), posterior synechiae in 18 (41.8%), and cataract in 22 patients (51%). Therapeutic and tectonic success was achieved in 42 patients (97.6%). Postoperative graft transparency was observed in 35 patients (83.3%) within the 1-year follow-up period and in 27 patients (71.0%) at 2 years. Among 27 patients with graft transparency, 23 had bacterial and 4 had viral etiologies (p=0.52); 16 patients had perforations smaller than 1 mm and 11 had perforations 1-3 mm in size (p=0.2).

Conclusion: Therapeutic-tectonic keratoplasty for perforated infectious corneal ulcer successfully restored globe integrity in 97.6% of cases. The rate of graft transparency was 71.0% at 2 years, with no effect of etiological agent or perforation size.

Keywords: Cornea, abscess, therapeutics, penetrating keratoplasty

Introduction

Corneal infections occasionally show resistance to medical treatment and may progress acutely to corneal perforation. Depending on the clinical course, interventions such as amniotic membrane transplantation, conjunctival flap shifting, cyanoacrylate tissue adhesive use, and therapeutic lamellar or penetrating keratoplasty may be performed.[1,2,3,4] In patients with corneal abscess, the aim of therapeutic-tectonic penetrating keratoplasty (TTPK) is to remove the infected tissue, thus reducing the infection load, and to restore globe integrity in patients who develop corneal perforation. TTPK performed in patients with corneal perforation due to ulcerative infection has a high complication rate, which also indirectly increases the probability of corneal graft failure. The aim of this retrospective study was to evaluate the outcomes of TTPK procedures performed in eyes with perforated infectious corneal ulcer in our hospital.

Materials and Methods

This study was conducted in the Cerrahpaşa Faculty of Medicine, Department of Ophthalmology in compliance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee (07.01.2016).

Address for Correspondence: Cezmi Doğan MD, İstanbul University Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 533 556 64 46 E-mail: cezmidogan@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6305-8176
Received: 13.07.2018 **Accepted:** 07.11.2018

We retrospectively evaluated the outcomes of TTPK procedures performed in our clinic between June 2008 and January 2018 in 43 eyes of 43 patients who developed perforated infectious corneal ulcer of varying etiology which was considered to threaten globe integrity and was resistant to medical therapy. Patients with non-infectious corneal ulcer were not included in this study. The patients' age and sex, follow-up time, presence of corneal perforation, pre- and postoperative visual acuity, postoperative graft transparency, complications, and recurrence of infection were evaluated. Visual acuity was measured preoperatively and postoperatively using a Snellen chart and was expressed in decimal. Swabs were taken from the site of infection for microbiological diagnosis. The samples were routinely Gram stained and Giemsa stained, and were also cultured in blood agar, chocolate agar, and Sabouraud dextrose agar. Corneal material was sent for polymerase chain reaction analysis for herpes simplex in necessary cases. Patients with suspected bacterial etiology were started on topical vancomycin (50 mg/mL) and amikacin or ceftazidime (50 mg/mL) fortified drops (one drop per hour) as empirical therapy until a microbiological diagnosis was made. In addition, patients suspected of fungal keratitis were treated with topical fluconazole (2 mg/mL) or voriconazole (10 mg/mL) (one drop per hour) and oral fluconazole 200 mg/mL or voriconazole 200 mg/mL twice daily. This initial medical treatment was modified according to the microbiological results. In selected cases, special growth media were used for the diagnosis of mycobacteria and acanthamoeba. Chlorhexidine 0.02% was used in combination with 0.1% propamidine isethionate Brolene® (Sanofi, UK) for the treatment of *Acanthamoeba* every hour until surgical intervention. After keratoplasty the medication was stopped.

Confocal microscopy was used for differential diagnosis when possible. Antimicrobial susceptibility testing of the isolated microorganisms was done with the disc diffusion method. When needed, B-scan ultrasonography was performed and repeated at regular intervals.

Surgical Method

Eyes with corneal perforations less than 1 mm in size were first treated by applying a tissue adhesive. Patients for whom this method provided long-term globe integrity were excluded from the study. Patients whose clinical condition progressed despite treatment were prepared for emergent TTPK surgery. All surgeries were performed by the same surgeon (O.Ş.A.) under general anesthesia. The center of the cornea was marked with a marking pen when applicable. Trephination was performed so as to include all infected tissue as well as 0.5 mm of healthy tissue. The lesion did not affect the limbal region in any of the cases.

Recipient corneas were excised using a trephine. The trephination step was performed by making a preincision without applying excessive pressure and manually dissecting with scissors guided by this preincision. The anterior chamber was filled with viscoelastic material, and peripheral and posterior synechiae were released. Membranes formed in the pupillary area were peeled off, and hypopyon and fibrotic material in the anterior chamber were removed by washing. Peripheral iridectomy was performed in all cases. The anterior chamber and cornea were washed with 1% vancomycin in cases of bacterial keratitis, and were washed continuously with 0.2% fluconazole or 1% voriconazole until the donor graft was placed in cases of fungal infection.

The covered cornea technique was used in cases with extremely shallow anterior chamber with protruding anterior segment structures from the incision site as described in our previous study.[5] Briefly, in the covered cornea technique, following corneal incision the recipient button was sutured to the recipient rim. Viscoelastic material was used to fill the anterior chamber and protect the endothelial side of the donor button, which was then sutured to the recipient rim. In the next step, the sutures between the recipient rim and recipient button were cut and the recipient button was removed through the unsutured segment of the donor button.

A graft 0.5 mm larger than the recipient bed was cut from the endothelial part of the donor cornea using a punch. The donor cornea was sutured to the recipient bed with frequent interrupted sutures or a combination of interrupted and running sutures. The corneal button was divided into two and sent to the relevant units for histopathological and microbiological assessment.

Fortified antibiotic therapy was administered postoperatively. Topical steroids were started at a dose varying between 3 and 6 drops daily, depending on the patient, and were gradually tapered. In fungal cases, topical cyclosporine was initiated in the first week, then topical steroid drops were added when no recurrence of keratitis was observed. Steroid therapy was started at low dose (twice daily) and gradually increased during the course of treatment. In cases of recurrent herpetic keratitis, systemic acyclovir 2 g/day was administered during the first postoperative week and continued at a dose of 800 mg/day for at least 1 year. In patients with inactive herpetic keratitis, acyclovir was started at a dose of 800 mg/day and continued at 400 mg twice a day for at least 1 year. Patients taking systemic acyclovir were regularly checked for kidney function and patients taking systemic antifungal medication were regularly checked for liver function. Topical antiviral therapy was not administered to patients who underwent TTPK for herpetic keratitis. For all patients, antiglaucomatous drops were added to the treatment when necessary. Loose sutures were removed immediately.

Statistical Analysis

A Fisher's exact test or Yates correction test was used to compare the ratios according to the number of the samples. P values below 0.05 were considered statistically significant. SPSS (version 20.0) was used for all statistical analyses.

Results

The patients were evaluated in terms of age and sex, duration of follow-up, size of corneal perforation, pre- and postoperative visual acuity, postoperative graft transparency, anterior chamber status, complications, and recurrence of infection. Forty-three eyes of 43 patients (31 males, 12 females) were included. The

mean age was 52.9±13.8 years. The mean follow-up time was 2.7±1.3 years (range, 7 months - 7 years). Mean graft dimensions varied between 6.5 mm and 8.00 mm depending on the size of the infectious corneal ulcer. Preoperatively, visual acuity was at the level of light perception, hand motion, or counting fingers; postoperatively, the best corrected visual acuity ranged from hand motion to 0.7 (Table 1). Corneal perforation (positive Seidel test) was present in all patients preoperatively. Size of the corneal perforation was less than 1 mm in size in 24 patients (group 1; 55.8%) and 1-3 mm in 19 patients (group 2; 44.2%) (Figures 1 and 2).

Infectious agents detected microbiologically included bacteria in 30 patients (69.7%), virus (positive herpes polymerase chain reaction test) in 6 patients (14%), fungi in 5 (*Candida in 1 case, Aspergillus* in 2 cases, and Fusarium in 2 cases) patients (11.6%), and *Acanthamoeba* in 2 patients (4.6%) (Figure 3). Direct bacteriological examination revealed gram-positive bacilli in 6 eyes, gram-positive cocci in 16 eyes, and gram-negative bacilli in 8 eyes. Among 30 eyes with bacterial keratitis, only 12 eyes (40%) had culture positivity, which consisted of coagulase-negative staphylococci in 3 eyes, *Staphylococcus aureus* in 2 eyes, *Streptococcus pneumoniae* in 2 eyes, Streptococcus viridans in 1 eye, *Pseudomonas aeruginosa* in 3 eyes, and Escherichia coli in 1 eye.

Anterior chamber reaction with 2+/3+ cells and flare was present postoperatively and fibrinoid membrane formation was observed in some patients. In patients suspected of infection recurrence, a sample was collected from the anterior chamber for microbiological evaluation.

Postoperative Complications

Eight patients (18.6%) had varying degrees of hyphema in the anterior chamber postoperatively. The hyphema was cleaned by washing the anterior chamber in only 2 patients (4.6%); in the remaining patients, it regressed spontaneously with medical treatment. Fourteen patients (32.5%) had elevated intraocular pressure which was controlled with antiglaucomatous treatment. None of the patients had elevated intraocular pressure refractory to treatment or required glaucoma surgery. Permanent posterior synechia formed in 18 patients (41.8%). Twenty-two patients (51%) developed cataracts (Table 2) (Figure 4).

Therapeutic and tectonic success was achieved in 42 patients (97.6%). Recurrence was observed in only 1 patient in the postoperative period. This was a case of fungal keratitis, and the etiological agent was identified as *Candida*. Postoperative graft transparency was observed in 35 patients (35/42, 83.3%) during the 1-year follow-up period and in 27 patients at 2 years (27/38, 71.0%). Among 27 patients with graft transparency, 16 were in group 1 and 11 were in group 2. No significant difference was detected between the groups in terms of graft transparency at 2 years (p=0.2). However, development of cataract (p=0.003), synechiae posterior (p=0.0002), and glaucoma (p=0.02) after keratoplasty were significantly more common in the group 2. When graft transparency at 2 years was compared according to the etiological agent, no significant difference was detected between bacterial and viral keratitis (p=0.52) (Table 3).

Table 1. Preoperative and postoperative visual acuity levels

Visual acuity	Preoperative	Postoperative
Light perception (LP)	9	2
Hand motions (HM)	15	9
Counting fingers (CF)	19	-
<0.2	-	21
≥0.2	-	11

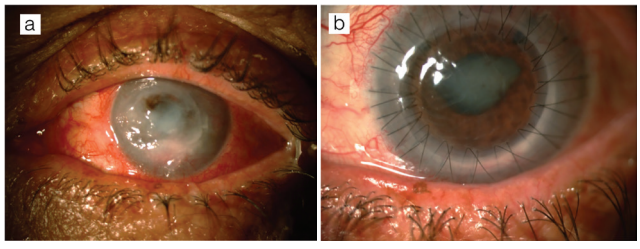

Figure 1. A case of bacterial keratitis. a) A central corneal perforation of 2-3 mm is evident and the anterior chamber is indistinct. b) At postoperative 1 month, the cornea is clear, there is no sign of recurrent infection, posterior synechia is present, and the peripheral iridectomies in the superotemporal and nasal quadrants are patent

Discussion

Although penetrating keratoplasty is easier to learn and practice compared to lamellar techniques (deep anterior lamellar

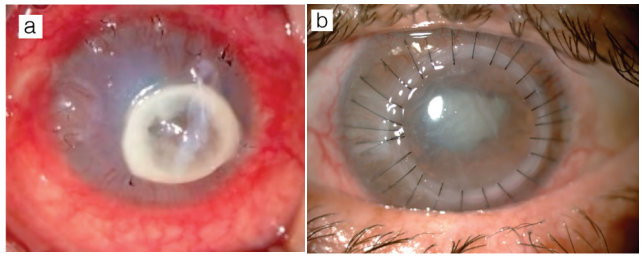

Figure 2. A case of fungal keratitis. a) Paracentral corneal perforation of 2-3 mm is evident. Emergent amniotic membrane transplantation was performed to preserve the integrity of the globe. During follow-up, the amniotic membrane dissolved and a portion can be seen covering the ulcer surface; sutures remaining from the membrane transplantation are visible in the peripheral cornea. b) At postoperative 1 month, corneal edema, posterior synechia, and cataract are apparent

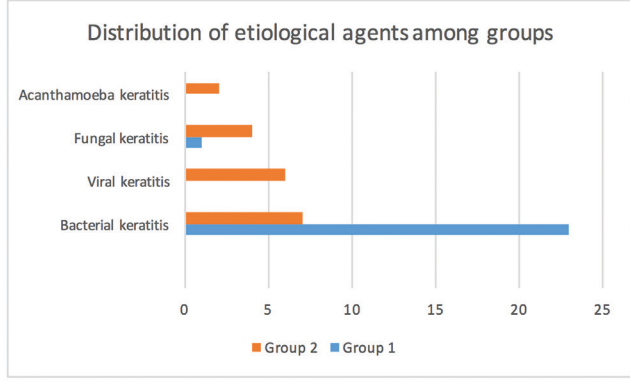

Figure 3. Distribution of etiological agents among groups. Size of the corneal perforation was less than 1 mm in group 1 and 1-3 mm in group 2

keratoplasty, Descemet membrane endothelial keratoplasty), performing penetrating keratoplasty in patients with perforated infectious corneal ulcer requires good surgical experience, surgical technique, and management. Intraoperative complications of penetrating keratoplasty are expected to occur at a higher rate in cases of perforated infectious corneal ulcer, possibly even leading to loss of the eye. Unlike conventional penetrating keratoplasty, postoperative success in cases of perforated infectious corneal ulcer is significantly influenced by the technique used by the surgeon (e.g., in choosing corneal graft diameter, performing peripheral iridectomy, and maintaining hemostasis) in addition to intraoperative complications. Because the intraocular structures may protrude through the perforation site or be damaged by the instrument when the recipient cornea is being excised using a trephine, the trephination step was performed by making a preincision without applying excessive pressure and manually dissecting with scissors guided by this preincision. In order to increase surgical success, effort was made in particular to open anterior synechiae, precautions were taken to enable fluid passage between the anterior and posterior chambers, and in necessary cases, a frequent symmetrical or asymmetrical (more frequent sutures in some quadrants) suture technique was used to prevent postoperative wound leakage. In eyes with a greater possibility of postoperative wound leakage, running sutures were applied in combination with interrupted sutures. Running sutures were placed between the interrupted sutures in order to achieve better donor-recipient apposition.

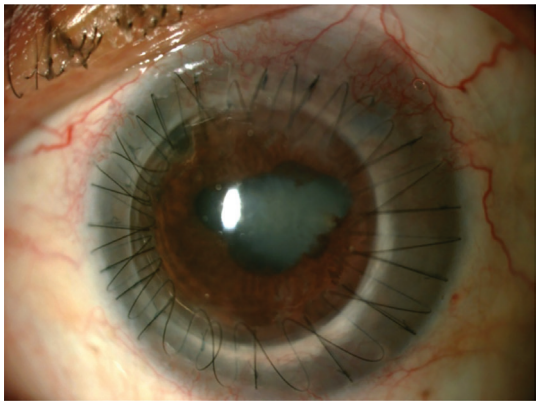

Figure 4. A patient with bacterial keratitis underwent therapeutic-tectonic penetrating keratoplasty due to a 2-3 mm corneal perforation. Loose sutures, posterior synechia, and cataract were observed at postoperative 2 months

Table 2. Postoperative complications according to size of corneal perforation

Postoperative complication	Number (n=43)	Group 1 (n=24)	Group 2 (n=19)	p value
Hyphema	8 (18.6%)	2	6	0.11
Cataract development	22 (51%)	7	15	0.003*
Glaucoma	14 (32.5%)	4	10	0.02*
Infection recurrence	1 (2.3%)	-	1	0.44
Endophthalmitis	1 (2.3%)	-	1	0.44
Posterior synechia	18 (41.8%)	4	14	0.0002*

*Rate of cataract, glaucoma, and posterior synechia was significantly higher in the patients with larger perforations (group 2)

Table 3. Graft transparency at 2 years according to the etiological agent

Diagnosis	Number (n=38)	Transparent (n=27)	Opaque (n=11)
Bacterial keratitis	26 (68.4%)	23	3
Viral keratitis	5 (13.1%)	4	1
Fungal keratitis	5 (13.1%)	-	5
Acanthamoeba keratitis	2 (5.2%)	-	2

All of our cases had perforated corneal ulcers of varying size. Emergency amniotic membrane transplantation or tissue adhesive was used in some cases in addition to medical treatment in order to preserve integrity of the globe and reduce inflammation. Particularly in patients with corneal perforations smaller than 1 mm (group 1), a tissue adhesive was applied in addition to medical treatment, and only those who exhibited progression despite this approach were operated.

Cases of bacterial keratitis usually respond quickly to medical treatment and require TTPK less often. Ti et al.[8] determined that *Pseudomonas aeruginosa* is the bacterial agent more commonly responsible for corneal perforation, though gonococcal and atypical mycobacterial infections may also require therapeutic keratoplasty.[6,7] In the present study, the majority of patients who underwent TTPK due to perforated infectious corneal ulcer had bacterial keratitis, representing 69.7% of our study group. *Pseudomonas* was detected in the cultures of 3 patients, and these accounted for 3 of the 19 cases with large corneal perforations (group 2). The fact that these patients were initially treated at other centers and referred to our clinic at a late stage resulted in higher rates of TTPK for perforated infectious corneal ulcers due to bacterial agents. Nearly all of the patients who were operated had started treatment at a different center and were later referred to us. No recurrent infections were observed in the bacterial keratitis cases in the postoperative period.

We had 5 cases of perforated infectious corneal ulcer due to fungal keratitis, accounting for 11.6% of our TTPK procedures. Of these, the etiological diagnosis was *Candida* in 1 case, *Aspergillus* in 2 cases, and *Fusarium* in 2 cases. Difficulty finding antifungal drugs, the low drug susceptibility of some fungus types, and delayed etiological diagnosis lead to progression despite antifungal therapy, and necessitate emergent tectonic keratoplasty to preserve globe integrity. Since fungal keratitis has poor prognosis, therapeutic lamellar keratoplasty is considered urgent in order to prevent deeper corneal layers from being affected while the infection is still superficial. However, in our cases, Descemet's membrane was affected and there was corneal perforation. Infection recurred and progressed to endophthalmitis in one of these 5 patients postoperatively; intravitreal antifungal therapy was able to preserve integrity of the globe. This was the only patient in our study with recurrent infection. There were few fungal cases in our study; Xie et al.[9] reported a 15.4% rate

of infection recurrence after keratoplasty for fungal keratitis. Key steps in managing recurrent infection are washing the anterior chamber with antifungal drugs intraoperatively and avoiding the use of steroids in the early postoperative period. A patient's systemic condition, particularly uncontrolled high blood sugar, also increases the recurrence of fungal infection. Said et al.[10] and Sedghipour et al.[11] found that penetrating keratoplasty was effective in the treatment of fungal keratitis, but noted a high rate of postoperative immune rejection (27.2%-29.6%).[8]

Herpetic keratitis recurrence has been reported at 20% in the literature.[12] Our cases did not have any recurrence during the follow-up period.

Two patients in our study underwent TTKP due to corneal perforation secondary to *Acanthamoeba* keratitis. No recurrence was observed during postoperative follow-up. However, the donor cornea showed decompensation and loss of transparency within 1 year of keratoplasty. In addition, their eyes also developed cataract and glaucoma which was controlled with medication. Despite the limited number of patients with *Acanthamoeba* keratitis in our study, a previous study determined recurrent infection to be among the most common complications after TTKP (40%).[13] Of the patients who did not have recurrent infection in that study, 36% required multiple keratoplasty and 32% developed glaucoma.[13]

Postoperative graft transparency declines as the average graft size exceeds 8 mm and the graft approaches the limbus. The most important factor affecting graft diameter is the size and location of the infectious corneal ulcer. In the present study, graft dimensions were determined based on the dimensions of the infectious corneal ulcer and ranged from 6.5 mm to 8.00 mm. Graft transparency varies between 23-84.6% in the literature and we had similar outcomes, with 83.3% at 1 year and 71% at 2 years.[8,9,14,15,16,17]

When the patients were classified according to corneal perforation size, we observed that the complication rate increased with perforation size (Table 2). However, there was no significant difference between the groups in terms of graft transparency at 2 years despite higher complication rates (cataract, synechiae posterior, and glaucoma) in group 2.

Perforations associated with fungal and viral keratitis etiologies were predominant in the large perforation group (group 2), while smaller perforations (group 1) comprised mostly bacterial keratitis cases. Although we had few cases with viral etiology, no significant difference was detected in terms of graft transparency at 2 years between the bacterial and viral groups.

Study Limitations

The limited number of patients and retrospective design of the study are two of its limitations. Since most of the patients were referred to our department after starting treatment in a different center, bacterial culture did not yield positive results to show the causative microorganism in most of the patients who had corneal perforation due to keratitis. Thus, their treatment was dependent on the results of direct microscopic examination.

Conclusion

TTPK in patients with perforated infectious corneal ulcer requires more surgical experience (with donor cornea diameter, peripheral iridectomy, hemostasis control) compared to conventional routine penetrating keratoplasty. Using TTPK to treat perforated infectious corneal ulcer, we achieved a 97.6% success rate in preserving the integrity of the globe and eliminating the infectious agent, and graft transparency was 71.0% at postoperative 2-year follow-up. Etiological agent did not seem to affect graft transparency at 2 years. In addition, although larger corneal perforations may have contributed to the development of more complications, perforation size was not associated with rate of graft transparency at 2 years.

Ethics

Ethics Committee Approval: İstanbul University Cerrahpaşa Faculty of Medicine, Clinical Research Ethics Committee (83045809-604.01.02-6302).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Osman Şevki Arslan, Concept: Osman Şevki Arslan, Cezmi Doğan, Design: Osman Şevki Arslan, Cezmi Doğan, Data Collection or Processing: Cezmi Doğan, Analysis or Interpretation: Osman Şevki Arslan, Cezmi Doğan, Literature Search: Cezmi Doğan, Writing: Cezmi Doğan.

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

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

References

1. Abdulhalim BE, Wagih MM, Gad AA, Boghdadi G, Nagy RR. Amniotic membrane graft to conjunctival flap in treatment of non-viral resistant infectious keratitis: a randomised clinical study. Br J Ophthalmol. 2015;99:59-63.
2. Grau AE, Duran JA. Treatment of a large corneal perforation with a multilayer of amniotic membrane and TachoSil. Cornea. 2012;31:98-100.
3. Kim HK, Park HS. Fibrin glue-assisted augmented amniotic membrane transplantation for the treatment of large noninfectious corneal perforations. Cornea. 2009;28:170-176.
4. Yokogawa H, Kobayashi A, Yamazaki N, Masaki T, Sugiyama K. Surgical therapies for corneal perforations: 10 years of cases in a tertiary referral hospital. Clin Ophthalmol. 2014;8:2165-2170.
5. Arslan OS, Unal M, Arici C, Cicik E, Mangan S, Atalay E. Novel method to avoid the open-sky condition in penetrating keratoplasty: covered cornea technique. Cornea. 2014;33:994-998.
6. Kawashima M, Kawakita T, Den S, Tomita M, Shimazaki J. Surgical management of corneal perforation secondary to gonococcal keratoconjunctivitis. Eye (Lond). 2009;23:339-344.
7. Susiyanti M, Mehta JS, Tan DT. Bilateral deep anterior lamellar keratoplasty for the management of bilateral post-LASIK mycobacterial keratitis. J Cataract Refract Surg. 2007;33:1641-1643.
8. Ti SE, Scott JA, Janardhanan P, Tan DT. Therapeutic keratoplasty for advanced suppurative keratitis. Am J Ophthalmol. 2007;143:755-762.
9. Xie L, Zhai H, Shi W. Penetrating keratoplasty for corneal perforations in fungal keratitis. Cornea. 2007;26:158-162.

10. Said DG, Otri M, Miri A, Kailasanathan A, Khatib T, Dua HS. The challenge of fungal keratitis. Br J Ophthalmol. 2011;95:1623-1624.
11. Sedghipour MR, Sorkhabi R, Shenasi A, Dehghan H. Outcome of penetrating keratoplasty in corneal ulcer: a single-center experience. Clin Ophthalmol. 2011;5:1265-1268.
12. Altay Y, Tamer S, Kaya AS, Balta O, Burcu A, Ornek F. The outcome of penetrating keratoplasty for corneal scarring due to herpes simplex keratitis. Arq Bras Oftalmol. 2017;80:41-45.
13. Kitzmann AS, Goins KM, Sutphin JE, Wagoner MD. Keratoplasty for treatment of Acanthamoeba keratitis. Ophthalmology. 2009;116:864-869.
14. Anshu A, Parthasarathy A, Mehta JS, Htoon HM, Tan DT. Outcomes of therapeutic deep lamellar keratoplasty and penetrating keratoplasty for advanced infectious keratitis: a comparative study. Ophthalmology. 2009;116:615-623.
15. Claerhout I, Beele H, Van den Abeele K, Kestelyn P. Therapeutic penetrating keratoplasty: clinical outcome and evolution of endothelial cell density. Cornea. 2002;21:637-642.
16. Hanada K, Igarashi S, Muramatsu O, Yoshida A. Therapeutic keratoplasty for corneal perforation: clinical results and complications. Cornea. 2008;27:156-160.
17. Nurözler AB, Salvarli S, Budak K, Onat M, Duman S. Results of therapeutic penetrating keratoplasty. Jpn J Ophthalmol. 2004;48:368-371.

DOI: 10.4274/tjo.galenos.2018.10734
Turk J Ophthalmol 2019;49:61-67

Original Article

Role of Oxidative Stress in Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma

Yasemin Aydın Yaz*, Nilgün Yıldırım**, Yetkin Yaz***, Neslihan Tekin****, Mine İnal*****, Fezan Mutlu Şahin******

*Eskişehir State Hospital, Ophthalmology Clinic, Eskişehir, Turkey
**Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
***Eskişehir Yunus Emre State Hospital, Ophthalmology Clinic, Eskişehir, Turkey
****Aksaray University Faculty of Arts and Sciences, Department of Biotechnology and Molecular Biology, Aksaray, Turkey
*****Eskişehir Osmangazi University Faculty of Medicine, Department of Biochemistry, Eskişehir Turkey
******Eskişehir Osmangazi University Faculty of Medicine, Department of Biostatistics, Eskişehir, Turkey

Abstract

Objectives: To investigate the role of oxidative stress on pseudoexfoliation formation and progression from pseudoexfoliation syndrome (XFS) to pseudoexfoliation glaucoma (XFG).

Materials and Methods: This study investigated oxidative stress biomarkers in blood samples from 58 patients with XFG, 47 patients with XFS, and 134 healthy age- and sex-matched controls.

Results: The highest serum malondialdehyde (MDA) levels were measured in XFG patients ($p<0.001$), and MDA level was higher in XFS patients than controls ($p<0.001$). Superoxide dismutase (SOD) and catalase (CAT) enzyme activities were significantly lower in XFS and XFG patients than in the control group, whereas a significant increase was observed in glutathione (GSH) levels ($p<0.001$ for all). However, levels of these three biomarkers did not differ significantly between XFS and XFG patients ($p=0.188$, $p=0.185$, and $p=0.733$, respectively). Nitric oxide (NO) concentration was significantly lower in XFG patients compared to XFS patients and controls ($p<0.001$) but did not differ between XFS patients and controls ($p=0.476$).

Conclusion: Elevated MDA levels suggest that lipid peroxidation is important in XFS and XFG development and progression from XFS to XFG. In addition, reduction in SOD and CAT enzyme activities is considered a deficiency in the enzymatic antioxidant protection system. Furthermore, GSH values may be evaluated as a compensatory response to oxidative stress in XFS and XFG. Alterations in NO indicate the role of a vascular regulatory factor in the progression from XFS to glaucoma.

Keywords: Pseudoexfoliation, glaucoma, oxidative stress

Introduction

Pseudoexfoliation syndrome (XFS) is an age-related extracellular matrix disorder that is associated with the excessive production and accumulation of abnormal fibrillar material in intra- and extraocular tissues. In all populations, the frequency of XFS increases with age and the incidence of the syndrome doubles every decade.[1] The accumulation of abnormal fibrillar aggregates in the outflow pathways leads to an increase in outflow resistance and intraocular pressure.[2] XFS is a significant cause of chronic open-angle glaucoma and can predispose individuals to a broad spectrum of intraocular and surgical complications. Furthermore, XFS is not only an ocular disease but is also considered to be a systemic disorder due to the accumulation of pseudoexfoliative material (XFM) in visceral organs such as the heart, lung, gallbladder, kidney, and cerebral meninges.[3]

It is well known that oxidative stress plays an important role in XFS and other age-related disorders such as cataract

Address for Correspondence: Yasemin Aydın Yaz MD, Eskişehir State Hospital, Ophthalmology Clinic, Eskişehir, Turkey
Phone: +90 506 274 28 53 E-mail: yaydinyaz@gmail.com **ORCID-ID:** orcid.org/0000-0002-2535-0651
Received: 31.01.2018 **Accepted:** 06.09.2018

and age-related macular degeneration.[4] Oxidative stress is defined as an imbalance between oxidants and antioxidants or an increase in the intracellular concentrations of reactive oxygen species (ROS) over physiological values. ROS such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and nitric oxide (NO) incorporate into proteins, lipids, carbohydrates, and nucleic acids, then promote DNA damage and cellular injury.[5] On the other hand, antioxidant defense systems can protect cells from the detrimental effects of ROS. Oxidative stress can induce an increase or decrease in the antioxidant defense system as a protective response or due to the ROS effect, respectively.[6]

Oxidative stress plays a key role in the pathogenesis of XFS and glaucoma.[7] Different ROS and antioxidants have been investigated in serum and aqueous samples in previous studies. Total oxidative stress (TOS)[8], malondialdehyde (MDA)[9], 8-hydroxydeoxyguanosin (8-OHdG)[10], protein carbonyl (PC)[9], and nitric oxide (NO)[9] were measured as oxidant markers, and total antioxidant status (TAS)[11], superoxide dismutase (SOD)[9,12], glutathione peroxidase (GPx)[12], catalase (CAT)[12], vitamin C[12], paraoxonase[8,13], and arylesterase[8] were measured as antioxidant markers in different studies.

Despite the recent studies, the exact pathogenesis of XFS and the progression from XFS to glaucoma remain unclear. In this study, we aimed to investigate the effect of oxidative stress on the development of XFS and progression from XFS to pseudoexfoliation glaucoma (XFG). Therefore, we measured the activity of the SOD and CAT enzymes (enzymatic antioxidants), MDA (an end product of lipid peroxidation), NO (a marker of nitrosative stress and vascular function), and GSH (a primary endogenous antioxidant) as oxidative stress biomarkers in patients with XFG, XFS, and healthy control subjects.

Materials and Methods

Study Population

The study population comprised 239 individuals, including 58 patients with XFG, 47 patients with XFS, and 134 healthy age- and sex-matched controls. Written informed consent was obtained from all participants. The study was approved by the ethics review board of the Eskişehir Osmangazi University Faculty of Medicine and adhered to the tenets of the Declaration of Helsinki.

All subjects underwent a standardized detailed ophthalmic examination that included assessments of refraction, visual acuity, and intraocular pressure (Goldmann applanation tonometry) as well as fundus and anterior segment biomicroscopy examinations. XFG was defined as the presence of XFM on the anterior lens capsule or pupillary margin, elevated intraocular pressure (IOP) (≥21 mmHg), glaucomatous optic disc changes (vertical cup-to-disc ratio [C/D] ≥0.5, C/D asymmetry ≥0.2), and characteristic visual field defects in computed perimetry (Zeiss Humphrey visual field analyzer white on white 30-2 threshold program). Patients who had XFM in the anterior lens capsule and pupillary margin but whose IOP, optic disc, and visual field findings were within normal limits were defined as having XFS. The control group was matched with the patient cohorts based on age and sex and underwent a standardized detailed ophthalmic examination. The controls did not exhibit XFM, had IOP within the normal range (<21 mmHg), and had no glaucomatous optic disc damage. All participants were questioned about systemic diseases (diabetes, hypertension, thyroid and rheumatic diseases) and drug usage. We excluded patients with ophthalmic diseases (e.g., uveitis, angle closure glaucoma, pigment dispersion syndrome, trauma, progressive retinal disease), smokers, and patients with uncontrolled major systemic diseases.

Sample Preparation

Blood samples were collected in two different tubes. The first tube was centrifuged at 3,500 x g for 10 minutes to separate the serum and was used for the determination of NO, MDA, and CAT concentrations. The second tube, which included EDTA, was used for the measurement of GSH and SOD. The samples were immediately centrifuged at 1,500 x g for 5 min, and the plasma was separated. After separating the plasma, the erythrocytes were washed three times with saline and erythrocyte packets were prepared. Erythrocyte hemolysates were then prepared and stored at -80 °C until GSH and SOD measurement.

Determination of MDA Level

Serum lipid peroxidation was estimated based on the measurement of malondialdehyde reacted with thiobarbituric acid (TBA), according to the method described by Ohkawa et al.[14] Absorbance was measured at 532 nm. MDA levels were presented in nmol/L.

Determination of SOD Activity

Erythrocyte SOD activity was assayed spectrophotometrically, according to the method described by Winterbourn et al.[15] This assay is based on the inhibitory effect of SOD on the reaction in which superoxide anion reduces nitroblue tetrazolium (NBT). Absorbance was measured at 560 nm. SOD activity was presented in U/Hb.

Determination of CAT Activity

Serum CAT activity was determined according to the method described by Beutler.[16] This method is based on the rate of hydrogen peroxide decomposition due to the activity of CAT in the examined samples. Absorbance was measured at 230 nm. CAT activity was presented in U/L.

Determination of GSH Level

Erythrocyte GSH levels were measured spectrophotometrically according to the method described by Ellman et al.[17] GSH is reacted with 5.5 dithiobis-2-nitrobenzoic acid (2 DTNB), resulting in the formation of a product that has a maximal absorbance at 412 nm. GSH levels were also presented in U/Hb.

Determination of NO Level

Serum nitrite (NO_2^-) and nitrate (NO_3^-) were assessed as an index of NO production, based on the cadmium reduction method described by Wakid and Cortas.[18] The samples were deproteinized, and total nitrite (nitrite + nitrate) was measured via spectrophotometry at 545 nm after the reduction of nitrate to nitrite with copperized cadmium granules. The results were presented in µmol/L.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 for Windows. The Shapiro-Wilk normality test was applied for continuous variables. Normally distributed variables were analyzed using a t test for independent groups and summarized using the mean and standard deviation. Non-normally distributed variables were compared using the Mann-Whitney U test and the Kruskal-Wallis test and summarized using the median and 25th and 75th percentiles. The Pearson chi-square test was used for categorical variables; the results were summarized using the sample size (n) and percentage (%). The comparisons of MDA, SOD, CAT, GSH, and NO between the groups were analyzed by Quade's Rank Analysis of Covariance. Systemic disease was used as a covariant. The Dwass-Steel-Critchlow-Fligner multiple comparison method was used to determine significantly different groups. P value less than 0.05 was accepted as the level of significance.

Results

A total of 239 individuals over 40 years of age were recruited for this study by the Eskişehir Osmangazi University Glaucoma Department as follows: 58 individuals with XFG, 47 with XFS, and 134 controls. The demographic data of the subjects are shown in Table 1.

The levels of MDA, SOD, CAT, GSH, and NO were summarized in Table 2. Patients under a treatment regimen for systemic diseases such as diabetes, hypertension, and others (e.g., cardiovascular disease, rheumatologic disease) were compared with those without systemic disease and no statistically significant difference was found ($p<0.001$). As a result, they were included in the study. The levels of oxidative stress markers between patients with and without systemic diseases in the different groups is shown in Table 3.

Serum MDA levels were significantly higher in XFG patients than in XFS patients or controls ($p<0.001$). In addition, XFS patients' MDA levels were also higher than those of the controls ($p<0.001$). The SOD and CAT enzyme activities of XFS and XFG patients were significantly lower than those of the control group ($p<0.001$). However, no differences were observed in SOD and CAT activity between XFS and XFG patients ($p=0.188$ and $p=0.185$, respectively). GSH levels were significantly higher in XFS and XFG patients when compared to control subjects ($p<0.001$). Similar to the SOD and CAT activities, no significant difference was observed in GSH concentration between the XFS and XFG groups ($p=0.733$). In addition, the concentration of NO was significantly lower in XFG patients than in XFS patients and control subjects ($p<0.001$). However, NO levels did not differ between XFS patients and controls ($p=0.476$).

Discussion

XFS is a multifactorial systemic disease in which genetic and environmental risk factors play a role in pathogenesis. Disturbances in the balance between ROS and antioxidant defense systems contribute to the development of XFS. There is increasing evidence that the oxidant-antioxidant balance is disrupted in XFS, not only in the anterior segment, but throughout the body. Intraocular secretion of XFM is closely related to aqueous circulation; therefore, examination of aqueous humour and lens epithelial cell composition in patients with XFS may reveal important pathogenetic factors.[19] In recent years, *LOXL1* single nucleotide polymorphisms (SNPs) have been identified as a risk factor for XFS. Despite the association between *LOXL1* SNPs and XFS, the high frequency of these SNPs in the non-XFS population indicates that different factors may play a role in the development of XFS.[20] Furthermore, results from several studies show that local production of growth factors, especially TGFβ1, seems to play an important role in XFS. TGFβ1 induces the expression of *LOXL1* and other extracellular matrix proteins in XFM.[21] Based on evidence of epigenetic correlations with XFG, metabolic, physical and environmental conditions would affect the biological functions of XFS-related proteins by changing their expression, secretion, and conformation.[22] Despite the effects of oxidative stress and genetic and epigenetic factors on XFS development, the exact pathogenesis of XFS remains unclear.

MDA is the end-product of polyunsaturated fatty acid peroxidation and reflects free radical damage caused by lipid peroxidation. It also seems to be a good biomarker for evaluating oxidative stress in serum.[7] In the current study, we observed differences in serum MDA levels between the study groups. The highest values were observed in the XFG group, and the MDA levels of XFS patients were higher than those of the control group. High MDA levels suggest that the effects of oxidative stress play a role in XFM formation and in XFG development.

Table 1. Demographic and clinical characteristics of all groups

	Controls (n=134)	XFS (n=47)	XFG (n=58)	p-value
Age (years), median (25th-75th percentiles)	68 (65-72)	67 (59-72.75)	66 (60-73)	0.107*
Gender (female), n (%)	77 (57%)	27 (48%)	20 (34%)	0.010**
Diabetes mellitus, n (%)	42 (30%)	13 (27%)	15 (26%)	0.718**
Hypertension, n (%)	40 (30%)	25 (53%)	20 (34%)	0.016**
Cardiovascular disease, n (%)	18 (13%)	13 (27%)	11 (19%)	0.084**

XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma
*Kruskal-Wallis test; $p<0.05$ was considered statistically significant
**Chi-square test; $p<0.05$ was considered statistically significant

In previous studies, similar results were found for MDA levels. Yağci et al.[23] and Yılmaz et al.[24] found elevated serum MDA levels in XFS patients in comparison to healthy controls. Gartaganis et al.[25] reported a 2.5-fold increase in MDA levels in lens epithelial cells of patients with XFS in comparison to lens epithelial cells from non-XFS patients. A study performed by Engin at al.[26] demonstrated that MDA levels in glaucoma patients with XFS were higher than in other glaucoma patients and the control group. Another study performed by Faschinger et al.[27] reported high levels of thiobarbituric acid-reacting substances (TBARS), which are major breakdown products of lipid peroxides, in aqueous samples from primary open angle glaucoma (POAG) patients and in serum samples from non-XFS cataract patients. However, no significant differences were observed between the groups. Similarly, Ocakoglu et al.[28] found the MDA levels in POAG patients to be twice those of the control group. In contrast, Tetikoğlu et al.[29] found no difference between the control and XFS groups. In the same study, the mean serum MDA levels in the XFS and XFG groups were comparable, with no statistically significant difference.

SOD and CAT are key antioxidant enzymes in the metabolism of ROS, and the levels of these enzymes reflect the oxidative stress status and oxidative stress response of the organism. SOD specifically converts superoxide radicals to hydrogen peroxide

Table 2. Levels of oxidative stress biomarkers in all groups

	Control (n=134) (0)	XFS (n=47) (1)	XFG (n=58) (2)		
	Mean ± Standard deviation Median (25^{th}-75^{th}) Percentiles			p-value*	Multiple comparion: p**
MDA (nmol/mL)	1.79±0.69 1.72 (1.21-2.22)	6.81±1.52 6.58 (5.96-7.68)	8.96±1.32 9.28 (7.94-9.91)	<0.001	0-1:<0.001 0-2:<0.001 1-2:<0.001
SOD (U/Hb)	32.10±9.10 32.55 (24.14-40.11)	10.15±2.68 10.16 (8.12-11.22)	11.16±2.69 10.57 (9.44-12.09)	<0.001	0-1:<0.001 0-2:<0.001 1-2:0.188
CAT (U/L)	51.17±6.93 50.79 (45.61-56.33)	27.47±5.56 27.65 (24.23-31.15)	30.73±5.39 30.20 (27.26-35.00)	<0.001	0-1:<0.001 0-2:<0.001 1-2:0.185
GSH (U/Hb)	4.03±1.81 3.75 (2.42-5.31)	6.57±1.97 6.84 (5.26-7.82)	6.30±2.36 6.31 (4.08-8.20)	<0.001	0-1:<0.001 0-2:<0.001 1-2:0.733
NO (µmol/L)	39.14±17.42 39.50 (25.06-49.71)	41.67±13.12 40.43 (32.43-53.71)	30.12±13.90 24.78 (18.97-38.83)	<0.001	0-1:0.476 0-2:<0.001 1-2:<0.001

XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma, MDA: Malonyldialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, NO: Nitric oxide
*Quade's Rank Analysis of Covariance test using systemic disease as a covariant; p<0.05 was considered statistically significant
**Dwass-Steel-Critchlow-Fligner method for multiple comparison test; p<0.05 was considered statistically significant

Table 3. The levels of oxidative stress markers between patients with and without systemic diseases among different groups

	Systemic sisease	Control	p-value	XFS	p-value	XFG	p-value
MDA (nmol/mL)	No	1.68 (1.13-2.16)†	0.209*	6.47 (5.59-7.45)†	0.730*	9.30±1.20‡	0.069**
	Yes	1.8 (1.21-2.44)†		6.6 (6-7.77)†		8.67±1.36‡	
SOD (U/Hb)	No	34 (24.67-40.23)†	0.449*	10.17 (8.74-10.91)†	0.877*	10.18 (9.17-11.6)†	0.279*
	Yes	32.14 (23.17-38.42)†		9.84 (8.01-11.54)†		11.16 (9.53-13.24)†	
CAT (U/L)	No	51.05±7.53‡	0.859**	26.36±5.12‡	0.405**	31.29±5.26‡	0.460**
	Yes	51.26±6.47‡		27.89±5.74‡		30.23±5.54	
GSH (U/Hb)	No	4.51 (2.81-5.45)†	0.304*	6.71±1.9‡	0.759**	6.77±2.34‡	0.156**
	Yes	3.56 (2.26-5.3)†		6.51±2.02‡		5.89±2.33‡	
NO (µmol/L)	No	42.21 (29.37-51.16)†	0.057*	35.94±13.2‡	0.063**	24.16 (18.85-31.96)†	0.173*
	Yes	32.67 (20.43-49.3)†		43.87±12.6‡		30.11 (20.18-44.47)†	

XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma, MDA: Malonyldialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, NO: Nitric oxide, Hb: Hemoglobin
*Mann-Whitney U test; p<0.05 was considered statistically significant.
**Independent t-test; p<0.05 was considered statistically significant.
†Median (25^{th} - 75^{th} percentiles)
‡Mean ± standard deviation

and oxygen. In our study, the SOD and CAT enzyme activities of XFS and XFG patients were significantly lower than the control group, while no significant differences were observed between XFS and XFG patients. These results suggest an inadequate antioxidant enzyme response and might demonstrate a role in pseudoexfoliation development. However, the progression from XFS to XFG could not be explained with these results. Similar findings were obtained in studies performed by Yağci et al.[23] and Engin et al.[26] reporting decreased serum SOD levels in XFS patients in comparison to control subjects. Additionally, SOD was investigated in aqueous and lens epithelium samples in different studies. Ucakhan et al.[30] reported an increase in SOD activity in the lens capsules of patients with XFS and cataracts. In another study in which Ferreira et al.[12] analyzed aqueous samples, higher SOD activity was observed in XFG patients than in the POAG and cataract groups. No significant differences were found between the two glaucoma groups, but a significant increase in SOD activity was found between the glaucoma group and cataract group. Despite the decrease in SOD in serum, an increase in aqueous and lens capsules could be a protective response of the eye against oxidative stress.[7]

CAT is an antioxidant enzyme that catalyzes the decomposition of hydrogen peroxide to molecular oxygen and water. In the current study, CAT activity was significantly lower in XFS and XFG patients compared to the control group. The reduction of CAT activity observed in XFS and XFG patients was interpreted as an insufficiency of antioxidant enzymes or a decrease in enzyme levels in response to oxidative stress. Koliakos et al.[31] found significantly lower CAT activity in both serum and aqueous samples from XFS and XFG patients compared with samples from controls. Similarly, a decrease in serum CAT activity was reported in a study performed by Zoric et al.[32] In another study, Ferreira et al.[21] found no significant differences in CAT activity between aqueous samples from the XFG, POAG, and cataract groups. Tetikoğlu et al.[29] reported an insignificant decrease in serum CAT activity in pseudoexfoliative group, in contrast to our findings.

GSH is a tripeptide and the major endogenous antioxidant molecule. This molecule is involved in the cellular portion of the antioxidant defense system.[25] In our study, the GSH levels of XFS and XFG patients were significantly higher than those of the control group, whereas no significant differences were observed between the XFS and XFG groups. The difference observed between the pseudoexfoliative and control groups was interpreted as a compensatory defense mechanism against oxidative damage. In contrast to SOD and CAT, GSH levels were higher in the pseudoexfoliation group than in the control group. SOD and CAT are enzymatic antioxidants; however, GSH is non-enzymatic and represents the first defense mechanism of the organism against oxidative stress. Our results were not consistent with those of previous studies. Gartaganis et al.[25] found a 2.2-fold decrease in GSH levels in XFS lens epithelial cells in comparison to non-XFS lens epithelial cells. In another study performed by the same group, aqueous humor samples from individuals with XFS exhibited a decrease in GSH concentrations of up to 28%.[33] These studies used different types of samples than our study, and their results might indicate a local response to oxidative stress.

Vascular-derived cellular mediators are important in glaucoma pathogenesis as well as IOP elevation. The vascular endothelium plays a major role in vascular homeostasis by producing these cellular mediators. Vascular microcirculation depends on the balance between vasodilation mediators (e.g., NO, prostacyclin, and hydrogen peroxide) and vasoconstrictor mediators (e.g., endothelin-1, angiotensin, and thromboxane). NO is a key molecule for vasodilation. In addition to its role as a vascular mediator, NO is also a neurotransmitter, a free radical, and an antioxidant. In vascular endothelial diseases, an increase in vascular permeability, disturbances in VEGF production, increased responses to endothelin-1, and decreased responses to NO have been observed.[34]

Ocular blood flow abnormalities play a role in the pathogenesis of glaucoma. Reduction in ocular blood flow is thought to be secondary to vascular dysregulation.[35] NO is the major vasodilator molecule in the choroid, optic nerve, and retina; therefore, NO is a key molecule for ocular blood circulation. Vascular endothelial disease in glaucoma also affects endothelial cells in the trabecular meshwork and Schlemm's canal, as well as in vascular endothelial cells. NO has a vasodilator effect on vascular endothelial cells, but in the trabecular meshwork, NO regulates trabecular outflow by contracting trabecular cells.[36] Furthermore, NO facilitates aqueous outflow and causes a decrease in IOP; in contrast, endothelin-1 increases IOP. Therefore, NO and endothelin-1 are associated with IOP elevation in glaucoma through a decrease in NO production or an excessive increase in endothelin-1 secretion.[37]

In our study, we found significantly lower NO levels in XFG patients than XFS and control groups. Reduced NO levels in XFG could be a contributory factor to glaucoma development with no specific role in XFS. This is supported by previous studies which have failed to find any statistically significant differences in NO levels between subjects with XFS and controls.[38,39] Borazan et al.[38] evaluated VEGF and NO levels in the plasma and aqueous humor of XFS and XFG patients and found no significant differences in plasma NO levels between the XFS, XFG, and control groups. In another study performed by Altintas et al.[39], NO levels were found to be slightly higher in XFS and XFG patients than in POAG and control patients, but the observed differences were not statistically significant. Yağci et al.[40] found that serum nitrite levels were significantly higher in the pseudoexfoliative group than in controls. Similarly, another study performed by Erdurmus et al.[9] reported higher NO levels in POAG and XFG patients than in controls.

Study Limitations

Our study has several limitations. We assessed MDA, SOD, CAT, GSH, and NO levels in serum samples. Although XFS is mostly diagnosed on the basis of ophthalmic findings, it is considered a complex disease that manifests in multiple systems. Therefore, we based our methodology on revealing differences in oxidative markers in the serum sample of the patients reflecting

the multisystem involvement of XFS. We included patients with systemic diseases but the results were not affected when the covariance analysis was performed. However, the presence of systemic diseases might be confounding and these patients could be excluded from the study.

Conclusion

Finally, the results of the present study revealed a difference in MDA levels between study groups. MDA levels were the lowest in the control group, followed by the XFS and XFG groups. The observed differences in MDA levels indicate that lipid peroxidation might play a role in XFS and XFG development. SOD and CAT activities were lower and GSH levels were higher in XFS and XFG patients than in the control group. The reduction observed in SOD and CAT activities might be interpreted as a deficiency in antioxidant defense systems. The elevated levels of GSH in the pseudoexfoliative group suggests a compensatory response to oxidative stress. NO levels were lower in XFG patients than in XFS and control patients. Impaired NO levels in XFG patients might have a dual negative effect on glaucoma development and progression by affecting ocular blood flow and trabecular outflow.

In conclusion, these results suggest that oxidative stress may play a role in XFS pathogenesis. Especially lipid peroxidation and decreased antioxidant enzyme activities were found to be associated with pseudoexfoliation development. In addition, lipid peroxidation and decreased NO levels were found to be related to glaucoma progression from XFS to XFG.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University Medical School Ethics Committee, 80558721/48.

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yasemin Aydın Yaz, Yetkin, Yaz, Nilgün Yıldırım, Neslihan Tekin, Concept: Yasemin Aydın Yaz, Nilgün Yıldırım, Design: Yasemin Aydın Yaz, Nilgün Yıldırım, Mine İnal, Data Collection or Processing: Yasemin Aydın Yaz, Yetkin Yaz, Analysis or Interpretation: Neslihan Tekin, Fezan Şahin, Literature Search: Yasemin Aydın Yaz, Writing: Yasemin Aydın Yaz.

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

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

References

1. Ritch R, Schlötzer-Schrehardt U. Exfoliation syndrome. Surv Ophthalmol. 2001;45:265-315.
2. Schlötzer-Schrehardt U. New pathogenetic insights into pseudoexfoliation syndrome/glaucoma. Therapeutically relevant? Ophthalmologe. 2012;109:944-951.
3. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Opthalmol. 2006;141:921-937.
4. Schlötzer-Schrehardt U. Oxidative stress and pseudoexfoliation glaucoma. Klin Monbl Augenheilkd. 2010;227:108-113.
5. Zierhut M, Cadenas E, Rao NA. Free radicals in ophthalmic disorders (1st ed). Informa; 2008:1-10.
6. Sies H, Berndt C, Jones DP. Oxidative stress. Annu Rev Biochem. 2017;86:715-748.
7. Benoist d'Azy C, Pereira B, Chiambaretta F, Dutheil F. Oxidative and Anti-Oxidative Stress Markers in Chronic Glaucoma: A Systemic Review and Meta-Analysis. PLoS One. 2016;11:e0166915.
8. Dursun F, Vural Ozec A, Aydin H, Topalkara A, Dursun A, Toker MI, Erdogan H, Arıcı MK. Total oxidative stress, paraoxonase and arylesterase levels at patients with pseudoexfoliation syndrome and pseudoexfoliative glaucoma. Int J Ophthalmol. 2015;8:985-990.
9. Erdurmuş M, Yağcı R, Atış Ö, Karadağ R, Akbaş A, Hepşen IF. Antioxidant status and oxidative stress in primary open angle glaucoma and pseudoexfoliative glaucoma. Curr Eye Res. 2011;36:713-718.
10. Sorkhabi R, Ghorbanihaghjo A, Javadzadeh A, Rashtchizadeh N, Moharrery M. Oxidative DNA damage and total antioxidant status in glaucoma patients. Mol Vis. 2011;17:41-46.
11. Abu-Amero KK, Kondkar AA, Mousa A, Osman EA, Al-Obeidan SA. Decreased total antioxidants status in the plasma of patients with pseudoexfoliation glaucoma. Mol Vis. 2011;17:2769-2775.
12. Ferreira SM, Lerner SF, Brunzini R, Evelson PA, Llesuy SF. Antioxidant status in the aqueous humour of patients with glaucoma associated with exfoliation syndrome. Eye (Lond) 2009;23:1691-1697.
13. Demirdögen BC, Ceylan OM, Işikoglu S, Mumcuoğlu T, Erel O. Evaluation of oxidative stress and paraoxonase phenotypes in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Clin Lab 2014;60:79-86.
14. Ohkawa H, Ohishi, N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95:351-358.
15. Winterbourn CC, Hawkins RE, Brian M, Carrell RW. The estimation of red cell superoxide dismutase activity. J Lab Clin Med. 1975;85:337-341.
16. Beutler E. Red cell metabolism a manual of biochemical method. New York; USA: Grune and Stratton; 1973:74.
17. Ellman B, Robson MJ, Buttenweiser E. The glutathione instability of drug sensivity red cells. J Lab Clin Med. 1957;49:84-95.
18. Cortas NK, Wakid NW. Determination of inorganic nitrate in serum and urine by a kinetic cadmium-reduction method. Clin Chem. 1990;36:1440-1443.
19. Simavli H, Tosun M, Bucak YY, Erdurmus M, Ocak Z, Onder HI, Acar M. Serum and aqueous xanthine oxidase levels, and mRNA expression in anterior lens epithelial cells in pseudoexfoliation. Graefes Arch Clin Exp Ophthalmol. 2015;253:1161-1167.
20. Schlötzer-Schrehardt U. Genetics and genomics of pseudoexfoliation syndrome/glaucoma. Middle East Afr J Ophthalmol. 2011;18:30-36.
21. Borrás T. Growth Factors, Oxidative Damage and Inflammation in Exfoliation Syndrome. J Glaucoma. 2018;27(Suppl 1):54-60.
22. Pasquale LR, Kang JH, Wiggs JL. Prospects for gene-environment interactions in exfoliation syndrome. J Glaucoma. 2014;23:64-67.
23. Yağci R, Gürel A, Ersöz I, Keskin UC, Hepşen IF, Duman S, Yiğitoğlu R. Oxidative stress and protein oxidation in pseudoexfoliation syndrome. Current Eye Res. 2006;31:1029-1032.
24. Yılmaz A, Adıgüzel U, Tamer L, Yıldırım Ö, Öz Ö, Vatansever H,Ercan B, Değirmenci U, Atik U. Serum oxidant/antioxidant balance in exfoliaition syndrome. Clin Exp Ophthalmol. 2005;88:523-527.
25. Gartaganis SP, Patsoukis NE, Nikolopoulos DK, Georgiou CD. Evidence for oxidative stress in lens epithelial cells in pseudoexfoliaiton syndrome. Eye (Lond). 2007;11:1406-1411.
26. Engin KN, Yemişçi B, Yiğit U, Ağaçhan A, Coşkun C. Variability of serum oxidative stress biomarkers relative to biochemical data and clinical parameters of glaucoma patients. Mol Vis. 2010;16:1260-1271.
27. Faschinger C, Schmut O, Wachswender C, Mossböck G. Glaucoma and oxidative stress. Determination of malondialdehyde-a product of lipid peroxidation. Ophthalmologe. 2006;103:953-959.

28. Ocakoglu O, Balci H, Ozkok A, Dincer Y, Koc EE, Ucar D, Akcay T. Primer Açık Açılı Glokomlu ve Senil Kataraktlı Hastalarda Oksidatif Stresin Rolü - Orijinal Araştırma. Turk J Ophthalmol. 2008;38:292-297.
29. Tetikoğlu M, Sağdik HM, Aktas S, Uçar F, Özcura F. Serum prolidase activity and oxidative stress in patients with pseudoexfoliation syndrome. Graefes Arch Clin Exp Ophthalmol. 2016;254:1339-1343.
30. Ucakhan OO, Karel F, Kanpolat A, Devrim E, Durak I. Superoxide dismutase activity in the lens capsule of patients with pseudoexfoliation syndrome and cataract. J Cataract Refract Surg. 2006;32:618-622.
31. Koliakos GG, Befani CD, Mikropoulos D, Ziakas NG, Konstas P. Prooxidant-antioxidant balance, peroxide and catalase activity in the aqueous humour and serum of patients with exfoliation syndrome or exfoliative glaucoma. Graefes Arch Clin Exp Ophthalmol. 2008;246:1477-1483.
32. Zoric L, Miric D, Milenkovic S, Jovanovic P, Trajkovic G. Pseudoexfoliation syndrome and its antioxidative protection deficiency as risk factors for age-related cataract. Eur J Ophthalmol. 2006;16:268-273.
33. Gartaganis SP, Georgakopoulos CD, Patsoukis NE, Gotsis SS, Gartaganis VS, Georgiou CD. Glutathione and lipid peroxide changes in pseudoexfoliation syndrome. Curr Eye Res. 2005;30:647-651.
34. Resch H, Garhofer G, Fuchsijager-Maryl G. Hommer A, Schmetterer L. Endothelial dysfunction in glaucoma. Acta Ophthalmol. 2009;87:4-12.
35. Sekeroglu MA, Irkec M, Mocan MC, Ileri E, Dikmenoglu N, Seringec N, Karaosmanoglu D, Orhan M. The association of ocular blood flow with haemorheological parameters in primary open-angle and exfoliative glaucoma. Acta Ophthalmol. 2011;89:429-434.
36. Stefan C, Dumitrica DM, Ardeleanu C. The future: nitric oxide in glaucoma, Oftalmologia. 2007;51:89-94.
37. Ivan 0, Dettmann HES. Nitric oxide and endothelin in the pathogenesis of glaucoma: An overview. In: Haefliger IO, Flammer J, eds. Nitric oxide and endothelin in the pathogenesis of glaucoma, New York; Lippincott- Raven; 1997:22-33.
38. Borazan M, Karalezli A, Kucukerdonmez C, Bayraktar N, Kulaksizoglu S, Akman A, Akova YA. Aqueous humor and plasma levels of vascular endothelial growth factor and nitric oxide in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma. J Glaucoma. 2010;19:207-211.
39. Altintaş O, Maral H, Yüksel N, Karabaş VL, Dillioğlugil MO, Cağlar Y. Homocysteine and nitiric oxide levels in plasma of patients with pseudoexfoliation syndrome, pseudoexfoliation glaucoma and primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 2005;243:677-683.
40. Yağci R, Gürel A, Ersöz I, Karadağ R, Hepşen IF, Duman S. The activities of paraoxonase, xanthine oxidase, adenosine deaminase and the level of nitrite in pseudoexfoliation syndrome. Ophthalmic Res. 2009;42:155-159.

DOI: 10.4274/tjo.galenos.2018.47897
Turk J Ophthalmol 2019;49:68-72

Original Article

The Preventive Effect of Oxytocin on Retinopathy in Streptozotocin-Induced Diabetic Rats

Cumali Değirmenci*, Filiz Afrashi*, Oytun Erbaş**, Hüseyin Aktuğ***, Dilek Taşkıran****

*Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**İstanbul Bilim University Faculty of Medicine, Department of Physiology, İstanbul, Turkey
***Ege University Faculty of Medicine, Department of Histology and Embryology, İzmir, Turkey
****Ege University Faculty of Medicine, Department of Physiology, İzmir, Turkey

Abstract

Objectives: The aim of this study was to investigate the impact of intravitreal and intraperitoneal use of oxytocin (OT) on retinopathy in streptozotocin-induced diabetic rats.

Materials and Methods: Twenty-four 6–8-week-old adult male and female Sprague Dawley rats were used in the study. Diabetes was induced in the rats with a single injection of intraperitoneal streptozotocin. Diabetes was verified after 48 hours by measuring blood glucose levels of 260 mg/dl (14.4 mmol/L) or higher in diabetic rats. The rats were divided into 4 groups and treated as follows: intravitreal physiological saline group (0.01 mL saline weekly), intravitreal OT group (10 µU/µL OT weekly), intraperitoneal physiological saline group (1 mL daily), and intraperitoneal OT group (100 IU/kg OT daily). Hamilton syringes fitted with 27-gauge needles were used for intraperitoneal injections while 31-gauge needles were used for intravitreal injection. After 4 weeks of treatment the rats were euthanized to evaluate outer nuclear layer (ONL) thickness, vascular endothelial growth factor (VEGF) immunoexpression, and plasma VEGF levels from blood samples obtained by cardiac puncture.

Results: Morphometric analysis of retinal cross-sections showed that intravitreal and intraperitoneal OT significantly increased ONL thickness compared to physiological saline-treated groups. Also, OT treatment significantly decreased VEGF protein expression compared with the physiological saline groups. Plasma VEGF level was significantly higher in the physiological saline treatment group compared to the OT treatment group.

Conclusion: OT reduces diabetic retinopathy progression, particularly when administered intravitreally. To our knowledge, this is the first attempt to investigate the impact of OT on diabetic retinopathy and may provide a new area for further research.

Keywords: Immunohistochemistry, oxytocin, retinopathy, streptozotocin, VEGF

Introduction

Diabetes mellitus is a progressive disease that afflicts over 230 million people worldwide. Diabetes affects both microvascular and macrovascular structures throughout the body and consequently can cause retinopathy, neuropathy, and nephropathy. Diabetic retinopathy (DR) is the leading cause of preventable blindness. Sustained hyperglycemia causes the blood vessels to swell and leak fluid, resulting in damage to the microvascular structure of the retina. This can result in retinal ischemia that leads to vascular endothelial growth factor (VEGF) secretion and the growth of immature, fragile new vessels. These new vessels lead to neovascularization and proliferative DR and result in macular edema, vitreous hemorrhages, and tractional retinal detachment.[1,2,3,4,5]

Address for Correspondence: Cumali Değirmenci MD, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone: +90 506 859 96 44 E-mail: cudegirmenci@yahoo.com **ORCID-ID:** orcid.org/0000-0002-8268-536X
Received: 17.05.2018 **Accepted:** 27.08.2018

Oxytocin (OT) is nonapeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. OT establishes its effects through the OT receptor, a G protein-coupled receptor. It stimulates uterine contractions at parturition, myoepithelial cell contraction in mammalian glands for milk ejection, and also has vasoconstrictor or vasodilator effects on different vascular beds.[6,7,8] Recent studies have also reported the anti-inflammatory and anti-oxidant effects of OT.[9,10] OT receptors have been found in cone photoreceptors and retinal pigment epithelium. OT exerts its effects by increasing intracellular levels of Ca^{+2}, which facilitates smooth muscle contraction, nitric oxide synthesis, prostaglandin production, activation of the MAP-kinase cascade, and protein synthesis.[11,12]

In view of these previous studies and observations, we aimed to detect the effect of intravitreal and intraperitoneal administration of OT in the retina of streptozotocin (STZ)-induced diabetic rats.

Materials and Methods

Animals

In this study, 24 adult male and female Sprague Dawley rats weighing 200–250 g were used. Animals were fed ad libitum and housed in pairs in steel cages having a temperature-controlled environment (22±2 ºC) with 12-hour light/dark cycles. The experimental procedures were approved by the Committee for Animal Research of Ege University. All animal studies strictly conformed to the Committee on Animal Research and Ethics guidelines. All chemicals were obtained from Sigma-Aldrich Inc. unless otherwise noted.

Experimental Protocol

Diabetes was induced by a single intraperitoneal injection of streptozocin (STZ) (Sigma-Aldrich, Inc., Saint Louis, MO) (60 mg/kg in 0.9% NaCl, adjusted to a pH 4.0 with 0.2 M sodium citrate). Diabetes was verified after 48 h by evaluating blood glucose levels with the use of glucose oxidase reagent strips (Boehringer Mannheim, Indianapolis). Rats with blood glucose levels of 260 mg/dl (14.4 mmol/L) and higher were included in this study as diabetic rats.

The 24 rats were equally divided into 4 groups as follows: intravitreal physiological saline group, intravitreal OT group, intraperitoneal physiological saline group, and intraperitoneal OT group. The rats in the intraperitoneal groups were treated daily with either 1 mL physiological saline or 100 IU/kg OT intraperitoneally; the rats in the intravitreal groups received topical anesthesia with proparacaine hydrochloride followed by 0.01 mL physiological saline or 10 µU/µL OT in weekly intravitreal injections. Hamilton syringes fitted with 27-gauge needles were used for intraperitoneal injections while 31-gauge needles were used for intravitreal injections. After 4 weeks of treatment the rats were euthanized and blood samples were collected by cardiac puncture for enzyme-linked immunosorbent assay (ELISA) of plasma VEGF levels in the intraperitoneal treatment groups, then enucleation was performed in all groups.

Immunohistochemistry

Cross-sections 2 µm in thickness were taken with a microtome (Leica MR 2145) from paraformaldehyde-fixed paraffin-embedded eye tissues, floated in a sterile bath, placed onto poly-L-Lysine-coated glass slides, and dried at room temperature. After overnight incubation at 60 °C, the slides were dewaxed in xylene for 30 min, rehydrated through a graded ethanol series (100%, 95%, 80%, and 70%, sequentially), washed in distilled H_2O and PBS for 10 min, treated with 2% trypsin containing 50 mM Tris buffer (pH 7.5) at 37 °C for 15 min, and then washed again with PBS. Sections were delineated with a Dako pen (Dako, Glostrup, Denmark), incubated in 3% H_2O_2 solution for 15 min to inhibit endogenous peroxidase activity, and washed with PBS. The slides were incubated with VEGF primary antibody at 57 °C followed by washing with PBS. Afterwards, a biotinylated secondary IgG antibody was applied and washed with PBS before incubating with the streptavidin-peroxidase conjugate (Histostain Plus, Invitrogen, Camarillo, CA, USA) for 30 min to visualize the immunostaining. The whole procedure was finished after counterstaining the sections with Mayer's hematoxylin (Sigma Chemical Co., St. Louis, MO, USA). All sections were examined and photographed with an Olympus C-5050 digital camera mounted on an Olympus BX51 microscope (Olympus Corp., Tokyo, Japan).

Outer Nuclear Layer (ONL) Measurements

All sections were photographed and measured with the same Olympus C-5050 digital camera mounted on an Olympus BX51 microscope. The mean ONL thickness in the physiological saline groups was accepted as 100%.

Measurement of Plasma VEGF Levels

Plasma VEGF levels were measured using a commercially available ELISA kit according to the manufacturer's instructions (RayBiotech, Inc., GA, USA). VEGF levels were expressed in pg/mL. The detection limit was less than 2 pg/mL, and intra-assay and interassay coefficients of variation were less than 10%.

Statistical Analysis

Data analyses were performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL). The groups of parametric variables were compared using Student's t-test. The groups of non-parametric variables were compared with the Mann-Whitney U test. The results were reported as mean ± standard error of mean. A value of $p<0.05$ was accepted as statistically significant.

Results

VEGF protein expression was examined by immunohistochemistry and ONL thickness was measured. The expression was scored as follows: 0 represented no expression while 1, 2, and 3 represented expressions of 0-24%, 25-49%, 50-74%, and >75%. All comparisons of ONL measurements and staining intensities were carried out at X40 magnification from 10 different sections.

ONL Measurements

Figure 1 represents the alterations in retinal ONL thickness in the study groups. Results from the comparison of ONL thickness between groups is shown in Table 1. Morphometric analysis of the rat retinal cross-sections showed that intravitreal and intraperitoneal OT significantly increased ONL thickness compared to physiological saline-treated groups (23% and 25%, respectively, $p<0.001$).

VEGF Protein Expression

Figure 2 demonstrates VEGF protein expression in the rat retina after cessation of treatment. The mean score for VEGF expression in the intraperitoneal physiological saline group was 1.6±0.2, which decreased significantly to 0.3±0.2 in the intraperitoneal OT group. In the intravitreal treatment groups, the VEGF expression score was 1.3±0.3 in the physiological saline group, which decreased significantly to 0.3±0.2 in the OT group.

Plasma VEGF Levels

Plasma VEGF level was 161.29±47.36 pg/mL (range: 115.75-225.25) in the intraperitoneal saline group and 76.74±14.15 pg/mL (range: 25.50-142.75) in the intraperitoneal OT group. There was a statistically significant difference between the groups.

Discussion

To the best of our knowledge, this is the first report describing the effects of OT on the retina of diabetic rats. The study revealed that OT has protective effects on diabetic rat retina, as evidenced by reduced VEGF protein expression and plasma VEGF levels, as well as prevention of outer nuclear layer thinning.

As the pathogenesis of DR is better understood, novel treatment options are likely to become available. Postulated mechanisms of DR are hyperglycemia, accumulation of advanced glycation end-products (AGEs), activation of protein kinase C, oxidative stress, and inflammation. Chronic hyperglycemia results in the production of reactive oxygen species, and low-grade inflammation. This induces apoptosis of the retinal pigment epithelium and progression of DR. Hyperglycemia also causes accumulation of AGEs beneath the endothelial layer and changes the vascular structure, increases vascular stiffness, and initiates intracellular signaling pathways that lead to increased oxidative stress and inflammation. Oxidative stress is considered to be the most common mechanism in the etiology of DR. Damage or dysfunction due to oxidative stress can proceed even after glycemic control. Inflammation also plays an important role in the progression of DR and its complications. Therefore, new treatment strategies should be developed that target oxidative stress and inflammation.[1,13,14,15,16,17,18,19,20]

Table 1. Comparison of outer nuclear layer thickness (x40 magnification)

Groups	Intraperitoneal (%)	Intravitreal (%)
Physiologic saline	100±5.1	100±8.3
Oxytocin	115.6±6.1	128.8±7.5

OT is nonapeptide and its receptors have been identified in different tissues including kidney, heart, pancreas, adipocytes, and thymus. The role of OT in immune and inflammatory modulation is well defined and attributed to the activation of its receptors.[6,7,8,21] Based on these studies, we hypothesized that OT may act as an antioxidant and anti-inflammatory agent and therefore serve as a therapeutic agent in DR. Cone photoreceptors and the retinal pigment epithelium have OT receptors. Activation of those receptors causes an increase in intracellular Ca^{+2} level and downstream activation of phospholipase C and phosphatidylinositol 4,5-bisphosphate.[13,14]

In diabetic patients, sustained hyperglycemia can cause dysregulation in retinal blood flow, loss of pericytes, basal membrane thickening, microaneurysms, capillary occlusion, and ischemia. Ischemia eventually leads to the production of VEGF

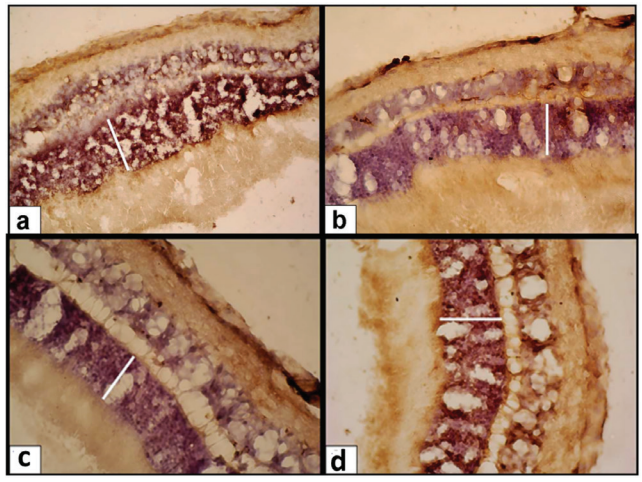

Figure 1. Outer nuclear layer of the a) intraperitoneal physiologic saline group, b) intravitreal physiologic saline group, c) intraperitoneal oxytocin group, and d) intravitreal oxytocin group

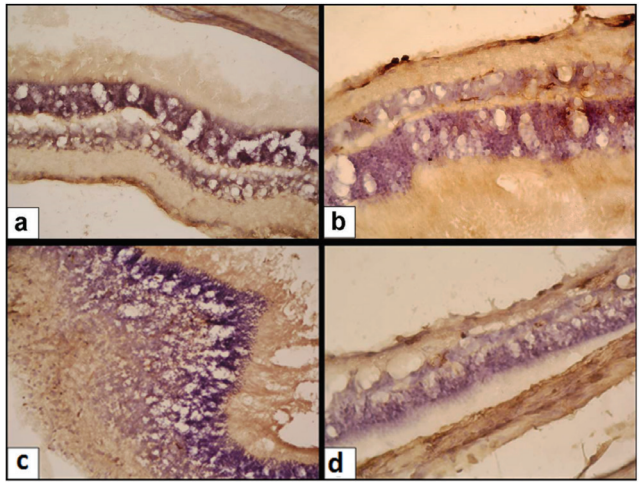

Figure 2. Vascular endothelial growth factor immunostaining in the a) intraperitoneal physiologic saline group, b) intravitreal physiologic saline group, c) intraperitoneal oxytocin group, and d) intravitreal oxytocin group

that activates tyrosine kinase receptors, VEGFR-1 and VEGFR-2.[22] VEGF is a growth factor and potent vasoactive cytokine that promotes angiogenesis, breakdown of the blood-retinal barrier, and induces endothelial cell growth and neovascularization.[23,24] Matsuoka et al.[25] reported that expression of VEGF in diabetic retinas was significantly increased while Funatsu et al.[26] suggested that VEGF levels in vitreous and plasma were elevated in diabetic patients with retinopathy when compared to normal subjects and diabetic patients without retinopathy. Consistent with this opinion, Aiello et al.[27] found that VEGF concentration was elevated in the ocular fluids of patients with retinal ischemia. The present study showed that VEGF expression in retina and plasma VEGF levels were elevated, but with OT treatment, the expression and plasma levels were significantly decreased.

Thinning of the outer nuclear layer has been reported in diabetic rats. A number of studies have implicated apoptosis for the thinning effect.[28,29,30] In the present study, in accordance with published reports, administration of OT was found to prevent the thinning of the ONL in STZ-induced diabetic rats when compared to the physiological saline group.

Conclusion

In conclusion, the treatment of STZ-induced diabetic rats with OT was effective in mitigating retinal degeneration. The significant reduction in VEGF expression and plasma VEGF levels and the protective effect against retinal thinning suggest that OT may be an alternative treatment in diabetic retinopathy. The beneficial effects of OT in diabetic retinal degeneration might be through its anti-oxidative and anti-inflammatory effects. To our knowledge this is the first report about the effect of OT on the retina of diabetic rats, and this subject needs to be explored with further studies.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Ethic Committee, (2011-162).

Informed Consent: Experimental animal research.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cumali Değirmenci, Concept: Cumali Değirmenci, Filiz Afrashi, Design: Oytun Erbaş, Cumali Değirmenci, Data Collection or Processing: Cumali Değirmenci, Filiz Afrashi, Analysis or Interpretation: Hüseyin Aktuğ, Dilek Taşkıran, Literature Search: Cumali Değirmenci, Filiz Afrashi, Hüseyin Aktuğ, Dilek Taşkıran, Oytun Erbaş, Writing: Cumali Değirmenci, Filiz Afrashi.

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

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

References

1. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res. 2007;2007:43603.
2. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, Costagliola C. Diabetic Retinopathy: Vascular and Inflammatory Disease. J Diabetes Res. 2015;2015:582060.
3. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Curr Diab Rep. 2012;12:346-354.
4. Stewart MW. The clinical utility of aflibercept for diabetic macular edema. Diabetes Metab Syndr Obes. 2015;8:473-482.
5. Behl T, Kaur I, Kotwani A. Implication of oxidative stress in progression of diabetic retinopathy. Surv Ophthalmol. 2016;61:187-196.
6. Iseri SO, Sener G, Sağlam B, Gedik N, Ercan F, Yeğen BC. Oxytocin ameliorates oxidative colonic inflammation by a neutrophil-dependent mechanism. Peptides. 2005;26:483-491.
7. Akman T, Akman L, Erbas O, Terek MC, Taskiran D, Ozsaran A. The preventive effect of oxytocin to Cisplatin-induced neurotoxicity: an experimental rat model. Biomed Res Int. 2015;2015:167235.
8. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev. 2001;81:629-683.
9. Rashed LA, Hashem RM, Soliman HM. Oxytocin inhibits NADPH oxidase and P38 MAPK in cisplatin-induced nephrotoxicity. Biomed Pharmacother. 2011;65:474-480.
10. Erbas O, Ergenoglu AM, Akdemir A, Yeniel AÖ, Taskiran D. Comparison of melatonin and oxytocin in the prevention of critical illness polyneuropathy in rats with experimentally induced sepsis. J Surg Res. 2013;183:313-320.
11. York N, Halbach P, Chiu MA, Bird IM, Pillers DM, Pattnaik BR. Oxytocin (OXT)-stimulated inhibition of Kir7.1 activity is through PIP(2)-dependent Ca(2+) response of the oxytocin receptor in the retinal pigment epithelium in vitro. Cell Signal. 2017;37:93-102.
12. Halbach P, Pillers DA, York N, Asuma MP, Chiu MA, Luo W, Tokarz S, Bird IM, Pattnaik BR. Oxytocin expression and function in the posterior retina: a novel signaling pathway. Invest Ophthalmol Vis Sci. 2015;15;56:751-760.
13. Wan TT, Li XF, Sun YM, Li YB, Su Y. Recent advances in understanding the biochemical and molecular mechanism of diabetic retinopathy. Biomed Pharmacother. 2015;74:145-147.
14. Wang XL, Yu T, Yan QC, Wang W, Meng N, Li XJ, Luo YH. AGEs Promote Oxidative Stress and Induce Apoptosis in Retinal Pigmented Epithelium Cells RAGE-dependently. J Mol Neurosci. 2015;56:449-460.
15. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54:1615-1625.
16. Chen M, Curtis TM, Stitt AW. Advanced glycation end products and diabetic retinopathy. Curr Med Chem. 2013;20:3234-3240.
17. Yu Y, Chen H, Su SB. Neuroinflammatory responses in diabetic retinopathy. J Neuroinflammation. 2015;12:141.
18. Kowluru RA, Mishra M. Oxidative stress, mitochondrial damage and diabetic retinopathy. Biochim Biophys Acta. 2015;1852:2474-2483.
19. Zong H, Ward M, Stitt AW. AGEs, RAGE, and diabetic retinopathy. Curr Diab Rep. 2011;11:244-252.
20. Deliyanti D, Zhang Y, Khong F, Berka DR, Stapleton DI, Kelly DI, Wilkinson-Berka JL. FT011, a Novel Cardiorenal Protective Drug, Reduces Inflammation, Gliosis and Vascular Injury in Rats with Diabetic Retinopathy. PLoS One. 2015;10:e0134392.
21. Petersson M, Wiberg U, Lundeberg T, Uvnas-Moberg K. Oxytocin decreases carrageenan induced inflammation in rats. Peptides. 2001;22:1479-1484.
22. Osaadon P, Fagan XJ, Lifshitz T, Levy J. A review of anti-VEGF agents for proliferative diabetic retinopathy. Eye (Lond). 2014;28:510-520.
23. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. ISRN Ophthalmol. 2013;2013:343560.
24. Kastelan S, Tomic M, Gverovic Antunica A, Salopek Rabatic J, Ljubic S. Inflammation and pharmacological treatment in diabetic retinopathy. Mediators Inflamm. 2013;2013:213130.
25. Matsuoka M, Ogata N, Minamino K, Matsumura M. Expression of pigment epithelium-derived factor and vascular endothelial growth factor in

fibrovascular membranes from patients with proliferative diabetic retinopathy. Jpn J Ophthalmol. 2006;50:116-120.
26. Funatsu H, Yamashita H, Ikeda T, Nakanishi Y, Kitano S, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with diabetic macular edema and other retinal disorders. Am J Ophthalmol. 2002;133:537-543.
27. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480-1487.
28. Boretsky A, Gupta P, Tirgan N, Liu R, Godley BF, Zhang W, Tilton RG, Motamedi M. Nicotine accelerates diabetes-induced retinal changes. Curr Eye Res. 2015;40:368-377.
29. Zhang J, Wu Y, Jin Y, Ji F, Sinclair SH, Luo Y, Xu G, Lu L, Dai W, Yanoff M, Li W, Xu GT. Intravitreal injection of erythropoietin protects both retinal vascular and neuronal cells in early diabetes. Invest Ophthalmol Vis Sci. 2008;49:732-742.
30. Park SH, Park JW, Park SJ, Kim KY, Chung JW, Chun MH, Oh SJ. Apoptotic death of photoreceptors in the streptozotocin-induced diabetic rat retina. Diabetologia. 2003; 46:1260-1268.

DOI: 10.4274/tjo.galenos.2018.84665
Turk J Ophthalmol 2019;49:73-77

Original Article

Dexamethasone Implant in Patients with Diabetic Macular Edema Resistant to Anti-VEGF Therapy

Serhad Nalçacı, Cezmi Akkın, Filiz Afrashi
Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Objectives: To investigate the efficacy of single dose intravitreal dexamethasone implant in patients with diabetic macular edema (DME) resistant to anti-VEGF therapy.

Materials and Methods: Twenty eyes of 14 patients (8 male, 6 female; mean age, 65±5.7 years) with DME resistant to intravitreal ranibizumab injections were studied. A single intravitreal dexamethasone implant was injected into each eye and patients were followed up for 6 months. Response to therapy was assessed monthly by measuring intraocular pressure (IOP), best-corrected visual acuity (BCVA), and central foveal thickness (CFT).

Results: Baseline (before injection) IOP was 14.9±2.7 mmHg and did not change significantly in the six months following injection. Baseline BCVA was 1.04±0.35 LogMAR and improved to 0.86±0.31 at month 1 without statistical significance (p=0.056). CFT was significantly lower in all monthly measurements compared to its baseline value of 682.2±229.2 µm. During the follow-up period, endophthalmitis, significant cataract, or rhegmatogenous retinal detachment were not detected.

Conclusion: Intravitreal dexamethasone implant injection is associated with significant CFT reduction for up to six months without causing any complications. Although BCVA did not improve in parallel with the CFT reduction, intravitreal dexamethasone implant should be considered as an effective and safe treatment option in the management of DME patients resistant to anti-VEGF injections.

Keywords: Dexamethasone, diabetic macular edema, ranibizumab, vascular endothelial growth factor

Introduction

Diabetic macular edema (DME) is the leading cause of visual loss in patients with diabetes, affecting an estimated 21 million individuals worldwide.[1] The presence of DME varies with the duration and stage of diabetic retinopathy. Its prevalence is 3% in mild non-proliferative retinopathy, 38% in moderate to severe non-proliferative retinopathy, and 71% in eyes with proliferative retinopathy.[2] Almost 50% of patients with DME lose two or more lines of visual acuity within two years of diagnosis.[3]

Macular laser photocoagulation has long been the standard of care of DME because it is effective in preserving vision.[4] However, this procedure has a limited effect in restoring lost vision, which may be due to expanded retinal scars over time and decrease in vision and contrast sensitivity.[5] The efficacy of intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF) has been proven in several randomized clinical trials, which reported better outcomes compared to macular laser photocoagulation in DME.[6,7] However, not all patients respond favorably to intravitreal anti-VEGF therapy.

Although first-line treatment of DME with anti-VEGF agents has become the gold standard, there is no consensus on the treatment of patients who do not respond to anti-VEGF agents.[8] Dexamethasone, a potent corticosteroid, has been approved for various ocular pathologies including DME and is

Address for Correspondence: Serhad Nalçacı MD, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone: +90 232 388 14 69 E-mail: serhadnalcaci@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0401-9492
Received: 28.04.2018 **Accepted:** 31.08.2018

recommended particularly in refractory cases.[9] Although many recent studies focused on the effect of intravitreal dexamethasone implant in DME patients resistant to anti-VEGF therapy, more evidence is still needed to draw more detailed conclusions.[7,10,11] Therefore, we aimed to investigate the efficacy of a single intravitreal dexamethasone implant in patients with DME that did not respond to multiple ranibizumab injections.

Materials and Methods

Study Design and Population

This was a retrospective study. Patients over 18 years of age who had DME resistant to at least 3 monthly ranibizumab injections and central foveal thickness (CFT) ≥300 µm on spectral-domain optical coherence tomography (SD-OCT) (Topcon 3D OCT-2000) were included in the study. Exclusion criteria were macular ischemia on fluorescein angiography (FA), retinal vasculopathies other than diabetic retinopathy, vitreomacular traction, glaucoma, ocular hypertension, advanced cataract, uncontrolled systemic disease, history of vitreoretinal surgery, intraocular surgery within the last 6 months, panretinal or focal laser treatments within the last 3 months, and being a steroid responder.

The study was conducted in compliance with Declaration of Helsinki and was approved by Ethics Committee of the Ege University Faculty of Medicine. Written informed consent was obtained from all patients enrolled.

Intravitreal Dexamethasone Implant Injection

After eye cleansing with 5% povidone-iodine solution, an intravitreal dexamethasone implant (Ozurdex®, Allergan Inc., Irvine, CA, USA) was injected through the pars plana under topical anesthesia in sterile operating room conditions. Topical ophthalmic antibiotic was applied for 7 days after the injection. After the injection, the patients were assessed monthly during a 6-month follow-up period.

Study Parameters

FA was performed only at the initial visit. Evaluation by slit-lamp biomicroscopy and fundus examination were performed at every visit. Response to the intravitreal dexamethasone implant was assessed monthly by measuring intraocular pressure (IOP) in mmHg, best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (LogMAR), and CFT measured on SD-OCT in µm. If IOP was over 25 mmHg, a topical anti-glaucoma medication was started.

Statistical Analysis

Study data were summarized using descriptive statistics such as mean, standard deviation, range, frequency, and percentage. Repeated measures analysis of variance (ANOVA) was used to test the statistical significance of change in continuous variables over time. The limit for statistical significance was set as $p<0.05$. All statistical analyses were performed with SPSS for Windows (Statistical Package for Social Sciences, ver. 22.0, SPSS Inc., Chicago, IL, USA) software.

Results

Twenty eyes of 14 patients (8 male, 6 female; mean age, 65±5.7 years) were included in the study. Half of these eyes were phakic and other half were pseudophakic. The eyes had not responded to an average of 4.85 (range, 3-10) ranibizumab injections. Panretinal or focal laser treatments had previously been applied to all eyes (Table 1).

Intravitreal dexamethasone implant injection was performed in both eyes of 6 patients (42.8%). In 5 eyes (25%), IOP increased to 25-30 mmHg within 1-3 months after the procedure, which was successfully treated with topical anti-glaucoma medication. Baseline (before injection) IOP was 14.9±2.7 mmHg and did not change significantly in the 6 months following injection (Table 2, Figure 1). Baseline BCVA was 1.04±0.35 LogMAR and improved to 0.86±0.31 LogMAR at 1 month after injection but without statistical significance ($p=0.056$). It remained at about this level over 6 months of follow-up with no additional improvement (Table 2, Figure 2). On the other hand, CFT was significantly lower in all monthly measurements after implant injection compared to its baseline value of 682.2±229.2 µm (Table 2, Figure 3). During the 6-month follow-up period, none of the eyes developed endophthalmitis, significant cataract, or rhegmatogenous retinal detachment.

Discussion

In this retrospective study, we evaluated the efficacy of a single intravitreal dexamethasone implant injection in patients with persistent DME after at least three ranibizumab injections. We primarily found that intravitreal dexamethasone implant injection effectively reduced CFT starting at 1 month and lasting up to 6 months after injection. The BCVA was also improved with intravitreal dexamethasone implant injection, but this improvement did not reach a statistical significance. Nevertheless, our findings indicate that intravitreal dexamethasone implant can be considered in patients with DME resistant to anti-VEGF therapy.

Table 1. Baseline demographics and ophthalmological history of patients

Parameters		Results
Number of patients		14
Number of eyes		20
Age (years), mean ± standard deviation (range)		65±5.7 (58-79)
Sex, n (%)	Male	8 (57.1%)
	Female	6 (42.9%)
Status of lens, n (%)	Phakic	10 (50%)
	Pseudophakic	10 (50%)
Previous laser treatment, n (%)	Panretinal photocoagulation	17 (85%)
	Focal laser	5 (20%)
Ranibizumab injection number, mean (range)		4.85 (3-10)

Today, the treatment paradigm for DME has shifted away from laser and toward intravitreal pharmacotherapy particularly with anti-VEGF agents.[8] Although treatment with anti-VEGF injections has obviously proved its efficacy, some patients exhibit poor functional and anatomic response.[12] Furthermore, multiple anti-VEGF injections can result in increased morbidity, multiple hospital visits, and severe damage to photoreceptors and retinal pigment epithelium in chronic DME.[7] It has also been shown that visual prognosis for many macular diseases is also correlated with integrity of the photoreceptor inner and outer segments junction and external limiting membrane lines on spectral domain OCT.[13,14] Therefore, intravitreal injection of corticosteroids has been suggested for the treatment of DME patients resistant to anti-VEGF therapy and to limit the number of injections for better visual prognosis.[8]

Dexamethasone is presented in the form of an intravitreal sustained-release implant, which has the advantage of extending the duration of intravitreal activity and limiting the number of injections.[9] The dexamethasone intravitreal implant showed similar or better outcomes for vision-related quality of life, CMT reduction, and BCVA improvement compared to anti-VEGF therapy in comparative studies.[15,16,17,18] Even a simultaneous treatment regimen combining two drugs has been suggested to provide effective management of DME with an acceptable safety profile.[19]

In recent studies, intravitreal dexamethasone implant in DME patients resistant to anti-VEGF therapy has been shown to improve both BCVA and CMT in both the short term and long term up to 18 months.[20,21,22,23] In a very recent meta-analysis of 3859 patients from 15 studies, intravitreal dexamethasone implant was found to be associated with significant mean improvement in BCVA in patients with DME who have a suboptimal response to anti-VEGF therapy.[24] In accordance with this literature, we found that dexamethasone implant was effective in patients with persistent DME. It decreased CFT from 1 to 6 months after the injection. The peak efficacy of the implant was reached at 1-3 months, then it decreased in months 4-6. Totan et al.[23] also reported that the therapeutic efficacy of intravitreal dexamethasone implant decreases between

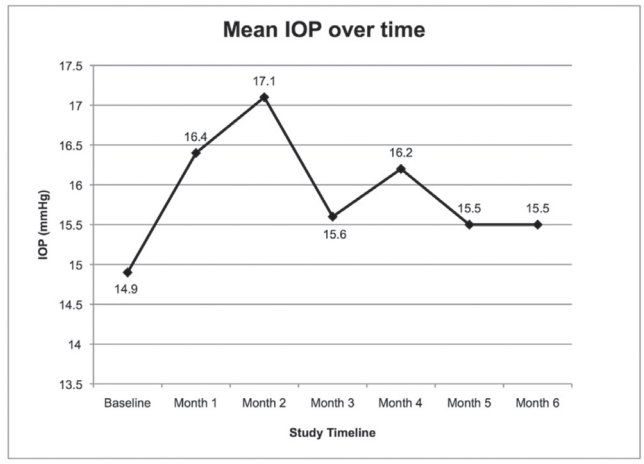

Figure 1. Mean intraocular pressure before (baseline) and over six months after the intravitreal dexamethasone implant injection
IOP: Intraocular pressure

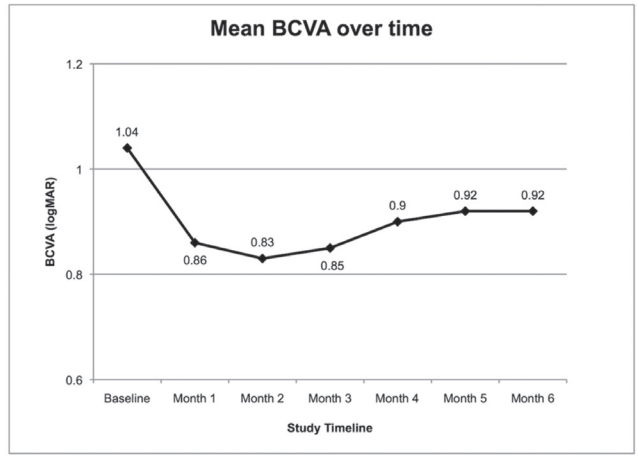

Figure 2. Mean best-corrected visual acuity before (baseline) and over six months after the intravitreal dexamethasone implant injection (LogMAR, logarithm of the minimum angle of resolution)
BCVA: Best-corrected visual acuity

Table 2. Outcome of ophthalmological evaluation during six months after intravitreal dexamethasone implant injection

Time of measurement	IOP (mmHg)	p*	BCVA (LogMAR)	p*	CFT (µm)	p*
Baseline	14.9±2.7	-	1.04±0.35	-	682.2±229.2	-
Month 1	16.4±3.9	0.686	0.86±0.31	0.056	336.5±186.7	<0.001
Month 2	17.1±4.4	0.229	0.83±0.33	0.137	271.8±135.7	<0.001
Month 3	15.6±3.6	1	0.85±0.25	0.120	335.7±167.6	<0.001
Month 4	16.2±4.2	1	0.9±0.27	0.309	471.0±237.3	0.004
Month 5	15.5±2.3	1	0.92±0.27	0.6	514.7±238.2	0.015
Month 6	15.5±2.3	1	0.92±0.29	0.6	520.4±232.5	0.019

*Repeated measures ANOVA for comparison with baseline
IOP: Intraocular pressure, BCVA: Best-corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, CFT: Central foveal thickness

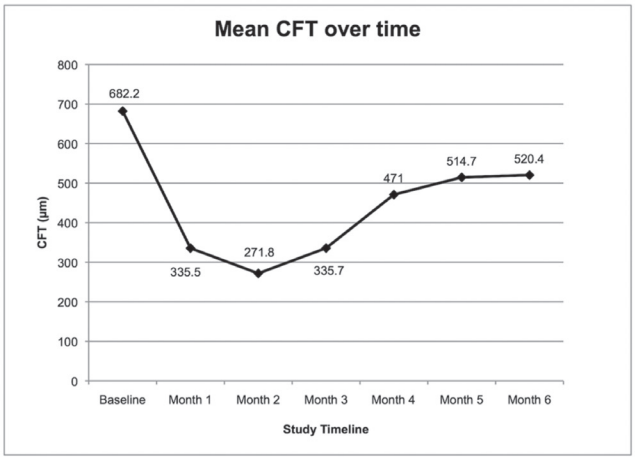

Figure 3. Mean central foveal thickness before (baseline) and over six months after the intravitreal dexamethasone implant injection
CFT: Central foveal thickness

3 and 6 months after injection. In contrast to the literature, in our study BCVA did not improve in parallel with the CFT decrement.[25,26] Visual prognosis for many macular diseases is correlated with integrity of the photoreceptor inner and outer segment junction and external limiting membrane lines on spectral domain OCT.[13,14] Chronic DME can also result in damage to photoreceptors and the retina pigment epithelium.[7] Therefore, avoiding delay in treatment of DME can result in better visual outcomes. In addition, the dexamethasone implant may facilitate longer sustained control of DME.

The incidence of IOP elevation was 25% in our study, which was similar to the 13-30% in the previous reports.[27,28,29] In addition, mean IOP did not show significant change during the study. In contrast to some previous studies that a reported high rate of cataract formation associated with intravitreal dexamethasone after multiple injections,[11,15,30] advanced cataract formation was not observed in our series, indicating that steroid-induced cataract is not a limiting factor for a single intravitreal dexamethasone implant.

Study Limitations

The main limitation of our study was its small sample size, which limits statistical power and precludes us from reaching a definitive conclusion. Nevertheless, our findings contribute to the literature on the use of intravitreal dexamethasone implant in the management of DME patients resistant to regular anti-VEGF injections.

Conclusion

Intravitreal dexamethasone implant injection is associated with significant CFT reduction for up to six months without causing any complications. Although our results did not show improvement in BCVA in parallel with the CFT reduction, intravitreal dexamethasone implant should still be considered as an effective and safe treatment option in the management of DME patients resistant to regular anti-VEGF injections.

Ethics

Ethics Committee Approval: The study was conducted in compliance with Declaration of Helsinki and was approved by Ethics Committee of the Ege University Faculty of Medicine.

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serhad Nalçacı, Concept: Filiz Afrashi, Design: Cezmi Akkın, Data Collection or Processing: Filiz Afrashi, Analysis or Interpretation: Cezmi Akkın, Literature Search: Serhad Nalçacı, Writing: Serhad Nalçacı.

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

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

References

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556-564.
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015;2:17.
3. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol. 2009;54:1-32.
4. Régnier S, Malcolm W, Allen F, Wright J, Bezlyak V. Efficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic macular edema: a systematic review and network meta-analysis. PLoS One. 2014;9:e102309.
5. Romero-Aroca P. Managing diabetic macular edema: The leading cause of diabetes blindness. World J Diabetes. 2011;2:98-104.
6. Blinder KJ, Dugel PU, Chen S, Jumper JM, Walt JG, Hollander DA, Scott LC. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). Clin Ophthalmol. 2017;11:393-401.
7. Lazic R, Lukic M, Boras I, Draca N, Vlasic M, Gabric N, Tomic Z. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. Retina. 2014;34:719-724.
8. Puliafito CA, Cousins SW, Bacharach J, Gonzalez VH, Holekamp NM, Merrill PT, Ohr MP, Parrish RK 2nd, Riemann CD. Forming a consensus: data and guidance for physicians treating diabetic macular edema. Ophthalmic Surg Lasers Imaging Retina. 2016;47(4 Suppl):4-15.
9. Cebeci Z, Kir N. Role of implants in the treatment of diabetic macular edema: focus on the dexamethasone intravitreal implant. Diabetes Metab Syndr Obes. 2015;8:555-566.
10. Calvo P, Abadia B, Ferreras A, Ruiz-Moreno O, Verdes G, Pablo LE. Diabetic Macular Edema: Options for Adjunct Therapy. Drugs. 2015;75:1461-1469.
11. Zalewski D, Raczyńska D, Raczyńska K. Five-month observation of persistent diabetic macular edema after intravitreal injection of Ozurdex implant. Mediators Inflamm. 2014;2014:364143.
12. Agarwal A, Sarwar S, Sepah YJ, Nguyen QD. What have we learnt about the management of diabetic macular edema in the antivascular endothelial growth factor and corticosteroid era? Curr Opin Ophthalmol. 2015;26:177-183.
13. Chhablani JK, Kim JS, Cheng L, Kozak I, Freeman W. External limiting membrane as a predictor of visual improvement in diabetic macular

edema after pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2012;250:1415-1420.
14. Uji A, Murakami T, Nishijima K, Akagi T, Horii T, Arakawa N, Muraoka Y, Ellabban AA, Yoshimura N. Association between hyperreflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. Am J Ophthalmol. 2012;153:710-717.
15. Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J, Goodwin S, Aroney C, McAllister IL, Fraser-Bell S. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology. 2014;121:2473-2481.
16. Aroney C, Fraser-Bell S, Lamoureux EL, Gillies MC, Lim LL, Fenwick EK. Vision-related quality of life outcomes in the BEVORDEX study: a clinical trial comparing ozurdex sustained release dexamethasone intravitreal implant and bevacizumab treatment for diabetic macular edema. Invest Ophthalmol Vis Sci. 2016;57:5541-5546.
17. Thomas BJ, Yonekawa Y, Wolfe JD, Hassan TS. Contralateral eye-to-eye comparison of intravitreal ranibizumab and a sustained-release dexamethasone intravitreal implant in recalcitrant diabetic macular edema. Clin Ophthalmol. 2016;10:1679-1684.
18. Shah AR, Xi M, Abbey AM, Yonekawa Y, Faia LJ, Hassan TS, Ruby AJ, Wolfe JD. Short-term efficacy of intravitreal dexamethasone implant in vitrectomized eyes with recalcitrant diabetic macular edema and prior anti-VEGF therapy. J Ophthalmic Vis Res. 2016;11:183-187.
19. Maturi RK, Bleau L, Saunders J, Mubasher M, Stewart MW. A 12-month, single-masked, randomized controlled study of eyes with persistent diabetic macular edema after multiple anti-VEGF injections to assess the efficacy of the dexamethasone-delayed delivery system as an adjunct to bevacizumab compared with continued bevacizumab monotherapy. Retina. 2015;35:1604-1614.
20. Pacella F, Romano MR, Turchetti P, Tarquini G, Carnovale A, Mollicone A, Mastromatteo A, Pacella E. An eighteen-month follow-up study on the effects of Intravitreal Dexamethasone Implant in diabetic macular edema refractory to anti-VEGF therapy. Int J Ophthalmol. 2016;9:1427-1432.
21. Shah SU, Harless A, Bleau L, Maturi RK. Prospective randomized subject-masked study of intravitreal bevacizumab monotherapy versus dexamethasone implant monotherapy in the treatment of persistent diabetic macular edema. Retina. 2016;36:1986-1996.
22. Kim M, Cho YJ, Lee CH, Lee SC. Effect of intravitreal dexamethasone implant on retinal and choroidal thickness in refractory diabetic macular oedema after multiple anti-VEGF injections. Eye (Lond). 2016;30:718-725.
23. Totan Y, Güler E, Gürağaç FB. Dexamethasone intravitreal implant for chronic diabetic macular edema resistant to intravitreal bevacizumab treatment. Curr Eye Res. 2016;41:107-113.
24. Khan Z, Kuriakose RK, Khan M, Chin EK, Almeida DR. Efficacy of the intravitreal sustained-release dexamethasone implant for diabetic macular edema refractory to anti-vascular endothelial growth factor therapy: meta-analysis and clinical implications. Ophthalmic Surg Lasers Imaging Retina. 2017;48:160-166.
25. Zucchiatti I, Lattanzio R, Querques G, Querques L, Del Turco C, Cascavilla ML, Bandello F. Intravitreal dexamethasone implant in patients with persistent diabetic macular edema. Ophthalmologica. 2012;228:117-122.
26. Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of intravitreal dexamethasone implant (OZURDEX(®)) in treatment of recalcitrant diabetic macular edema: A case series. Oman J Ophthalmol. 2012;5:79-82.
27. Aknin I, Melki L. Longitudinal study of sustained-release dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmologica. 2016;235:187-188.
28. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
29. Bansal P, Gupta V, Gupta A, Dogra MR, Ram J. Efficacy of Ozurdex implant in recalcitrant diabetic macular edema--a single-center experience. Int Ophthalmol. 2016;36:207-216.
30. Wallsh J, Sharareh B, Gallemore R. Therapeutic effect of dexamethasone implant in retinal vein occlusions resistant to anti-VEGF therapy. Clin Ophthalmol. 2016;10:947-954.

DOI: 10.4274/tjo.galenos.2018.88972
Turk J Ophthalmol 2019;49:78-83

Original Article

Repeatability and Agreement of Macular Thickness Measurements Obtained with Two Different Scan Modes of the Optovue RTVue Optical Coherence Tomography Device

Mehmet Kola, Mehmet Önal, Adem Türk, Hidayet Erdöl

Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey

Abstract

Objectives: To evaluate the repeatability and agreement of macular thickness measurements obtained with E-MM5 and MM6, two different scan modes, on the Optovue RTVue optic coherence tomography (OCT) device.

Materials and Methods: Three consecutive macular thickness measurements in 30 healthy volunteers were taken using the OCT device E-MM5 and MM6 scan modes. The repeatability and agreement of these measurements obtained from the two scan modes and divided into nine anatomical regions based on early treatment diabetic retinopathy study were subjected to statistical analysis.

Results: The mean age of the participants was 29.7±6.39 years. Intraclass correlation (all ICC values ≥0.86) and coefficient of variation (all coefficient of variation values ≤2%) analyses of consecutive OCT measurements in the nine regions of the macula obtained in both E-MM5 and MM6 scan modes gave high repeatability rates. Mean macular thickness values in the foveal region were 243.76±21.79 µm in E-MM5 mode and 247.04±19.83 µm in MM6 mode (p=0.543). Values for measurements obtained in E-MM5 and MM6 scan modes in parafoveal macular regions were also statistically similar (p>0.05 for all). However, a statistically significant difference was observed between the two modes in perifoveal macular measurements, except in the superior region.

Conclusion: The Optovue RTVue OCT device gives highly repeatable measurement results for macular thicknesses in both E-MM5 and MM6 scan modes. However, it should be considered that measurements performed in E-MM5 and MM6 modes give different results in perifoveal regions.

Keywords: Eye, optical coherence tomography, retina

Introduction

With advances in optical coherence tomography (OCT) technology, images of the ocular tissues can now be acquired in high resolution. OCT examinations provide useful information for the diagnosis of numerous ocular disorders and enable more detailed follow-up and more sensitive evaluation of treatment response.[1,2,3,4,5,6] As a result, OCT is used extensively in the diagnosis and treatment of many eye disorders.[7,8,9,10,11,12] This has led to the need for more sensitive and reproducible OCT measurements.

There are currently various OCT devices being produced by many different manufacturers.[13] These devices use different algorithms, and are reported to give different measurement results.[14,15] Of these, the Optovue RTVue is a spectral domain OCT device that uses 830 nm light to acquire 26000 A-scans per second for image resolution of 5 µm. Two different scanning modes of the device, E-MM5 and MM6, enable the acquisition

Address for Correspondence: Adem Türk MD, Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey
Phone: +90 462 377 10 45 E-mail: doktorademturk@yahoo.com **ORCID-ID:** orcid.org/0000-0002-9652-9317
Received: 23.03.2018 **Accepted:** 15.09.2018

of fovea-centered macular images.[16] Comparing these two modes and determining their repeatability in patients with whom they are used for macular evaluation may result in more accurate diagnosis and treatment. However, there are few studies on this subject in the literature. Therefore, this study was performed to evaluate the repeatability and agreement of macular thickness measurements obtained using two different retinal scan modes, E-MM5 and MM6, of the Optovue RTVue OCT device.

Materials and Methods

Ethics committee approval was obtained prior to this cross-sectional study, and all participants were informed about the study and provided informed consent. Volunteers aged 9-44 years with no systemic diseases or ocular disorders other than refractive error were included in the study.

All participants underwent a detailed ophthalmological examination including autorefractometry, best corrected visual acuity and intraocular pressure measurement, and slit-lamp examination of the anterior and posterior segments. Participants whose eye examination revealed ocular pathologies other than refractive error (strabismus, nystagmus, ptosis, corneal opacity, uveitis, cataracts, maculopathy, glaucoma, etc.), refractive error greater than ±4 D spherical equivalent, cup/disc ratio ≥0.4 or asymmetry ≥0.2 between the cup/disc ratios of both eyes, or intraocular pressure >21 mmHg were excluded from the study. In addition, participants with a history of ocular surgery or trauma and those who were unwilling to participate or uncooperative during the examination were also excluded. Individuals with signs of systemic disease were not included.

The Optovue RTVue (RT100 software version 6.3, Optovue Inc., Fremont, CA, USA) spectral-domain OCT device was utilized in this study. For each participant, fovea-centered macular measurements were acquired in 3 consecutive scans using both of the device's preprogrammed scanning modes: E-MM5 (0.9 s; outer 6 x 6 mm grid of 13 horizontal and 13 vertical lines with 668 A-scans each and inner 4 x 4 mm grid of 8 horizontal and 8 vertical lines with 400 A-scans each) and MM6 (0.27 s; 12 radial scans with 1024 A-scans each in a circular area 6 mm in diameter).[16] All measurements were performed in the same session within a period of 10 minutes, with participants remaining seated at the OCT device and resting by lifting their heads from the device. The device's internal fixation system was used to prevent eye movements during OCT measurements and the participants' pupils were not dilated before the scan. All measurements were performed by the same researcher experienced in performing OCT.

Criteria used to ensure reliable OCT image acquisition in the study were that the images had no artifacts, were properly centered, clearly showed distinct retinal layers, and had signal strength index (a scan quality indicator) greater than 50.

OCT measurements of the macular area were divided into nine anatomical regions according to ETDRS (Early Treatment Diabetic Retinopathy Study) (Figure 1).[17] The inner and outer macula are delineated by rings 3 mm and 5 mm in diameter in E-MM5 mode and 3 mm and 6 mm in diameter in MM6 mode, respectively. In both scan modes, the central 1 mm diameter ring represents the fovea.

SPSS 13.0.1 (SPSS, Chicago, IL, USA; license no: 9069728, KTU, Trabzon, Turkey) software was used for statistical analyses. Numerical data were presented as mean ± standard deviation. The one-sample Kolmogorov–Smirnov test was used to analyze whether the numerical data were normally distributed. Data from the participants' right eyes were used in the analysis of OCT measurements. Repeated measures were compared using paired-samples t test. Agreement between measurements was assessed using intraclass correlation (ICC) test and coefficient of variation (CV) values. CV was calculated as the percentage of the ratio of the standard deviation to the mean ([standard deviation/mean] x 100). A CV <10% was considered high repeatability, and CV <5% was considered very high repeatability. ICC values of 0-0.2 were accepted as very poor repeatability, 0.21-0.4 as poor repeatability, 0.41-0.6 as moderate repeatability, 0.61-0.8 as good repeatability, and ≥0.81 as excellent repeatability. A p value ≤0.05 was considered statistically significant.

Results

The study included a total of 30 patients, 18 females (60%) and 12 males (40%), with a mean age of 29.7±6.39 (19-44) years. For all participants, best corrected visual acuity was 20/20, intraocular pressure was normotonic, and findings in slit-lamp anterior and posterior segment examination were within normal limits. OCT measurement results obtained from the participants' right eyes using E-MM5 and MM6 scan modes are shown in Tables 1 and 2. The ICC values of all measurements made in both modes indicated excellent repeatability (ICC>0.81 for all).

Tables 3 and 4 show the CV values for comparisons of consecutive measurements performed in each scan mode. The CV values obtained using both modes also indicated very high repeatability (CV ≤2% for all).

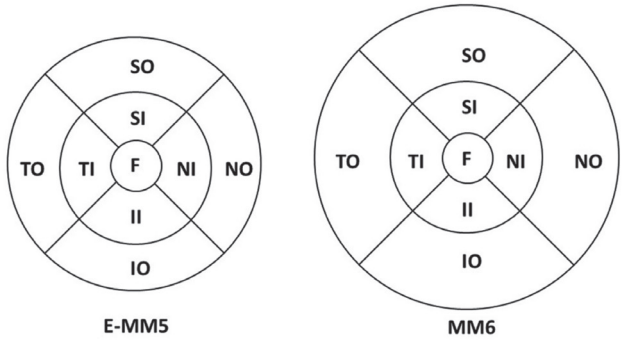

Figure 1. The early treatment diabetic retinopathy study grid divides optic coherence tomography measurements into nine anatomic zones: Central fovea (F), nasal inner (NI), temporal inner (TI), inferior inner (II), superior inner (SI), nasal outer (NO), temporal outer (TO), superior outer (SO), inferior outer (IO) macula. The central ring is 1 mm in diameter, the inner ring is 3 mm in diameter, and the diameter of the outer ring is 5 mm in E-MM5 scan mode and 6 mm in MM6 scan mode

The mean values of consecutive measurements obtained using the E-MM5 and MM6 scan modes are presented in Table 5. Central and paracentral macular measurements were similar between the two modes, while perifoveal macular measurements showed significant differences in all but the superior quadrant.

Discussion

The repeatability of a diagnostic tool is very important for making an accurate diagnosis. Repeatability of retinal thickness measurements is critical in the follow-up of progression or treatment in retinal diseases. In this study, we evaluated the repeatability of OCT measurements of the macula obtained in two different scan modes and the agreement between them.

There are various studies in the literature analyzing the repeatability of OCT measurements. Even with older generation time-domain OCT devices, the ICC values of macular thickness measurements demonstrated excellent repeatability.[18,19] In a study using Fourier-domain OCT in pediatric patients, Altemir et al.[20] reported CV and ICC values of 0.97% and 0.942 for macular thickness measurement and 1% and 0.94 for macular volume measurement, respectively. Therefore, the repeatability of consecutive OCT measurements in the macular area is known to be very high. Similarly, in our study, the ICC and CV values of repeated OCT measurements supported the reliability of the results.

When the macular measurements obtained using E-MM5 mode were evaluated according to the ETDRS map, those in

Table 1. The mean (± standard deviation) and intraclass correlation coefficient values of three consecutive measurements of the participants' right eyes (n=30) using the E-MM5 scanning mode of the optical coherence tomography device

Variable	Measurement 1	Measurement 2	Measurement 3	ICC (95% confidence interval)
Fovea (µm)	244.47±21.88	242.12±21.33	244.63±23.33	0.981 (0.965-0.99)
Superior inner macula (µm)	323.9±16.95	322.7±15.35	322.6±13.86	0.98 (0.964-0.99)
Inferior inner macula (µm)	314.63±15.62	314.4±15.46	313.87±14.56	0.982 (0.967-0.991)
Nasal inner macula (µm)	322.13±15.48	321.37±14.55	320.43±15.01	0.979 (0.961-0.989)
Temporal inner macula (µm)	305.77±14.52	305.43±16.43	305.57±15.43	0.972 (0.948-0.986)
Superior outer macular (µm)	289.2±14.26	288.83±13.8	288.67±12.75	0.991 (0.983-0.995)
Inferior outer macular (µm)	292.83±17.94	291.03±16.32	291.87±16.92	0.985 (0.973-0.992)
Nasal outer macular (µm)	311.23±16.9	310.63±17.47	310.5±16.6	0.984 (0.971-0.992)
Temporal outer macular (µm)	285.13±15.94	284.03±14.24	283.53±14.41	0.976 (0.957-0.988)
Macular volume (1 mm) (mm^3)	0.19±0.18	0.19±0.17	0.19±0.19	0.975 (0.953-0.987)
Macular volume (3 mm) (mm^3)	1.99±0.97	1.98±0.9	1.98±0.88	0.985 (0.972-0.992)
Macular volume (5 mm) (mm^3)	3.7±0.2	3.69±0.18	3.69±0.18	0.984 (0.97-0.992)

ICC: Intraclass correlation coefficient

Table 2. The mean (± standard deviation) and intraclass correlation coefficient values of three consecutive measurements of the participants' right eyes (n=30) using the MM6 scanning mode of the optical coherence tomography device

Variable	1st Measurement	2nd Measurement	3rd Measurement	ICC (95% confidence interval)
Fovea (µm)	245.77±21.62	248.93±24.94	246.43±19.77	0.873 (0.766-0.935)
Superior inner macula (µm)	327.33±21.44	324.9±15.90	326.27±15.07	0.942 (0.894-0.971)
Inferior inner macula (µm)	321±18.39	320.27±16.77	322.97±14.56	0.904 (0.825-0.951)
Nasal inner macula (µm)	324.43±14.93	325.3±14.89	324.93±14.58	0.985 (0.973-0.993)
Temporal inner macula (µm)	310.63±15.23	310.13±15.05	309.57±14.43	0.948 (0.905-0.974)
Superior outer macular (µm)	283.23±14.11	283.23±12.62	283.4±12.41	0.981 (0.965-0.99)
Inferior outer macular (µm)	276.7±14.7	277.9±15.59	277.67±15.71	0.962 (0.929-0.98)
Nasal outer macular (µm)	300.87±15.7	300.5±15.86	300.63±15.22	0.983 (0.968-0.991)
Temporal outer macular (µm)	272.73±14.26	272.4±13.14	272.53±13.2	0.978 (0.96-0.98)
Macular volume (1 mm) (mm^3)	0.19±0.02	0.195±0.02	0.19±0.02	0.866 (0.754-0.932)
Macular volume (3 mm) (mm^3)	2.02±0.10	2.01±0.1	2.02±0.09	0.976 (0.955-0.988)
Macular volume (6 mm) (mm^3)	6.01±0.29	6.09±0.29	6.06±0.28	0.99 (0.981-0.995)

ICC: Intraclass correlation coefficient

the temporal inner macula had the lowest ICC while those in the superior outer macula had the highest ICC. Similarly, CV values of measurements acquired in E-MM5 mode were lowest for superior outer thickness and perifoveal macular volume and highest for foveal thickness and volume measurements.

With MM6 mode, foveal thickness and volume measurements had the lowest ICC, while nasal inner macular thickness and perifoveal macular volume measurements had the highest ICC. CV values for MM6 measurements were lowest for perifoveal macular volume measurements and highest for inferior inner macular and temporal outer macular thickness measurements.

In a study by Garcia-Martin et al.[13] using a different Fourier-domain OCT device than the one used in our study, the lowest CV for repeated measures was in the nasal inner macula (0.6%), while the highest was in the foveal and inferior outer macula (1.8%). In the same study, measurements of the nasal inner macula had the highest ICC values (0.992), while the lowest ICC was in the superior outer macular area (0.832). In another Fourier-domain OCT study, Menke et al.[21] reported that the CV values of all macular thickness measurements obtained according to the ETDRS map varied between 0.38% and 0.86%, with the lowest CV observed in the outer temporal macula and the highest in the inner temporal macula.[21] In a comparative study by Pinilla et al.[6] using two different Fourier-domain OCT devices, it was reported that the CV values for repeated mean macular thickness measurements of the devices were between 2.2-2.95% and all ICC values were over 0.919. The authors also reported differences in the measurements obtained using the two different OCT devices.[6] In their study, measurements obtained according to the ETDRS map in healthy eyes using the Cirrus OCT device showed the lowest CV in the nasal outer macula (0.7%; ICC=0.963) and the highest CV in the inferior inner macula (3.4%; ICC=0.92). In measurements of healthy eyes obtained using a Spectralis OCT device, the lowest CV was in the inferior inner macula (0.3%; ICC=0.996) and the highest CV was in the temporal outer macula (1.3%; ICC=0.927).[6]

As the studies mentioned above suggest, the different scanning algorithms in different OCT devices can cause various deviations in the repeatability values of OCT measurements made according to the ETDRS map. Moreover, in some studies, these discrepancies may have been due in part to measuring different retinal areas or having multiple operators performing OCT measurements. Thus, a direct comparison of studies in the literature is not possible. Nevertheless, it is still clear that

Table 3. Coefficients of variation for pairwise comparisons of three consecutive measurements of the participants' right eyes (n=30) using the E-MM5 scanning mode of the optical coherence tomography device

Variable	1st-2nd Measurements (%)	1st-3rd Measurements (%)	2nd-3rd Measurements (%)
Fovea (µm)	2	1	1
Superior inner macula (µm)	0.8	1	0.8
Inferior inner macula (µm)	0.9	0.8	0.8
Nasal inner macula (µm)	0.8	0.9	0.8
Temporal inner macula (µm)	0.9	1	1
Superior outer macular (µm)	0.4	0.7	0.7
Inferior outer macular (µm)	1	1	0.8
Nasal outer macular (µm)	0.6	0.6	0.8
Temporal outer macular (µm)	0.9	1	1
Macular volume (1 mm) (mm^3)	1	1	1
Macular volume (3 mm) (mm^3)	0.8	0.6	0.8
Macular volume (5 mm) (mm^3)	0.5	0.7	0.6

ICC: Intraclass correlation coefficient

Table 4. Coefficients of variation for pairwise comparisons of three consecutive measurements of the participants' right eyes (n=30) using the MM6 scanning mode of the optical coherence tomography device

Variable	1st-2nd Measurements (%)	1st-3rd Measurements (%)	2nd-3rd Measurement (%)
Fovea (µm)	0.7	1	1
Superior inner macula (µm)	1	0.8	0.9
Inferior inner macula (µm)	1	1	0.9
Nasal inner macula (µm)	0.8	0.8	0.7
Temporal inner macula (µm)	1	1	0.8
Superior outer macular (µm)	0.8	0.8	0.9
Inferior outer macular (µm)	*0.8*	1	1
Nasal outer macular (µm)	0.6	0.9	0.8
Temporal outer macular (µm)	1	0.9	1
Macular volume (1 mm) (mm^3)	0.8	1	0.8
Macular volume (3 mm) (mm^3)	0.9	0.7	0.7
Macular volume (6 mm) (mm^3)	0.7	0.6	0.6

Table 5. Comparisons of mean measurements obtained from the participants' right eyes (n=30) using the E-MM5 and MM6 scanning modes of the optical coherence tomography device

Variable	E-MM5	MM6	p-value
Fovea (µm)	*243.76±21.79*	*247.04±19.83*	0.543
Superior inner macula (µm)	323.07±15.14	326.17±16.76	0.455
Inferior inner macula (µm)	314.3±14.95	321.41±15.25	0.073
Nasal inner macula (µm)	320.2±12.76	324.89±14.59	0.19
Temporal inner macula (µm)	305.59±15.06	310.11±14.19	0.236
Superior outer macular (µm)	288.9±13.49	283.29±12.83	0.104
Inferior outer macular (µm)	*291.9±16.82*	*277.42±14.86*	0.001
Nasal outer macular (µm)	310.79±16.73	300.67±15.33	0.018
Temporal outer macular (µm)	284.23±14.54	272.56±13.26	0.002
Macular volume (1 mm) (mm^3)	0.19±0.02	0.19±0.02	0.463
Macular volume (3 mm) (mm^3)	1.99±0.09	2.01±0.09	0.238
Macular volume (5/6 mm) (mm^3)	3.7±0.18	6.01±0.28	<0.001

macular thickness measurements performed using OCT devices have satisfactory repeatability.

Conclusion

This study evaluated the repeatability of measurements obtained using the E-MM5 and MM6 scan modes of the Optovue RTVue OCT device in healthy individuals, and compared the agreement between them. The CV and ICC values for repeated measures were similar to those reported in other studies in the literature. Macular thickness measurements performed using both E-MM5 and MM6 scan modes of the Optovue RTVue OCT device yielded results with highly repeatability. This could make an important contribution to patient follow-up. However, it must be kept in mind that perifoveal measurements obtained using E-MM5 and MM6 modes yielded different results. This is due to the different software algorithms of the scan modes. In E-MM5, the outer macula is shown in a 3-5 mm zone within a scan area 5 mm in diameter, while in MM6 the outer macula is shown in a zone between 3-6 mm in a scan area 6 mm in diameter. Therefore, consistently using the same retinal scan mode throughout a patient's follow-up is the best approach. Furthermore, Schneider et al.[22] reported that radial scans were superior when evaluating small macular holes. Thus, the MM6 scan mode, which has a radial scanning protocol, may be more useful than E-MM5 scan mode in the evaluation of these macular pathologies.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Karadeniz Technical University Medical Faculty.

Informed Consent: It was taken.

Authorship Contributions

Concept: Mehmet kola, Adem Türk, Hidayet Erdöl, Design: Mehmet kola, Adem Türk, Data Collection or Processing: Mehmet Önal, Mehmet kola, Adem Türk, Analysis or Interpretation: Mehmet Kola, Adem Türk, Literature Search: Adem Türk, Writing: Adem Türk.

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

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

References

1. Bressler SB, Edwards AR, Andreoli CM, Edwards PA, Glassman AR, Jaffe GJ, Melia M, Sun JK; for the Diabetic Retinopathy Clinical Research Network/Writing Committee. Reproducibility of Optovue RTVue Optical Coherence Tomography Retinal Thickness Measurements and Conversion to Equivalent Zeiss Stratus Metrics in Diabetic Macular Edema. Transl Vis Sci Technol. 2015;4:5.
2. Wojtkowski M. High-speed optical coherence tomography: basics and applications. Appl Opt. 2010;49:30-61.
3. Turk A, Kola M, Akyol N, Erdol H, Imamoglu HI. Optical coherence tomography findings of active ocular toxoplasmosis complicating with serous macular detachment. Turkiye Klinikleri J Med Sci. 2010;30:1409-1412.
4. Ceylan OM, Turk A, Erdurman C, Mumcuoglu T, Erdem U, Gokce G, Dagli S. Comparison of oculus pentacam and stratus optical coherence tomography for measurement of central corneal thickness. Cornea. 2011;30:670-674.
5. Wojtkowski M, Kaluzny B, Zawadzki RJ. New directions in ophthalmic optical coherence tomography. Optom Vis Sci. 2012;89:524-542.
6. Pinilla I, Garcia-Martin E, Fernandez-Larripa S, Fuentes-Broto L, Sanchez-Cano AI, Abecia E. Reproducibility and repeatability of Cirrus and Spectralis Fourier-domain optical coherence tomography of healthy and epiretinal membrane eyes. Retina. 2013;33:1448-1455.
7. Kola M, Kalkisim A, Karkucak M, Turk A, Capkin E, Can I, Serdar OF, Mollamehmetoglu S, Ayar A. Evaluation of choroidal thickness in ankylosing spondylitis using optical coherence tomography. Ocul Immunol Inflamm. 2014;22:434-438.
8. Turk A, Ceylan OM, Arici C, Keskin S, Erdurman C, Durukan AH, Mutlu FM, Altinsoy HI. Evaluation of the nerve fiber layer and macula in the eyes of healthy children using spectral domain optical coherence tomography. Am J Ophthalmol. 2012;153:552-559.
9. Kola M, Duran H, Mungan S, Turk A, Mollamehmetoglu S, Bahat E. Spectral domain optical coherence tomography findings in a pediatric

case with type II membranoproliferative glomerulonephritis. Ret-Vit. 2015;23:246-248.
10. Kola M, Erdöl H, Ertuğrul Atasoy S, Türk A. Evaluation of Retinal Changes Using Optical Coherence Tomography in a Pediatric Case of Susac Syndrome. Turk J Ophthalmol. 2017;47:59-62.
11. Erdol H, Kola M, Turk A. Optical coherence tomography findings in a child with posterior scleritis. Eur J Ophthalmol. 2008;18:1007-1010.
12. Türk A, Erdöl H, Akyol N, İmamoğlu Hİ. Retina arter tıkanıklıklarında görülen erken dönem optik koherens tomografi bulguları. Ret-Vit. 2008;16:137-140.
13. Garcia-Martin E, Pinilla I, Idoipe M, Fuertes I, Pueyo V. Intra and interoperator reproducibility of retinal nerve fibre and macular thickness measurements using Cirrus Fourier-domain OCT. Acta Ophthalmol. 2011;89:23-29.
14. Menke MN, Dabov S, Sturm V. Comparison of three different optical coherence tomography models for total macular thickness measurements in healthy controls. Ophthalmologica. 2009;223:352-356.
15. Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, Iliev ME, Frey M, Rothenbuehler SP, Enzmann V, Wolf S. Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci. 2009;50:3432-3437.
16. Ho J, Sull AC, Vuong LN, Chen Y, Liu J, Fujimoto JG, Schuman JS, Duker JS. Assessment of artifacts and reproducibility across spectral- and time-domain optical coherence tomography devices. Ophthalmology. 2009;116:1960-1970.
17. [No authors listed. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:786-806.
18. Polito A, Del Borrello M, Isola M, Zemella N, Bandello F. Repeatability and reproducibility of fast macular thickness mapping with stratus optical coherence tomography. Arch Ophthalmol. 2005;123:1330-1337.
19. Paunescu LA, Schuman JS, Price LL, Stark PC, Beaton S, Ishikawa H, Wollstein G, Fujimoto JG. Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using StratusOCT. Invest Ophthalmol Vis Sci. 2004;45:1716-1724.
20. Altemir I, Pueyo V, Elía N, Polo V, Larrosa JM, Oros D. Reproducibility of optical coherence tomography measurements in children. Am J Ophthalmol. 2013;155:171-176.
21. Menke MN, Dabov S, Knecht P, Sturm V. Reproducibility of retinal thickness measurements in healthy subjects using spectralis optical coherence tomography. Am J Ophthalmol. 2009;147:467-472.
22. Schneider EW, Todorich B, Kelly MP, Mahmoud TH. Effect of optical coherence tomography scan pattern and density on the detection of full-thickness macular holes. Am J Ophthalmol. 2014;157:978-984.

DOI: 10.4274/tjo.galenos.2018.58908
Turk J Ophthalmol 2019;49:84-88

Original Article

Optical Coherence Tomography Characteristics of Quiescent Type 1 Neovascularization in Eyes with Nonexudative Age-related Macular Degeneration

Jale Menteş*, Şeyda Yıldırım**

*Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**Adıyaman University Training and Research Hospital, Department of Ophthalmology, Adıyaman, Turkey

Abstract

Objectives: To describe the lesion characteristics of nonexudative, quiescent, asymptomatic type 1 neovascularization (NV) on B-scan and en face spectral domain optical coherence tomography (SD-OCT) in eyes with nonexudative age-related macular degeneration (AMD).

Materials and Methods: In this retrospective, observational, consecutive case series, 27 patients who were already being followed and treated for exudative AMD in one eye were included in the study for their fellow eyes, which were initially nonexudative but developed exudative findings during follow-up. Initial B-scan and en face SD-OCT, fluorescein angiography (FA), and indocyanine green angiography (ICGA) images of these 27 eyes were examined retrospectively. The characteristic B-scan SD-OCT features of type 1 NV in this silent and asymptomatic stage were described.

Results: The 27 eyes of 27 patients (13 males and 14 females; mean age 69.5±8.2 years) with nonexudative AMD had a mean best corrected visual acuity (BCVA) of 0.6±0.3 Snellen. Initial B-scan OCT images of all eyes (100%) showed retinal pigment epithelium (RPE) elevations and irregularities caused by a moderately reflective material in the sub-RPE space without fluid accumulation in the intraretinal/subretinal or sub-RPE space. Twenty-four eyes (88.8%) showed sub-RPE hyperreflective lesions consistent with type 1 NV on en face OCT images. While none of the eyes showed signs of type 1 NV in FA, macular plaque was observed in 8 eyes (29.6%) in ICGA. The mean time to onset of exudative findings was 8.3±4.03 months.

Conclusion: In eyes with nonexudative AMD, there may be quiescent and asymptomatic type 1 NV lesions which do not yet show exudative changes. This NV has characteristic features on B-scan SD-OCT and can also be detected with en face OCT. Detection and close monitoring of these quiescent and inactive type 1 NV lesions during the asymptomatic, pre-exudative period are important for early treatment.

Keywords: Age-related macular degeneration, quiescent type 1 choroidal neovascularization, spectral domain optical coherence tomography, en face optical coherence tomography

Introduction

Neovascular age-related macular degeneration (NVAMD) is a destructive disease characterized by neovascularization (NV) in the macula that causes exudative changes affecting all retinal layers. It is currently among the leading causes of permanent and severe vision loss in people over 55 years old.[1,2,3]

In eyes with AMD, findings of new hemorrhages on clinical examination, subretinal, intraretinal, or sub-retinal pigment epithelium (RPE) fluid on spectral domain optical coherence

Address for Correspondence: Şeyda Yıldırım MD, Adıyaman University Training and Research Hospital, Department of Ophthalmology, Adıyaman, Turkey
Phone: +90 536 817 81 67 E-mail: stheveny@hotmail.com **ORCID-ID:** orcid.org/0000-0003-1473-9001
Received: 08.08.2018 **Accepted:** 19.10.2018

tomography (SD-OCT) imaging and leakage consistent with these findings on fluorescein angiography (FA) are almost always indicative of active NV and are therefore accepted as signs of NVAMD.[1,2,3,4,5]

Neovascularization is classified into three types: Type 1 and type 2 NV originate from the choroidal circulation. Type 1 NV is located under the RPE, while type 2 NV occurs between the retina and RPE. Type 3 NV originates from the retinal circulation and is also called retinal angiomatous proliferation.[3] Using multimodal imaging methods, it was shown that eyes with nonexudative AMD may have quiescent type 1 NV that does not yet show signs of activation (i.e., exudative symptoms).[2,3,4,5,6,7,8] Knowing the characteristic SD-OCT features of these quiescent, subclinical type 1 NV lesions will facilitate early diagnosis and close follow-up of the lesions, enabling early treatment before severe losses in visual acuity.

SD-OCT is a noninvasive, fast, and easy to apply imaging method extensively used in ophthalmology clinics. It is repeated at almost every visit in patients being followed up and treated for NVAMD, and SD-OCT imaging plays a particularly essential role in making re-treatment decisions.

In this retrospective, observational clinical study, we examined B-scan and en face SD-OCT characteristic features during the quiescent, asymptomatic stage of type 1 NV lesions that later showed activation in patients who were under treatment and follow-up for NVAMD in one eye and developed exudative findings in their nonexudative AMD fellow eye.

Materials and Methods

This retrospective, observational clinical case series included 27 eyes with nonexudative AMD of 27 patients who were being followed and treated for NVAMD in the fellow eye in the Ege University Faculty of Medicine Retina Unit between April 2013 and May 2016. The study was conducted using anonymized data and was approved by the Ege University Rectorate, Faculty of Medicine Dean's Office, and Clinical Research Ethics Committee (18-2/39).

At initial presentation, patients diagnosed with NVAMD in one eye underwent best corrected visual acuity (BCVA) assessment using Snellen chart, intraocular pressure measurement, and biomicroscopic examinations of the anterior and posterior segments. In addition, color fundus photography, infrared fundus photography, fundus autofluorescence, B-scan SD-OCT (Topcon OCT-2000, Topcon, Tokyo, Japan), FA, and indocyanine angiography (ICGA) (Heidelberg Spectralis HRA+OCT, Heidelberg, Germany) were performed.

The patients received intravitreal anti-VEGF therapy in their eyes with NVAMD, and BCVA and SD-OCT assessment were repeated in both eyes at each follow-up visit. We retrospectively reviewed the initial B-scan and en face SD-OCT, FA, and ICGA images of 27 nonexudative eyes that developed exudative findings and active type 1 NV while the patients were receiving anti-VEGF therapy for NVAMD in the fellow eye. All SD-OCT images taken at presentation and during follow-up were analyzed to investigate signs of quiescent type 1 NV during the preclinical stage and identify common lesion characteristics.

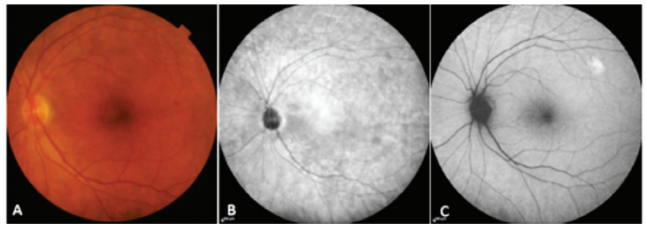

Figure 1. An eye with nonexudative age-related macular degeneration: A) Color fundus photograph shows pigment changes with no drusen; B) Infrared photography, C) Fundus autofluorescence image

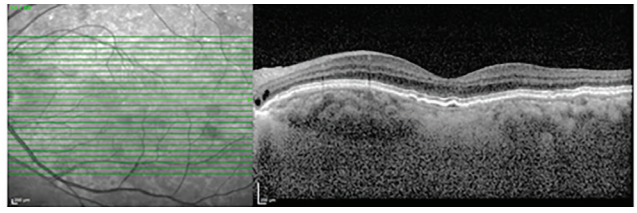

Figure 2. B-scan spectral domain optical coherence tomography shows elevations and irregularities in the retinal pigment epithelium layer, hyperreflective Bruch's membrane, moderately reflective material between the two layers (double-layer sign), quiescent type 1 neovascularization

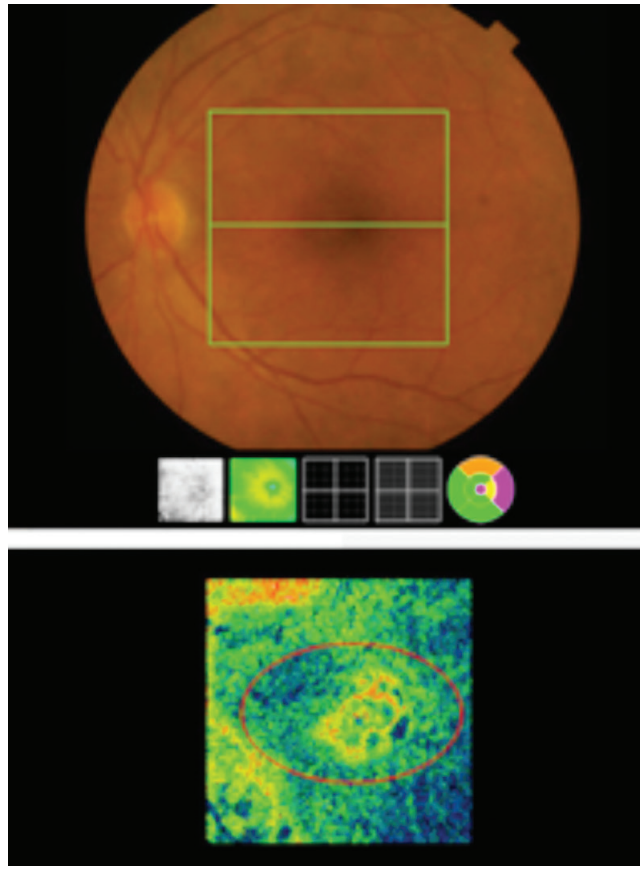

Figure 3. En face spectral domain optical coherence tomography shows hyperreflective lesion in the macula (red circle)

Results

The mean age of the 27 patients (13 males, 14 females) included in the study was 69.5±8.2 (55-87) years. Mean BCVA of the 27 eyes with nonexudative AMD was 0.6±0.3 (0.3-1) Snellen at first examination and remained stable until the emergence of exudative findings. The mean time between first examination and appearance of exudative signs was 8.3±4.03 (2-20) months.

At initial examination, both posterior segment slit-lamp biomicroscopic examination and color fundus and infrared fundus images demonstrated pigmentary changes in nearly all of 27 nonexudative AMD eyes, while no drusen were detected (Figure 1).

In B-scan SD-OCT imaging, features common to all eyes (100%) included a moderately reflective material between the RPE and Bruch's membrane (BM) associated with slightly elevated, irregular, and undulating RPE (double-layer sign) and hyperreflective BM, but without SR, IR, or sub-RPE fluid accumulation (Figure 2). In en face SD-OCT (C-scan) imaging, 24 eyes (88.8%) showed sub-RPE hyperreflective lesions likely corresponding to type 1 NV (Figure 3).

In FA imaging, none of the eyes showed staining specific to macular type 1 NV or leakage until the late phase, but some eyes had focal hyperfluorescence limited to the macula. In ICGA imaging, mildly hypercyanotic macular plaques were detected in 8 eyes (29.6%) in the middle and late phases. The location of these plaques was consistent with the hyperreflective lesions detected in en face SD-OCT (Figure 4). One eye showed transformation to NVAMD with reduced BCVA, subretinal fluid accumulation, and emergence of exudative findings in SD-OCT at 3.5 months after the initial examination (Figure 5).

In another eye, type I NV that was quiescent in initial examination transformed into active type 1 NV after 9 months, and its B-scan SD-OCT features are shown in Figure 6.

Discussion

In this study, using B-scan SD-OCT images we retrospectively determined that quiescent type 1 NV was present prior to the emergence of exudative symptoms in 27 nonexudative AMD eyes of 27 patients being followed and treated for NVAMD in the fellow eye, and we identified characteristic features of these subclinical lesions (100%). Some eyes exhibited findings associated with inactive NV on en face SD-OCT and ICGA imaging (88.8% and 29.6%, respectively), whereas no findings specific to the lesions were observed in FA imaging.

The most common type of NV in eyes with AMD is known to be type 1 NV, located in the sub-RPE space. This form originates in the choriocapillaris, penetrates BM over time, and expands between the RPE and BM, progressively growing and eventually causing fibrovascular pigment epithelial detachment.[2,3,4,8] In our study, we found that these lesions show moderate reflectivity and cause the RPE to appear slightly elevated, irregular and undulating, leading to separation of the RPE and BM layers to create the "double-layer sign". Various

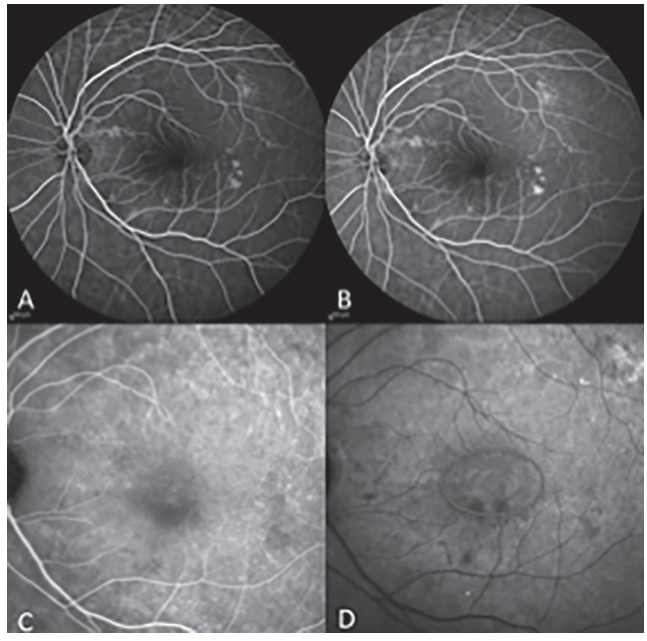

Figure 4. A and B) Early and late phase fluorescein angiography, no leakage. C and D) Early and late phase indocyanine green angiography, macular plaque evident in late phase (red circle)

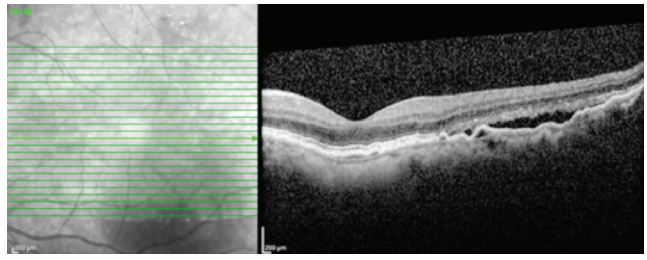

Figure 5. B-scan spectral domain optical coherence tomography shows subretinal fluid accumulation and active type 1 neovascularization 3.5 months after the initial diagnosis

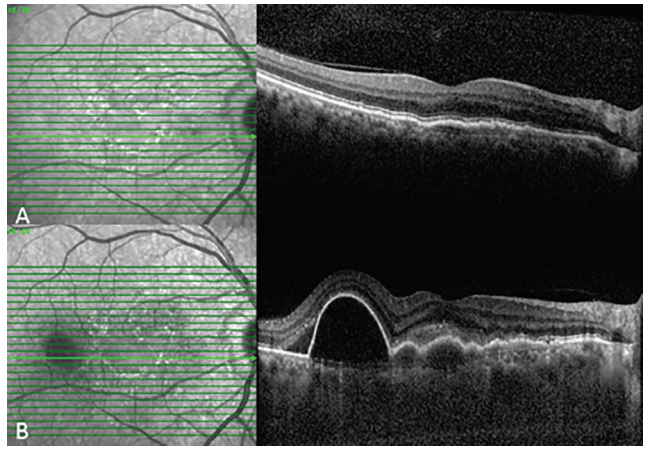

Figure 6. A) B-scan spectral domain optical coherence tomography shows moderately reflective material between the retinal pigment epithelium layer and hyperreflective Bruch's membrane (double-layer sign) and quiescent type 1 neovascularization. B) B-scan spectral domain optical coherence tomography shows active type 1 neovascularization 9 months later

clinical studies using SD-OCT, ICGA, and optical coherence tomography angiography (OCTA) have shown that quiescent NV lesions not yet causing exudative findings may be present in eyes with nonexudative AMD, polipoidal choroidal vasculopathy, and angioid streaks.[2,3,4,5,6,7,8,9]

Hanutsaha et al.[10] reported that of 432 patients who underwent FA and ICGA due to NVAMD findings in one eye, focal spot and macular plaque were detected in 11% of fellow eyes that exhibited only drusen. Exudative changes emerging in 24% of those eyes during the mean follow-up time of 21.7 months and the risk of progression to exudative disease was 2.60 times higher compared to eyes without plaques. Querques et al.[2] presented the outcomes of 6-month follow-up with multimodal morphological and functional results obtained by SD-OCT, FA, ICGA, and microperimetry in 11 consecutive eyes with asymptomatic, quiescent choroidal NV. They found that NV lesions associated with slight RPE elevation and irregularity in SD-OCT but no fluid leakage exhibited a speckled pattern in the late phases of FA without leakage and appeared as plaques that uptake dye in middle/late phases of ICGA. In addition, they observed horizontal enlargement of the NV lesions during follow-up. Menteş et al.[7] defined the multimodal imaging characteristics of quiescent type 1 NV lesions before the appearance of exudative findings in an eye with angioid streaks using SD-OCT, FA, ICGA, and OCTA.

Motulsky et al.[4] referred to the appearance of RPE and BM as two hyperreflective bands with a small space between them on SD-OCT as the "double-layer sign." They emphasized that the top layer is RPE, the bottom layer is BM, and the space between them is type 1 choroidal NV that is in a quiescent phase. The authors stated that in addition to SD-OCT, OCTA may be useful in detecting these lesions. Palejwala et al.[6] detected quiescent choroidal NV using OCTA in 2 (6.25%) of 32 eyes with drusen and pigmentary changes in patients with NVAMD in the fellow eye. Roisman et al.[3] investigated the presence of inactive NV in asymptomatic eyes using B-scan SD-OCT, FA, ICGA and swept-source (SS)-OCTA in 11 consecutive patients with nvAMD in one eye and asymptomatic, "intermediate AMD" in the fellow eye. In 3 (27.2%) of the 11 asymptomatic eyes with no signs of exudation on SD-OCT, they observed irregular RPE elevations on B-scan SD-OCT, macular plaque on ICGA, and the appearance of NV on SS-OCTA. The authors also concluded that a new classification delineating NVAMD and nonexudative AMD is needed. Similarly, de Oliveira Dias et al.[8] investigated the presence of subclinical macular NV using SS-OCTA in 160 consecutive patients with NVAMD in one eye and nonexudative AMD in the fellow eye. They detected type 1 and 3 subclinical NV in 14.4% of the eyes, and found that all type 1 NV lesions caused RPE elevation in SS-OCT. In addition, they reported that although OCTA revealed no signs of sublinical NV, 3 eyes with RPE elevations in SS-OCT developed exudation 8 weeks later.

OCTA is a relatively new but extremely useful imaging modality that is noninvasive, reproducible, and detects NV based on blood flow.[3,4,5,6,8] However, this method is still a developing technology and is not yet in widespread clinical use. Moreover, our study shows that B-scan SD-OCT imaging, one of the indispensable tools in retina clinics, is a reliable method that provides early and specific evidence of preclinical type 1 NV under the RPE even in eyes not yet exhibiting exudative symptoms.

Conclusion

Based on the literature and the results of our study, we conclude that B-scan OCT is an easily applicable, reproducible, and sensitive imaging method that has positive specific findings in almost all cases for the early detection of quiescent (inactive) type 1 NV formations.

Ethics

Ethics Committee Approval: Approved by the Ege University Rectorate, Faculty of Medicine Dean's Office, and Clinical Research Ethics Committee (18-2/39).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Jale Menteş, Şeyda Yıldırım, Concept: Jale Menteş Şeyda Yıldırım, Design: Jale Menteş Şeyda Yıldırım, Data Collection or Processing: Jale Menteş Şeyda Yıldırım, Analysis or Interpretation: Jale Menteş Şeyda Yıldırım, Literature Search: Jale Menteş Şeyda Yıldırım, Writing: Jale Menteş, Şeyda Yıldırım.

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

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

References

1. Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, Fahrbach K, Probst C, Sledge I. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology. 2008;115:116-126.
2. Querques G, Srour M, Massamba N, Georges A, Ben Moussa N, Rafaeli O, Souied EH Functional characterization and multimodal imaging of treatment-naive "quiescent" choroidal neovascularization. Invest Ophthalmol Vis Sci. 2013;54:6886-6892.
3. Roisman L, Zhang Q, Wang RK, Gregori G, Zhang A, Chen CL, Durbin MK, An L, Stetson PF, Robbins G, Miller A, Zheng F, Rosenfeld PJ. Optical Coherence tomography angiography of asymptomatic neovascularization in intermediate age-Related macular degeneration. Ophthalmology. 2016;123:1309-1319.
4. Motulsky E, Rosenfeld PJ. Double-Layer Sign and Type 1 CNV; How OCT can be a powerful tool for detecting choroidal neovascularization in a variety of retinal diseases. June 2017;http://www.retina-specialist.com/article/ Double-Layer Sign and Type 1 CNV
5. Roisman L, Rosenfeld PJ. Subclinical MNV: Do We Watch or Treat? March 2016;http://www.retina-specialist.com/article/subclinical-mnv-do-we-watch-or-treat

6. Palejwala NV, Jia Y, Gao SS, Liu L, Flaxel CJ, Hwang TS, Lauer AK, Wilson DJ, Huang D, Bailey ST. Detection of non-exudative choroidal neovascularization in age-related macular degeneration with optical coherece tomography angiography. Retina. 2015;35:2204-2211.
7. Menteş J, Karaca I, Sermet F. Multimodal imaging characteristics of quiescent type 1 neovascularization in an eye with angioid streaks. Am J of Ophthalmol Case Rep. 2018;10;132-136.
8. de Oliveira Dias JR, Zhang Q, Garcia JMB, Zheng F, Motulsky EH, Roisman L, Miller A, Chen CL, Kubach S, de Sisternes L, Durbin MK, Feuer W, Wang RK, Gregori G, Rosenfeld PJ. Natural history of subclinical neovascularization in nonexudative age-related macular degeneration using swept-source OCT angiography. Ophthalmology. 2018;125:255-266.
9. Sato T, Kishi S, Watanabe G , Matsumoto H, Mukai R. Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. Retina. 2007;27:589-594.
10. Hanutsaha P, Guyer DR, Yannuzzi LA, Naing A, Slakter JS, Sorenson JS, Spaide RF, Freund KB, Feinsod M, Orlock DA. Indocyanine green videoangiography of drusen as a possible predictive indicator of exudative maculopathy. Ophthalmology. 1998;105:1632-1636.

DOI: 10.4274/tjo.galenos.2018.65928
Turk J Ophthalmol 2019;49:89-98

Review

A Common Approach to Low Vision: Examination and Rehabilitation of the Patient with Low Vision

Esra Şahlı, Aysun İdil

Ankara University Faculty of Medicine, Department of Ophthalmology, Low Vision Rehabilitation and Research Center, Ankara, Turkey

Abstract

Due to the increasing age of the global population, rates of visual disability are increasing. Visual rehabilitation is an effective method for increasing quality of life among individuals with low vision or blindness due to unpreventable or untreatable causes. The goal of low vision rehabilitation is to produce people who are independent, have an economically viable profession or skill, and are able to enjoy their lives. The stages of modern low vision rehabilitation include the intake interview, assessment of residual visual functions, assessment of residual functional vision, interventions and recommendations, and vision rehabilitation therapies.

Keywords: Low vision, low vision rehabilitation, assessment of residual visual functions, assessment of residual functional vision, low vision aids

Intraduction

According to World Health Organization (WHO) data from 2010, there were an estimated 285 million people living with visual impairment worldwide. Of these, 39 million were reported as blind and 246 million as having low vision. The most common causes (80%) of these visual impairments are treatable conditions such as uncorrected refractive errors and cataract. These are followed by age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy. It has been reported that 65% of visually impaired and 82% of blind people are 50 years of age or older. Considering that the population is aging, this suggests that more people will be at risk in the future.[1]

Definitions of low vision and blindness may vary between countries. According to the definition accepted in the USA, best corrected visual acuity less than or equal to 20/200 in the better eye or a visual field less than or equal to 20° in the better eye is considered legal blindness.[2] In the 2016 version of the International Classification of Disease (ICF)-10, visual impairment is classified in 5 categories based on presenting visual acuity. While older definitions were based on best corrected visual acuity of the better eye, the current definition is based on presenting visual acuity (with glasses if any, without glasses if not) in order to emphasize the burden of uncorrected refractive errors (Table 1). According to this, presenting visual acuity in the better eye equal to or better than 6/18 is defined as mild or no visual impairment; equal to or better than 6/60 and worse than 6/18 as moderate visual impairment (category 1); equal to or better than 3/60 and worse than 6/60 as severe visual impairment (category 2); and worse than 3/60 as blindness. Blindness is also separated into 3 categories: visual acuity worse than 3/60 (category 3), worse than 1/60 (or counting fingers at 1 meter) (category 4), and no light perception (category 5).[3] According to this classification, those with moderate and severe visual impairment (visual acuity worse than 6/18 and equal to or better than 3/60) and those with a visual field less than or equal to 20° are defined as having "low vision" and require rehabilitation. Functionally, low vision can be regarded as a level of vision that prevents someone from performing their everyday activities. Having a presenting visual acuity worse than 3/60 and a corresponding visual field smaller than 10° is defined as blindness.[3] Because this new definition also includes uncorrected refractive errors which were previously unaccounted for, the

Address for Correspondence: Esra Şahlı MD, Ankara University Faculty of Medicine, Department of Ophthalmology, Low Vision Rehabilitation and Research Center, Ankara, Turkey Phone: +90 505 643 54 07 E-mail: esracansizoglu@gmail.com **ORCID-ID:** orcid.org/0000-0002-1355-7284
Received: 06.09.2018 **Accepted:** 19.10.2018

prevalence of blindness in various countries increases to 15% in all age groups and 25-30% among older adults. Studies have shown that the prevalence of low vision is up to 60% among older adults.[4,5,6,7,8]

The prevalence and causes of blindness and low vision in different societies vary based on their level of development. According to WHO data, the prevalence of blindness is 7.3/1000 in Africa, 3.5/1000 in the USA, 8.5/1000 in the Eastern Mediterranean Region, 3.0/1000 in Europe, 6.9/1000 in Southeast Asia except India, and 5.3/1000 in the Western Pacific Region except China. Global data indicate there are 3 people with low vision for each blind person; in the USA and Europe, which have the lowest rates of blindness, the prevalence of low vision is 25.6 and 28.7 per 1000, respectively. This rate is 25.4/1000 in Africa and 32/1000 in Southeast Asia.[9,10]

According to data from 2000, it was estimated that there were 937,000 (0.78%) blind and 2.4 million (1.98%) people with low vision over 40 years of age in the USA. Age-related macular degeneration (AMD) is the most common cause of blindness among Caucasians, accounting for 54.4% of cases. By 2020, the prevalence of blindness in the USA is predicted to increase by 70% to reach 1.6 million, and a similar increase is expected in the low vision population.[11]

Globally, 42% of visual impairment is due to uncorrected refractive errors, while 33% is caused by cataract. Other major causes include glaucoma, diabetic retinopathy (DR), trachoma, AMD, and corneal opacities. The primary cause of blindness is cataract (51%) (Figures 1 and 2).[1] In North America and other developed countries, the main causes of vision loss are AMD, DR, and glaucoma. Other causes include herpes simplex keratitis, retinal detachment, retinal vascular diseases, and hereditary retinal degenerative diseases. In developing countries, the primary causes of vision loss are uncorrected refractive errors and cataract, followed by glaucoma, infectious diseases, injuries, and xerophthalmia.[12] In short, visual impairment in developed countries is a result of unpreventable and/or currently untreatable causes, whereas preventable (infectious, e.g. trachoma, or nutritional, e.g. vitamin A deficiency) and/or treatable (e.g. cataracts) causes still play a major role in developing countries. The fact that most of the diseases that cause blindness and low vision are preventable or treatable has prompted many organizations to take action, especially WHO. According to the VISION 2020 report from WHO, low vision prevention and rehabilitation are among the primary global goals.[9]

A person's ability to perform important sight-based tasks is defined as "visual functioning". Reduced visual functioning due to disorders of the eye or visual system results in low vision. In addition to visual acuity, visual functioning should be assessed using parameters such as visual field, contrast sensitivity,

Table 1. Classification of visual impairments according to the International Classification of Disease-10 2016 revision

Category	Presenting distance visual acuity	
	Worse than	Equal to or better than
- Mild or no visual impairment		6/18 3/10 (0.3) 20/70
- Moderate visual impairment	6/18 3/10 (0.3) 20/70	6/60 1/10 (0.1) 20/200
- Severe visual impairment	6/60 1/10 (0.1) 20/200	3/60 1/20 (0.05) 20/400
- Blindness	3/60 1/20 (0.05) 20/400	1/60* 1/50 (0.02) 5/300 (20/1200)
- Blindness	1/60* 1/50 (0.02) 5/300 (20/1200)	Light perception
- Blindness	No light perception	

*or counts fingers at 1 meter

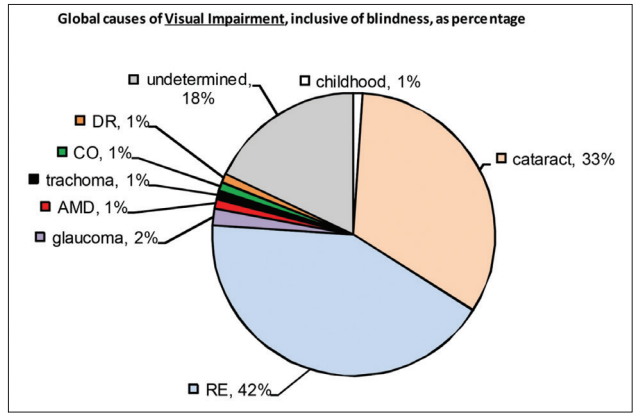

Figure 1. Distribution of global causes of visual impairment (taken from WHO report entitled Global Data on Visual Impairments 2010)
RE: Refractive errors, AMD: Age-related macular degeneration, CO: Corneal opacity, DR: Diabetic retinopathy

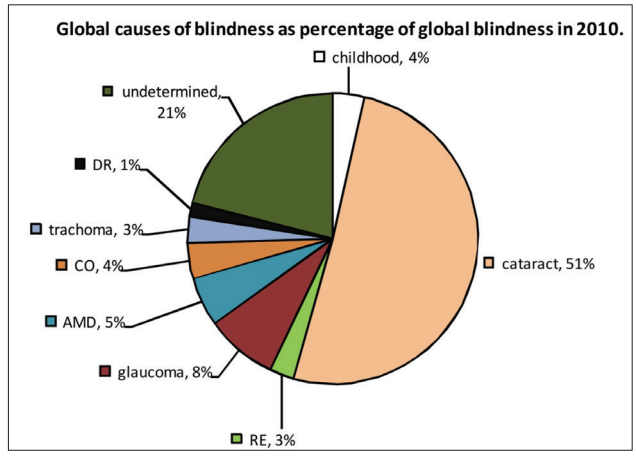

Figure 2. Distribution of global causes of blindness (taken from WHO report entitled Global Data on Visual Impairments 2010)
RE: Refractive errors, AMD: Age-related macular degeneration, CO: Corneal opacity, DR: Diabetic retinopathy

electrophysiological tests, adequacy of preferred retinal locus, color vision, binocularity, and stereopsis.

Low vision rehabilitation aims to increase quality of life by enabling patients to live independently, have a vocation or skill with which they can financially support themselves, and enjoy life. The stages of modern low vision rehabilitation include the intake, assessment of residual visual function, assessment of residual functional vision, interventions and recommendations, and vision rehabilitation therapy.[13]

1. The Intake

The purpose of low vision assistance and rehabilitation is to enable individuals to perform the sight-based activities they want to do but currently cannot, using special methods and/or equipment.

The initial interview is of key importance, as it will influence the entire rehabilitation process. The patient's family members should also be involved in some parts of this process, and it is imperative that sufficient time be allocated. History-taking from a patient with low vision differs from that in the classical ophthalmologic examination. The patient's sociocultural characteristics, medical and ocular history, priorities, and goals must be questioned in detail and recorded. A patient is asked which tasks are difficult or impossible for them to perform in order to gain insight into their visual functioning. In particular, they should be asked about which activities they are limited in and wish to continue doing. It should be determined whether they use any methods to help them perform the activities that they have difficulty with. The environmental conditions in locations such as their home, school, and workplace should be questioned, as well as what provisions are needed to increase their visual functioning in these places.

It must be kept in mind that patients may have different needs, and each patient should be offered personalized solutions. Visual needs important to the patient may include reading, doing crafts, watching television, seeing the board in school, or reading road signs or bus numbers. Some patients can have unrealistic expectations of low vision rehabilitation, such as being able to drive. Although rehabilitation has a high success rate in regaining abilities such as reading, patients with low vision are not eligible to receive a driver's license in Turkey. It may be necessary to inform patients what expectations are realistic without being discouraging. In cases where the patient and their family cannot adapt to their current situation and are pessimistic, the negatives of the patient's visual impairment and disease should not be emphasized during the interview; instead, they should be guided and encouraged about what they can do.

When planning the rehabilitation program, questionnaires and scales about activities of daily living can be used to determine in detail what difficulties the patient faces in daily life. These scales are also used to evaluate the effectiveness of low vision rehabilitation. One of these scales is the Low Vision Quality of Life Questionnaire (LVQOL), developed by Wolffsohn and adapted to Turkish by Idil et al.[21] and another is the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ 25), which was adapted to Turkish by Toprak et al.[15] The purpose of these scales is to characterize and determine the impact of visual impairment in daily life. The Turkish version of the LVQOL consists of a total of 24 items in 5 dimensions, including 12 items about distance vision, mobility, and lighting, 3 items about adjustment, 5 items about reading and fine skills, and 4 items on activities of daily living. The NEI-VFQ 25 comprises 25 items in 11 subgroups and 12 optional items. This scale includes items assessing general vision, difficulty in activities requiring near and distance vision, limitations of peripheral and color vision, ocular pain, vision-related limitation of social functions, role limitations, dependency, mental health symptoms, and driving difficulties, and general health. Higher scores in these scales correspond to better quality of life.[14,15] When evaluating the patient with low vision, quality of life scales are useful for assessing the patient's perceptions of their disease and whether rehabilitation has resolved their vision-related problems.

2. Assessment of Residual Visual Functions

Examination should be performed after identifying the patient's priorities. Determining visual function is essential when examining the patient with low vision. Low vision examination differs from routine ophthalmologic examination in some respects. Distance and near visual acuity are assessed in detail. Best visual acuity should be determined with the most appropriate correction, because the patient's residual vision will inform the selection of rehabilitation methods.

Measurement of Distance Visual Acuity

Visual acuity measurement is the easiest and most useful method of assessing visual functioning, although it does not fully reflect a low vision patient's performance in daily life. At this stage, it is essential to use charts that a person with low vision can see and place them at an appropriate test distance. A person with low vision gaining the ability to read some letters on a suitable and correctly applied chart when they could not read any letters in previous examinations is an important positive initial experience in the rehabilitation process. Accurate determination of visual acuity in a patient with low vision is also important to monitor disease, determine the amount of magnification needed for glasses or other optical device, evaluate response to therapy if provided, and to create disability reports if required. Examination should be performed under standard conditions (e.g., fixed chart distance and lighting) and with suitable charts. The Snellen chart is not appropriate for examination of the low vision patient because it has low sensitivity in the 6/10-6/24 range due to its irregular geometric arrangement and because the top lines are easier to read due to the crowding phenomenon. Instead, the logMAR-based Bailey-Lowie or Early treatment diabetic retinopathy study charts are preferred. Advantages of these charts are that they use logarithmic scales and the lines include equal numbers of letters of similar legibility. The spacing between the letters and lines is determined based on the size of

the letters in each line. More lines are included at the low vision levels. Visual acuity is scored as 0.1 logMAR for each line and 0.02 logMAR for each correctly read letter. Better visual acuity corresponds to a lower logMAR score.[2,16] Depending on visual acuity, measurement can be performed by adjusting the distance between the patient and chart to 2 meters or even 1 meter. It is suitable for use in low vision examination because it provides more sensitive measurement at low vision levels, facilitates refraction examination, and is preferred for academic purposes.

Measurement of Near Visual Acuity

For patients with low vision, charts that include text samples are better for assessing near vision than charts that use optotypes. This enables the evaluation of reading performance, detection of any scotomas, and assessment of the effectiveness of therapy or rehabilitation. During examination, it must be ensured that the distance between the individual and the near vision chart is appropriate and fixed. The patient's near vision is measured monocularly and binocularly using an addition suitable for the working distance of the reading chart. The metric M-unit is used for letter size. Near vision acuity is recorded as reading distance in meters divided by letter size in M-units. The Minnesota Low Vision Reading Chart (MNREAD), which can be applied using a computer screen or printed cards, is one of the charts frequently used in patients with normal or low vision, especially for international comparisons.[16]

Refraction Test-Retinoscopy

Refraction testing must be performed more carefully in a patient with low vision. When examining low vision patients with abnormal head position, eccentric gaze, or nystagmus, the use of trial frames and lenses should be preferred over phoropter.

For patients with eccentric fixation or nystagmus and for uncooperative patients, cycloplegia and dynamic retinoscopy should be performed when measuring refractive error. Although refractive error can be measured using an autorefractometer in patients with low vision, determining refractive error by retinoscopy is ideal. When a clear reflection cannot be obtained, the patient should be approached until a reflection is seen, and necessary adjustments should be made based on this distance. After retinoscopy, the patient's refractive error is confirmed using subjective methods such as fogging and cross-cylinder.

Remarkably, for approximately 15% of patients referred for low vision rehabilitation, functional vision can be restored by simply prescribing appropriate distance and/or near vision spectacles.

Visual Field

Visual field is one of the most important parameters of visual function in the low vision patient. Diseases involving the macula, such as AMD, hereditary macular dystrophies, and macular edema, lead to scotomas that significantly impact visual functioning and reading performance. The Amsler Grid test is especially useful for identifying the location and size of central scotomas. However, this test is inadequate for small scotomas and conditions such as macular diseases in which fixation is commonly extrafoveal and unstable. These types of visual field defects are best evaluated by scanning laser ophthalmoscope (SLO). Because SLO provides instant retinal images, visual field defects and the related area of the retina can be evaluated simultaneously. Microperimetry using SLO technology enables the detection of important parameters such as preferred retinal locus and fixation stability in low vision patients with central scotoma, and trained retinal locus training can be provided.[2,16]

Peripheral visual field loss adversely affects an individual's orientation in unfamiliar environments, mobility, and hazard perception. These defects are often seen in patients with advanced glaucoma and retinitis pigmentosa. Kinetic (Goldman) and static (Humprey, Octopus) perimetries can be used to evaluate such defects.[2,16]

High-power prism designs are used for hemianopias and quadrantanopias of neurological origin and cases of tunnel vision due to diseases such as retinitis pigmentosa.[17]

Assessment of Contrast Sensitivity

Contrast sensitivity is the power to distinguish differences in shade between two regions. Although contrast sensitivity tests are not used in clinical practice for every patient with low vision, they can be performed for patients whose visual functioning is poorer than expected based on their measured visual acuity. Clinically, deficits in contrast sensitivity are especially common in corneal edema, cataract, optic nerve diseases, and some retinal diseases. Patients with low contrast sensitivity might require more magnification than expected for their visual acuity and may benefit from increased ambient light. Closed-circuit television systems that increase contrast and broaden the visual field can be recommended to these patients.[2] Many contrast sensitivity charts are used in clinical practice to measure perceived contrast, such as the Vistech VCTS test, Pelli-Robson Letter chart, Arden chart, CSV-1000 chart, and Regan chart. For patients with low vision, contrast sensitivity tests designed specifically for low vision should be used, such as the CSV-1000LV, ELCT, and CSV-1000 1.5 cycles/degree.

Color Vision

Hereditary and acquired color vision disorders have several distinguishing features. Hereditary color blindness (protanopia and deuteranopia) is a stable, binocular, usually red-green color vision deficiency that preferentially affects males. Other visual functions are normal. Acquired color vision deficiencies can be monocular and asymmetrical, are often progressive, and usually involve blue-yellow color blindness. Most color vision disorders in patients with low vision are blue-yellow dischromatopsia. Pseudoisochromatic plates are the most commonly used color vision tests. They are simple and can be performed quickly. They comprise colored numbers or paths on a background of equal saturation. The Ishihara test, the most well known pseudoisochromatic table, only tests red-green vision. For blue-yellow dischromatopsia, which is more common among patients with low vision, color arrangement tests such as the Farnsworth 100 Hue and D 15 tests or the Wang & Wang color vision plates are more appropriate than the Ishihara test. In addition, the reliability of pseudoisochromatic tests decreases at visual acuity

levels lower than 6/20. In general, blue-yellow color blindness is considered to be associated with large lesions involving the outer retina, while red-green color blindness occurs in lesions involving the inner retina and optic nerve. Furthermore, blue-yellow color blindness is seen in cataract and glaucoma, while red-green color blindness occurs in cone dystrophy. As part of rehabilitation, patients can be advised to seek high color and tone contrast.[16,18]

Glare Test

Glare refers to excessive brightness in the visual field and can be accompanied by asthenopia, headache, and squinting. Glare can be associated with media opacities such as cataracts and corneal scar, or albinism, achromatopsia, or aniridia. It can be assessed simply during visual acuity measurement by holding a light source near the fixation line and observing the reduction in the number of lines or letters the patient can read.[2,16]

3. Assessment of Residual Functional Vision

Low vision patients with similar residual visual functions may have very different performance when it comes to utilizing their vision. Assessment of residual functional vision determines how and to what extent the low vision patient can use their residual vision and the individual and environmental factors that affect this ability. This also includes educational vision assessment to facilitate appropriate education planning.

As explained in detail in ICF system, in addition to their visual functions, an individual's activity and participation and environmental factors must be evaluated in a rehabilitation program. In other words, visual functions determine a person's capacity, whereas functional vision refers to their performance.[19]

Therefore, functional vision assessment identifies how the patient uses their vision and what visual skills and environmental adjustments they need to better use their vision. It is based on the patient's actual performance in the target activity and measurement of the adequacy of this performance. For example, in a patient whose primary goal is to read, residual visual function is determined using methods such as visual acuity, refractive error, and visual field, while residual functional vision is measured using a performance index such as reading speed. Reading performance should be assessed using continuous text cards instead of solitary optotypes. Continuous text cards must be representative of commonly read materials and commonly used words in the population, be standardized in terms of length and width, and be printed in the native language of the population.

An objective measure of reading performance is maximum reading speed. Other parameters that can be used in assessment include reading acuity, critical print size, and Reading Accessibility Index. Maximum reading speed is the reading rate that is not limited by print size. Reading acuity is the smallest print size that can be read without making any errors; critical print size is the smallest print size that can be read at maximum speed. The recently developed Reading Accessibility Index indicates the visual accessibility of familiar printed material and is calculated as the mean reading speed across the ten largest print sizes on an MNREAD chart. It represents reading performance in daily life.[20] MNREAD cards, developed at the University of Minnesota, can be used to assess reading performance. They provide corresponding values for reading acuity in Snellen, logMAR, and M-units from 40 cm. Although originally in English, they have been validated in various languages. A Turkish version has also been developed and validated and is of equal difficulty to versions in other languages to allow its use in international studies (Figure 3).[21]

Quality of life scales can be used in the subjective evaluation of functional vision. It is also possible to evaluate the effectiveness of rehabilitation with these scales.

Daily visual goals usually include reading, writing, watching television, dressing, performing personal care, moving around, cooking, doing home maintenance, cleaning, and working. A rehabilitation program is designed taking into account the patient's visual priorities and their distance, near, or intermediate distance vision needs. This planning requires a multidisciplinary low vision team. In order to increase the patient's participation and motivation, their family should be involved in planning and implementing the low vision rehabilitation.

4. Interventions

The data obtained in the first three stages are evaluated and an individualized intervention program is planned for each

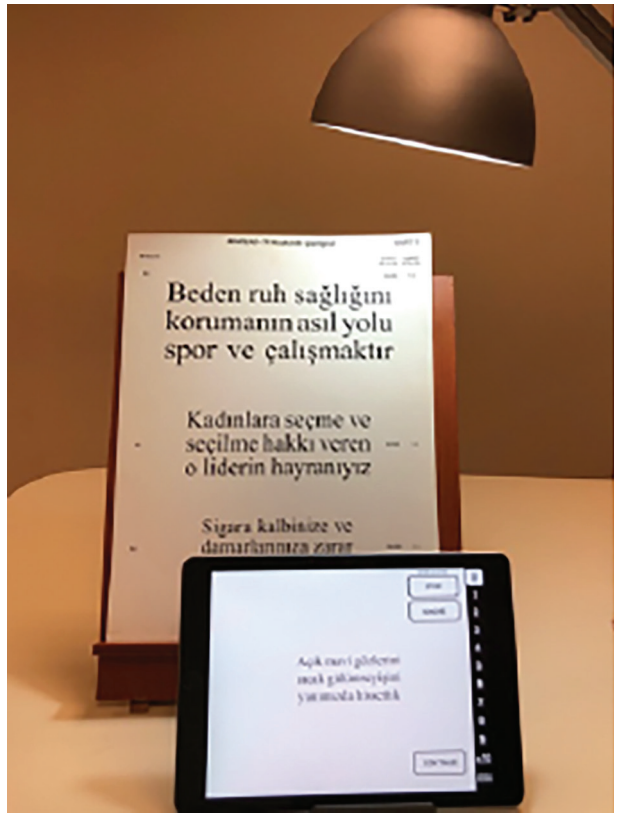

Figure 3. Assessment of reading performance using MNREAD cards

low vision patient. This program encompasses the necessary techniques and/or assistive technology.

Devices Used in Low Vision Rehabilitation

Optical systems

I. Telescopes

Advantages of telescopes include being able to magnify an image at long working distances with hands-free use; however, they also have disadvantages such as being difficult and dangerous to use when moving due to narrowing of the visual field, causing difficulty in achieving binocularity, and being costly, and they can also cause esthetic concerns. They can be integrated into the patient's own prescription glasses, and some models are also focusable (Figure 4). Their length increases with their magnifying power, and visual field narrows as their length increases and diameter decreases. Bioptic telescopes can be used at magnifications of up to 6x. When a telescope is prescribed for a patient with low vision, they must be trained in its use.

Telescopes are either Galilean or Keplerian depending on their optical principles. The Galilean telescope consists of two lenses, a low-power plus objective lens and a high-power minus eyepiece lens, and it gives an upright image. The Keplerian telescope also consists of two lenses, a low-power plus objective lens and high-power plus eyepiece lens. The inverted image obtained with Keplerian telescopes is corrected with prisms. Although Galilean telescopes have certain advantages such as being shorter and lighter and having a larger visual field, Keplerian telescopes have better image quality because they use light more efficiently. Keplerian telescopes are more complex with a wider range of focus. The telescopes used in low vision rehabilitation are usually Keplerian.[22]

Figure 4. Some types of telescopes used in our clinic

Telescopes can be focusable or fixed-focus depending on their focusing characteristics. In focusable telescopes, the patient's spherical error can be corrected and a base lens may be required for high astigmatism. With fixed-focus telescopes, the patient's refractive error (spherical + cylindrical) must be given as the base lens.

Depending on the patient's vision level, telescopes can be prescribed monocularly or binocularly. For near vision, a +3.00 to +12.00 D cap (reading cap) can be attached. Telescopes can be hand-held, clip-on, or spectacle-mounted (large-scale, bioptic, mini-telescope). Spectacle-mounted telescopes are mostly used for watching television or by school-aged children for looking at the board, whereas a monocular hand telescope is hung around the neck and used only when needed, allowing the user to continue their everyday activities.

Although telescopes are not suitable for use when moving due to narrowing of the visual field, various special designs have been developed in an effort to overcome this limitation. These designs, which are used when in motion, are bioptic telescopes and autofocus telescopes. In bioptic telescopes, a compact, low-power magnifying telescope is placed in an area in the patient's visual field, usually the superotemporal region. When the patient looks through their glasses, the magnified image from the telescope can be viewed when needed by adjusting their head or eye position. With autofocus telescopes, this process is modified with a motorized focusing system so that the user can easily follow objects at different distances (Figure 5).[22] Although bioptic telescopes are useful for distance viewing, their use is limited by their appearance and the ring scotoma surrounding the magnified image. This led to the recent development of 'in-the-spectacle-lens' telescopes, a design in which a wide-field Keplerian telescope is built completely within the spectacle lens. By simultaneously using the magnified and nonmagnified view of the viewing area, the vision multiplexing feature provided by these devices facilitates the patient's orientation and navigation.[23]

II. Microscopes (High-Diopter Near Spectacles)

After correcting hyperopia, near addition and reading distance are calculated according to Kestenbaum's rule. For example, in a patient with a corrected visual acuity of 20/100, the near add is the inverse of visual acuity, 100/20=5 D, and near reading distance is 1/5=20 cm. The add is gradually increased to the dioptric power that allows the patient to comfortably read a text size of 1 M. The actual value will be higher than the predicted value in patients with low contrast sensitivity or macular scotoma and those who want to read letters smaller than 1 M. Binocular vision up to +10 D is possible. As the dioptric power increases, reading distance is reduced accordingly. If the reading distance is too short, it can be increased with high-power plus lenses held away from the eye with special clip-on systems. The effect of additional illumination must also be assessed during examination. The advantages of microscopes include their wide visual field, hands-free operation, and pleasing esthetic appearance. Negative aspects are their short working distance and inability to tolerate values greater than 10 D binocularly (Figure 6).[2,24]

In patients whose binocular vision is better than their monocular vision (i.e., with similar visual acuity in both eyes), a base-in prism can be added to facilitate accommodative convergence (Figure 7). Although there are various formulas to calculate Δ addition, a base-in Δ roughly twice the D power addition can be added to both eyes. If the patient's reading performance is better when their less sighted eye is closed (i.e., the patient is functionally monocular), a frosted lens can be prescribed for the less sighted eye or the patient can be instructed to close the weaker eye when reading.[24]

Because high D (greater than +4.5 D) additions in bifocal and progressive lenses are difficult to tolerate binocularly and the likelihood of problems at intermediate and far distances increases in parallel with D power, dedicated reading glasses should be recommended to patients with low vision. Moreover, as the use of near vision spectacles provides a larger visual field, it will enable eccentric viewing.

III. Magnifiers

Magnifiers can be used in addition to near vision spectacles in order to meet the needs of low vision patients when reading and performing tasks requiring near vision. They can be used simultaneously with near vision spectacles, and do not require myopic correction in most patients. Remember that with magnifiers, the greater the working distance, the smaller the visual field. Magnifiers are available as hand-held, stand, illuminated, fiberoptic, and dome/bar magnifiers.

Advantages of hand-held magnifiers are that they are

Figure 5. Various examples of bioptic telescopes

Figure 6. Some types of microscopes used in our clinic

Figure 7. Microscopes with prism additions

portable, can be used at longer working distances than spectacles, and are inexpensive. Some have built-in illumination. The virtual image can be brought closer to the focal plane at the back of the eye by changing the object distance. Aspheric magnifiers provide better image quality. They are useful when looking at mobile phone screens and price tags while shopping. However, they must be held steady at a fixed working distance (Figure 8).[25]

With stand magnifiers, the object distance can be adjusted easily. They require a fixed, flat surface and usually include a built-in light source. This increases contrast and reduces the amount of magnification needed, thus increasing reading speed. Stand magnifiers should be used in conjunction with near vision spectacles of about +3.00 to +3.50 D in older patients. They may be preferable for those who cannot use hand-held magnifiers due to tremor, paralysis, arthritis, or poor hand-eye coordination, or those who require more magnification than spectacles provide (Figure 9).[26]

IV. Filtering Lenses

These lenses filter certain wavelengths of light while allowing the passage of other wavelengths. This reduces the patient's photophobia and provides clearer vision by increasing contrast sensitivity. According to the patient's needs, different filtering lenses can be prescribed for both indoors and outdoors. The lenses are different colors based on the wavelength they filter. Although there are filters recommended for certain diseases, it is more appropriate to try a set of filtering lenses to identify the filter the patient is most comfortable with (Figure 10).[27]

V. Electro-optical Systems

Closed-circuit television (CCTV) systems are systems that project visuals such as written text or images to a screen and enable adjustments such as magnifying the image and changing brightness and contrast. They are so called because of the direct cable connection between the camera imaging system and the display. Features such as variable magnification, auto-focus, magnification without focusing, reverse contrast, voice-command controls, and automatic forwarding have also been added to these systems. Electro-optical systems mitigate or overcome many problems associated with magnifying systems, such as narrow visual field, short working distance, reduced contrast, aberrations, and illumination. The main problem with electro-optical systems is that they are large and costly. However, with technological advances, systems now come in portable sizes and have become relatively less expensive (Figure 11).[2,28]

Mouse magnifiers are devices that look like a computer mouse and contain a camera that is moved over the material to be viewed. They are easy to carry, cheaper than CCTV systems, and can be connected to most personal computers. They can have variable magnification, reverse contrast, and focusing features. Their main disadvantage is limited viewing area (Figure 12).

Figure 8. Hand-held magnifiers

Figure 9. Stand magnifiers

Figure 10. Filtering lenses

Today, electronic tablets have become more popular than most optical systems due to their many functions and applications that assist those with low vision, especially school-age children. Most individuals with low vision can benefit from electronic reading devices such as the iPad (Apple, Cupertino, CA, USA) and Kindle (Amazon, Seattle, WA, USA).[29] A prospective study showed that these types of electronic devices increased reading performance in most patients.[30] These devices include applications that enable the user to increase the size and darkness of characters, adjust the contrast, brightness, and color of the display background, magnify and zoom, zoom by taking a photograph of an image, take spoken commands, and read text aloud. Their advantages include ease of access, relatively low cost, and combination of different functions that can be used for both distant and near tasks.[31]

Non-Optical Systems

Non-optical systems increase the patient's residual visual function or use signals that stimulate one of the other senses. Illumination, large-print books, increased contrast, typoscope, reading stands, and sunglasses or spectacles with filtering lenses to reduce glare can be used alone or in conjunction with optical systems in patients with low vision.

Illumination reduces the need for magnification and increases reading performance, particularly in macular degeneration patients who have reduced contrast sensitivity. Patients must be taught how to properly direct table lamps while reading. The built-in illumination in hand-held and stand magnifiers increases reading performance for most patients. On the other hand, patients complaining of excessive glare will benefit from reducing the light level and using hats, sunglasses, filtering lenses, and light-blocking glasses. Patients can be advised to increase the contrast when printing documents, try different contrasts such as a light-colored object on a dark background, use glasses with contrast-enhancing yellow or orange filtering lenses, and use a typoscope or electro-optical system.[2]

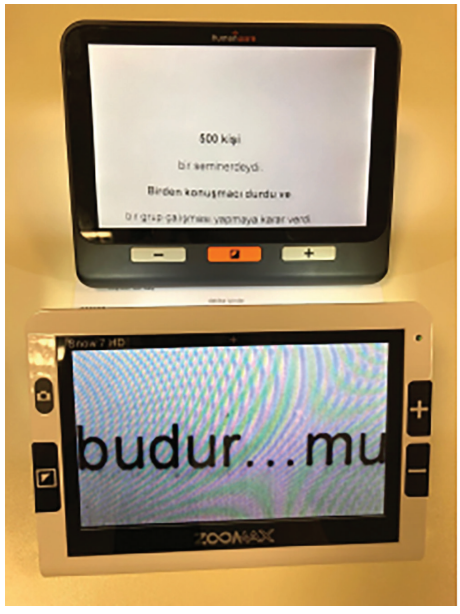

Figure 11. Examples of electro-optical systems

5. Recommendations and Vision Rehabilitation Therapy

As visual impairment progresses, patients can be offered alternate tools and techniques such as white cane training, use of the Braille alphabet, audio books, and voice recording devices. It is also very important to modify the patient's living conditions. Taking measures such as sitting students in the middle of the front row of the classroom, organizing the kitchen and other home environments in a contrasting and appropriate way, and accentuating steps and handrails will make daily life easier. Vision loss can have a major impact on some quality of life and emotional state in some individuals. These people should receive psychological counseling to help them adjust and overcome the emotional problems they are experiencing.

Low vision rehabilitation is not just the prescription of a low vision aid. Training programs consisting of habituation exercises practiced in the clinic or at home constitute one of the most important stages of rehabilitation. Various training programs and courses are implemented in vision rehabilitation therapy to develop related functions and improve performance. Some of these programs are reading and writing skills, orientation and mobility, and driving education in countries where it is legal. Occupational therapists conduct assessments at the patient's home, school, or workplace to improve orientation and mobility and facilitate adaptation. If there are target activities in the patient's real life environments, they are also practiced using the auxiliary devices and the necessary environmental adjustments are recommended.[13]

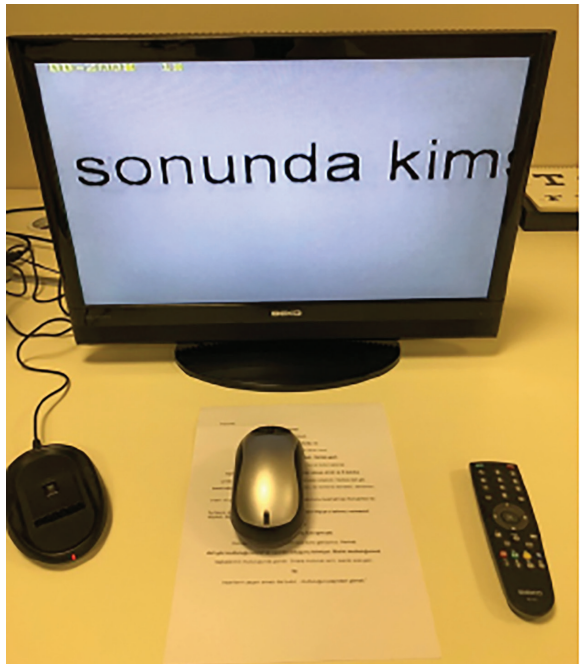

Figure 12. Mouse electronic magnifier

Ethic

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Esra Şahlı, Aysun İdil, Concept: Esra Şahlı, Design: Aysun İdil, Data Collection or Processing: Esra Şahlı, Aysun İdil, Analysis or Interpretation: Esra Şahlı, Aysun İdil, Literature Search: Esra Şahlı, Writing: Esra Şahlı, Aysun İdil.

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

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

References

1. World Health Organization, Global Data on Visual Impairments 2010, 2012. http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf?ua=1 (erişim Mayıs 2018).
2. Görsel Rehabilitasyon: Klinik Optik. American Academy of Ophthalmology. Temel ve Klinik Bilimler Kursu. Cilt 3. Güneş Kitabevi2009:243-267.
3. ICD-10 Version: 2016. http://www.who.int/classifications/icd/icdonlineversions/en (erişim Mayıs 2018).
4. Michon JJ, Lau J, Chan WS, Ellwein LB. Prevalence of visual impairment, blindness, and cataract surgery in Hong Kong elderly. BR J Ophthalmol. 2002;86:133-139.
5. Nirmalan PK, Thulasiraj RD, Maneksha V, Rahmathullah R, Ramakrishnan R, Padmavathi A, Munoz SR, Ellwein LB. A population based eye survey of older adults in Tirunelveli district of South India: blindness, cataract surgery, and visual outcomes. Br J Ophthalmol. 2002;86:505-512.
6. Salomao SR, Cinoto RW, Berezovski A, Araujo-Filho A, Mitsuhiro MR, Mendieta L, Morales PH, Pokharel GP, Belfort R Jr, Ellwein LB. Prevalence and causes of visual impairment and blindness in older adults in Brazil: the Sao Paulo Eye Sudy. Ophthalmic Epidemiol. 2008;15:167-175.
7. Salomao SR, Mitsuhiro MR, Belfort R Jr. Visual impairment and blindness: an overview of prevalence and causes in Brazil. An Acad Bras Cienc. 2009;81:539-549.
8. Dineen BP, Bourne RR, Ali SM, Huq DM, Johnson GJ. Prevalence and causes of blindness and visual impairment in Bangladeshi adults: results of the National Blindness and Low Vision Survey of Bangladesh. Br J Ophthalmol. 2003;87:820-828.
9. World Health Organization. Blindness: Vision 2020 – The Global Initiative for the Elimination of Avoidable Blindness. Action plan 2006-2011. 2015. http://www.who.int/mediacentre/factsheets/fs213/en/.
10. Resnikoff S, Pscolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82:844-852.
11. Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P; Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004;122:477-485.
12. Vaghan D, Asbury T. Vaghan and Asbury's General Ophthalmology. Eighteenth ed. USA; Mc Grawl-Hill Companies Inc; 2011:383-395.
13. Merdoğan İdil A. Yaşa bağlı maküla dejenerasyonunda az görme rehabilitasyonu. Güncel Retina. 2017;1:246-250.
14. İdil A, Ozen M, Atak N, Elhan A, Pehlivan S. Validity and reliability study of Turkish version on low vision with quality of life questionnare. Int J Ophthalmol. 2011;4:546-551.
15. Toprak AB, Eser E, Güler C, Baser FE, Mayali H. Cross-validation of the Turkish version of the 25-item National Eye Institute Visual Functioning Questionnare (Ne1-VFQ 25). Ophthalmic Epidemiol. 2005;12:259-269.
16. Jackson AJ. Assessment of visual function. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. (1st ed). Butterworth Heinemann Elsevier, PA, USA; 2007:129-166.
17. Giorgi RG, Woods RL, Peli E. Clinical and laboratory evaluation of peripheral prism glasses for hemianopia. Optom Vis Sci. 2009;86:492-502.
18. Or KH. Kontrast duyarlılık ve renk görme. Turkiye Klinikleri J Ophthalmol-Special Topics2017;19:15-19.
19. ICF İşlevsellik, yeti yitimi ve sağlığın uluslar arası sınıflandırması, Dünya Sağlık Örgütü; 2004.
20. Calabrese A, Owsley C, McGwin G, Legge GE. Development of a reading accessibility index using the MNREAD acuity chart. JAMA Ophthalmol. 2016;134:398-405.
21. Idil SA, Calıskan D, Idil NB. Development and validation of the Turkish version of the MN-Read visual acuity charts. Turk J Med Sci. 2011;41:565-570.
22. Wolffsohn JS. Telescopes. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. (1st ed). Butterworth Heinemann Elsevier, PA, USA; 2007:241-256.
23. Peli E, Vargas-Martin F. In-the-spectacle-lens telescopic device. J Biomed Opt. 2008;13:034027.
24. Rumney NJ. Spectacle magnifiers. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. (1st ed). Butterworth Heinemann Elsevier, PA, USA; 2007:223-240.
25. Rumney NJ. Hand magnifiers. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. 1st ed. Butterworth Heinemann Elsevier, PA, USA; 2007:198-209.
26. Wolffsohn JS. Stand magnifiers. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. (1st ed). Butterworth Heinemann Elsevier, PA, USA; 2007:210-222.
27. Ceyhan D, İdil A. Körlük ve az görme epidemiyolojisi ve örgütlenme. Turkiye Klinikleri J Ophthalmol-Special Topics2017;10:87-92.
28. Wolffsohn JS. Electronic vision enhancement systems. In: Jackson AJ, Wolfaohn JS, eds. Low Vision Manual. (1st ed). Butterworth Heinemann Elsevier, PA, USA; 2007:257-272.
29. Shah P, Schwartz SG, Gartner S, Scott IU, Flynn HW Jr. Low vision services: a practical guide for the clinician. Ther Adv Ophthalmol. 2018;10:2515841418776264.
30. Morrice E, Johnson AP, Marinier JA, Wittich W. Assessment of the Apple iPad as a low-vision reading aid. Eye 2017;31:865-871.
31. http://www.perkinselearning.org/technology/getting-started/ipad-low-vision.

DOI: 10.4274/tjo.galenos.2018.28909
Turk J Ophthalmol 2019;49:99-101

Case Report

Bilateral Anterior Uveitis Revealing Relapsing Polychondritis

Murat Hasanreisoğlu*, Hüseyin Baran Özdemir**, Fulya Yaylacıoğlu*, Mestan Ertop*, Zeynep Aktaş*

*Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Ophthalmology Clinic, Ankara, Turkey

Abstract

Relapsing polychondritis is a potentially lethal but rare systemic autoimmune disease. The major site of inflammation is the connective tissue, usually involving the ears, nose, larynx, tracheobronchial tree, and cardiovascular system. Although scleritis and episcleritis are known to be the most probable ocular manifestation, it may also present with uveitis. We present the case of a 22-year-old young lady who initially referred with bilateral red and painful eyes caused by anterior uveitis. Her right ear was also red and painful, consistent with cartilaginous inflammation. She was diagnosed with relapsing polychondritis with bilateral anterior uveitis and chondritis of the ear in conjunction with the rheumatology department. Bilateral anterior uveitis should evaluated and monitored carefully in patients with relapsing polychondritis.

Keywords: Anterior uveitis, relapsing polychondritis, systemic autoimmune disease

Introduction

Relapsing polychondritis (RP) is an idiopathic inflammatory disease of cartilaginous structures that can involve the ears, nose, larynx, tracheobronchial tree, and cardiovascular system.[1,2] The latter are responsible for the high morbidity and mortality of the disease. The diagnostic criteria for RP are based on characteristic clinical manifestations.[1]

Ocular manifestations occur in approximately 60% of patients with RP.[3] The most common manifestations are scleritis, episcleritis, keratitis, and conjunctivitis. Relapses and exacerbations are common. Uveitis occurs in approximately 25% of patients with RP, which is most commonly either in the form of anterior uveitis or a sclerouveitis.[4] Proptosis, corneal perforation, retinal vasculitis, and optic neuritis leading to blindness are other possible ocular manifestations of RP.[4] In this paper, we report a case with anterior uveitis as an ophthalmic manifestation of RP.

Case Report

A 22-year-old woman was referred to Gazi University, Department of Ophthalmology with photophobia and redness in both eyes starting one week earlier. Best corrected visual acuity was 20/20 in both eyes, although she described discomfort with her vision. Slit-lamp examination revealed bilateral conjunctival injection and anterior chamber reaction which was graded as +4 accompanied by fine, non-granulomatous bilateral keratic precipitates (Figure 1). Dilated fundus examination demonstrated normal retinal findings, with no vascular sheathing or any sign of retinitis (Figure 2). Optical coherence tomography (OCT), enhanced depth imaging-OCT, and fundus autofluorescence (FAF) were all normal (Figure 3). In addition to her ophthalmic symptoms, the patient had redness and pain in her right ear. Physical examination of the patient showed cartilaginous inflammation of the right ear (Figure 3). The patient was referred to the rheumatology department for further systemic evaluation. Hematological examination demonstrated elevated

Address for Correspondence: Hüseyin Baran Özdemir MD, Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone: +90 505 871 92 39 E-mail: baranozdemir@gmail.com **ORCID-ID:** orcid.org/0000-0002-5585-253X
Received: 15.04.2018 **Accepted:** 13.08.2018

serum erythrocyte sedimentation rate and C-reactive protein level (69 mm/hr ve 126 mg/L, respectively). Complete blood count and other biochemical parameters were within normal ranges. Infective and inflammatory markers were also normal (anti-DNA, ANA, C3 and C4 immunoglobulin, anti-SSA, anti-SSB, anti-SM, anti-SCL, and anti-JO). The patient was treated with topical dexamethasone 0.1 mg/5 mL ophthalmic solution hourly, cyclopentolate 1 %3 times a day, and systemic oral 1 mg/kg/day prednisolone therapy with a plan to taper.

After one month of this combination of topical and oral steroid therapy, her best corrected visual acuity was stable and visual deterioration was resolved. Slit-lamp biomicroscopy revealed a dramatic regression in the anterior chamber reaction, with only trace anterior chamber cells/flare and few keratic precipitates (Figure 4). Treatment continued with slow tapering.

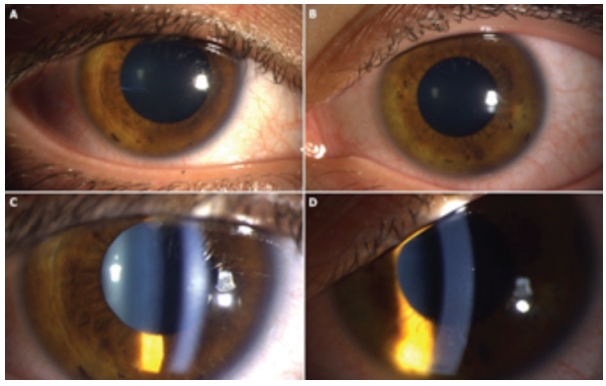

Figure 1. Anterior segment photography of the right eye (A) and left eye (B) at initial presentation showing bilateral conjunctival hyperemia. Slit-lamp photography of the right eye (C) and left eye (D) showing bilateral anterior chamber reaction and non-granulomatous keratic precipitates which were more prominent in the left eye

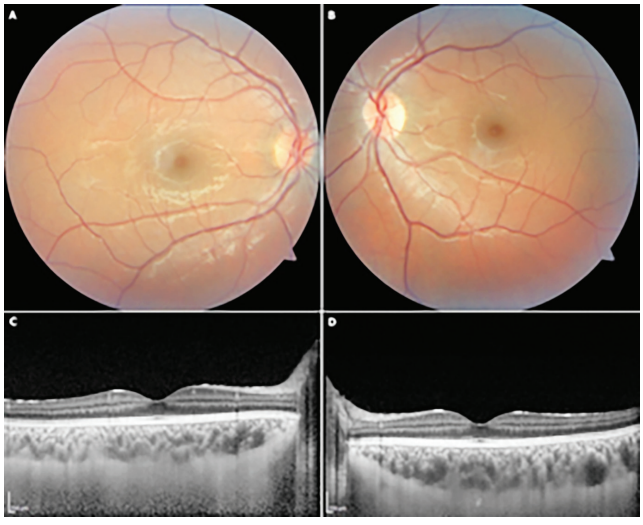

Figure 2. Fundus photography of the right eye (A) and left eye (B) with normal findings. Enhanced depth imaging spectral-domain optical coherence tomography of the right eye (C) and left eye (D) showing fovea and choroidal thickness, which was unaffected

Discussion

RP is a rare autoimmune disorder characterized by recurrent episodes of inflammation involving cartilaginous structures containing type 2 collagen throughout the body, resulting in tissue damage and destruction.[1] The disease causes repetitive inflammation mainly affecting the ears, nose, and tracheobronchial tract. Proteoglycan-rich structures throughout the body such as the joints, eyes, inner ear, blood vessels, heart, and kidneys may also be involved.[5] The most common early signs of RP are auricular chondritis and polyarthritis, occurring in over 80% of patients.[6] However, common symptoms are often absent in the early stages; therefore, it may mimic any other rheumatologic disease involving joint, ocular, cutaneous, or audio-vestibular dysfunction, resulting in diagnostic delays.

Ocular manifestations are found in 50-70% of patients and are of great importance since they are correlated with disease activity.[7] Although two major ocular manifestations documented in the literature include episcleritis or scleritis, uveitis has also

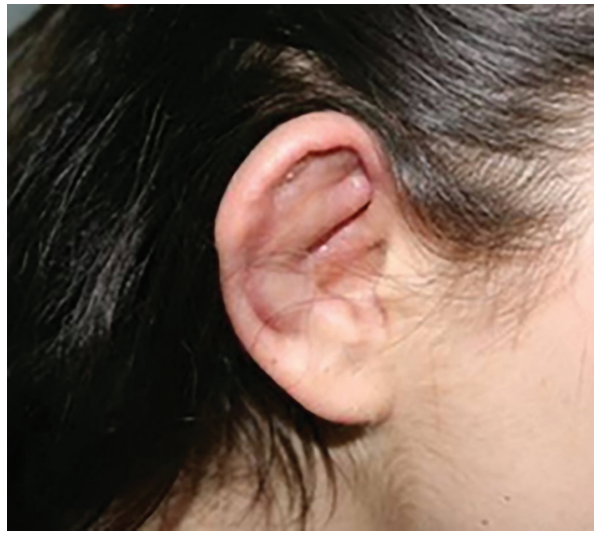

Figure 3. Right auricular chondritis as a presenting sign

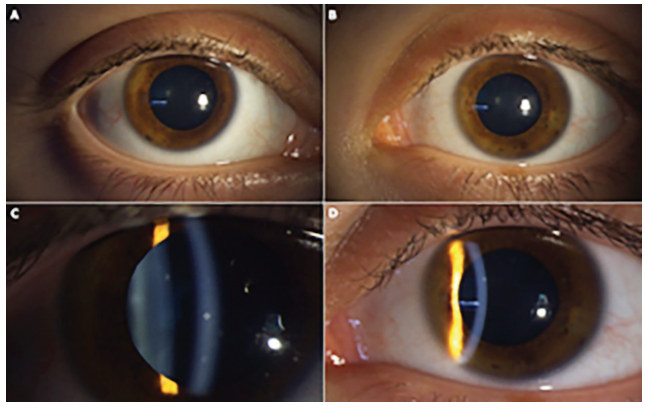

Figure 4. Anterior segment photography (A, C: right eye; B, D: left eye) after one month of treatment showing decrease of anterior chamber reaction with few keratic precipitates, trace anterior chamber reaction, and no synechia

been reported in 3-22% of cases and can compromise visual outcomes.[7] Uveitis, though uncommon, is reported to be anteriorly located and non-granulomatous. This is consistent with the present case, which presented with bilateral anterior uveitis concurrent with chondritis of one ear, the knees, and fingers. The diagnostic criteria for RP are based on characteristic clinical manifestations. Biopsy confirmation may be needed if the diagnosis is suspected. In our case, biopsy did not seem crucial, since the auricular chondritis was typical as an early manifestation of her disease. Although RP is most common in patients between the ages of 40 and 60,[1] it can also affect young adults or children, as in the present case. The prognosis of patients with RP is also variable and depends on the organ involvement and response to treatment.[8] Treatment is customized according to the severity and site of the disease. Mild forms are treated with anti-inflammatory and anti-neutrophilic agents but advanced cases, including those involving acute airway obstruction, multiple relapses, and cardiovascular disease, may require high doses of prednisone (1 mg/kg per day) or even intravenous pulse methylprednisolone.[6] In our case, topical steroids and low-dose oral prednisolone treatment was administered initially. Because response to treatment was slow and the chondritis and uveitis were controlled only to a limited degree, the oral prednisolone dose was increased gradually to the maximum level of 1 mg/kg. This effectively reduced disease activity.

To sum up, RP is an inflammatory disease of unknown etiology that affects the connective tissue. The diagnosis is difficult to confirm and it is even more challenging to predict and manage disease progression. Ocular manifestations, although not rare, should be evaluated carefully, as relatively less common presentations such as uveitis can lead to vision loss if not detected and treated.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Hasanreisoğlu, Fulya Yaylacıoğlu, Mestan Ertop, Concept: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Zeynep Aktaş, Design: Murat Hasanreisoglu, Huseyin Baran Özdemir, Zeynep Aktaş, Data Collection or Processing: Murat Hasanreisoğlu, Fulya Yaylacıoglu, Mestan Ertop, Analysis or Interpretation: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Zeynep Aktaş, Literature Search: Murat Hasanreisoğlu, Mestan Ertop, Writing: Murat Hasanreisoğlu, Hüseyin Baran Özdemir, Mestan Ertop.

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

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

References

1. Longo L, Greco A, Rea A, Lo Vasco VR, De Virgilio A, De Vincentiis M. Relapsing polychondritis: A clinical update. Autoimmun Rev. 2016;15:539-543.
2. Hansson AS, Heinegárd D, Holmdahl R. A new animal model for relapsing polychondritis, induced by cartilage matrix protein (matrilin-1). J Clin Invest. 1999;104:589-598.
3. Shimizu J, Oka H, Yamano Y, Yudoh K, Suzuki N. Cutaneous manifestations of patients with relapsing polychondritis: an association with extracutaneous complications. Clin Rheumatol. 2016;35:781-783.
4. Suzuki S, Ikegami A, Hirota Y, Ikusaka M. Fever and cough without pulmonary abnormalities on CT: relapsing polychondritis restricted to the airways. Lancet. 2015;3:385:88.
5. Nakajima T, Sekine Y, Yasuda M, Yasufuku K, Iyoda A, Suzuki M, Shibuya K, Iizasa T, Fujisawa T. Long-term management of polychondritis with serial tracheobronchial stents. Ann Thorac Surg. 2006;81:24-26.
6. Zeuner M, Straub RH, Rauh G, Albert ED, Schölmerich J, Lang B. Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. J Rheumatol. 1997;24:96-101.
7. Isaak BL, Liesegang TJ, Michet CJ Jr. Ocular and systemic findings in relapsing polychondritis. Ophthalmology. 1986;93:681-689.
8. Ben Salah R, Frikha F, Hentati Y, Kallel S, Ghorbel A, Mnif Z, Bahloul Z. Recurrent anterior uveitis with hypopyon revealing relapsing polychondritis. Intern Med. 2012;51:3173-3176.

DOI: 10.4274/tjo.galenos.2018.04453
Turk J Ophthalmol 2019;49:102-105

Case Report

Pediatric Canaliculitis: A Case Report

Elif Eraslan Yusufoğlu, Sabiha Güngör Kobat

Elazığ Training and Research Hospital, Ophthalmology Clinic, Elazığ, Turkey

Abstract

Canaliculitis is a rare disease that relapses when not properly diagnosed and treated. It usually occurs in middle-age and advanced age. It is extremely rare in children and infants. A healthy 12-year-old girl presented with lower eyelid swelling and watery discharge in her right eye. During the last 2 years, the patient had been examined several times for the same complaints but there was no improvement despite treatment. Examination showed that the lower punctum had a pouting punctum appearance, and applying pressure to the lacrimal sac area resulted in purulent discharge. Lavage showed that the lacrimal passage was patent. In light of these clinical findings, the patient was diagnosed with canaliculitis. Punctoplasty with surgical curettage of the dacryoliths were performed. After the surgical procedure, a topical antibiotic was prescribed. Histopathological examination of the dacryoliths revealed that the infective cause was *Actinomyces*. No recurrence or complications were observed during 12 months follow-up.

Keywords: Canaliculitis, punctoplasty, curettage, *Actinomyces*

Introduction

Canaliculitis is a rare condition caused by infection of the canalicular system by various pathogens. It accounts for about 2% of lacrimal system diseases.[1]

It can be easily diagnosed based on clinical findings; however, because it is rarely encountered by practitioners, patients are often followed long-term for inaccurate diagnoses, resulting in delay of effective treatment. In this article we present a case of primary canaliculitis in a pediatric patient with a long history of misdiagnosis and inappropriate treatment.

Case Report

A 12-year-old girl presented with a 2-year history of swelling of the medial lower lid and persistent discharge in the right eye. She reported that during this time, she had seen different ophthalmologists and her symptoms had improved slightly with medical treatment, but never completely resolved. Review of her hospital records showed that she had been prescribed various antibiotic and steroid eye drops and ointments for diagnoses of conjunctivitis, chalazion, and lacrimal duct stenosis. External examination of the right eye revealed thick purulent secretion and swelling in the punctum area of the medial lower lid (Figure 1). The lower punctum was enlarged and compression resulted in purulent secretion from the punctum. The lacrimal duct was patent upon irrigation. However, the presence of dacryoliths was felt as the cannula tip was inserted into the lacrimal duct.

Based on the examination findings, the patient was diagnosed with canaliculitis. Due to her history of poor response to long-term medical treatment, we decided to remove the dacryoliths surgically. The patient was admitted for surgery under general anesthesia. We first attempted to spare the canaliculus and remove the dacryoliths by expanding the punctum with a dilator. When this failed to provide a large enough opening, a one-snip punctoplasty was performed. A chalazion curette was used to completely remove the dacryoliths (Figures 2 and 3). The lacrimal system was washed with 5% povidone-iodine solution (Batticon). Postoperatively, the patient was given topical 100,000 U/mL crystallized penicillin 8 times a day for 10 days. The removed dacryoliths were sent for histopathological

Address for Correspondence: Elif Eraslan Yusufoğlu MD, Elazığ Training and Research Hospital, Ophthalmology Clinic, Elazığ, Turkey
Phone: +90 533 414 73 86 E-mail: elif.eraslan@yahoo.com **ORCID-ID:** orcid.org/0000-0003-2480-8971
Received: 18.06.2018 **Accepted:** 07.11.2018

and microbiological examination. Histopathology revealed sulfur granules associated with *Actinomyces* (Figure 4). Hyphal structures consistent with *Actinomyces* were observed in Gram staining, but culture was negative. At the patient's last follow-up 12 months later, her symptoms had completely resolved with no recurrence.

Discussion

Canaliculitis is a suppurative or nonsuppurative infection of the canalicular system and is seen more frequently among women and in the lower canaliculus.[2] The most common clinical findings are watering, discharge, a pouting punctum appearance, conjunctival redness, and swelling of the canalicular part of the eyelid.[3,4] Although many cases have been documented in the literature and it is a straightforward clinical diagnosis, it is one of the most misdiagnosed conditions because it is so infrequently encountered.[1] Patients are often subjected to long-term inappropriate or inadequate treatment for diagnoses such as conjunctivitis, blepharitis, chalazion, mucocele, or dacryocystitis, delaying an accurate diagnosis.[3] Our patient had also been treated for various diagnoses over a period of 2 years, but had not responded.

Figure 1. Discharge and swelling in the punctum area of the lower lid of the right eye

Figure 2. Intraoperative photograph of the patient

Canaliculitis appears at an average age of 60-65 years.[4,5] However, younger patients have also been reported.[6,7,8] When seen in infants and children, the clinician should be vigilant for other underlying lacrimal system pathologies.[9,10] Our patient presented to our center at 12 years of age and her symptoms had started 2 years earlier. There was no accompanying lacrimal system pathology. Therefore, it should be kept in mind that although canaliculitis usually affects older adults, it can also be seen in pediatric patients.

Actinomyces spp. are the pathogens most commonly associated with canaliculitis.[11,12,13] However, the most frequently isolated pathogens in recent microbiological studies are streptococci,[4,14] staphylococci,[3,15] or mixed infections.[16] This difference may be attributable to the difficulty of culturing and microbiologically demonstrating *Actinomyces*. Therefore, histopathological examination of dacryoliths is the best method for demonstrating *Actinomyces*. In fact, this is supported by a report from Ciftci et al.[13] that although Actinomyces was detected histopathologically in all cases, cultures were positive for only 53.9% of the patients in their study. Similarly, although culture from our patient showed no growth, Actinomyces was detected by histopathology.

Canaliculitis can be treated using a conservative or surgical approach. Conservative treatment employs topical and systemic antibiotics, warm compresses, local massage, and lacrimal system irrigation with antibiotic or iodine-povidone solution. However, resistance and recurrence are common with only topical/systemic

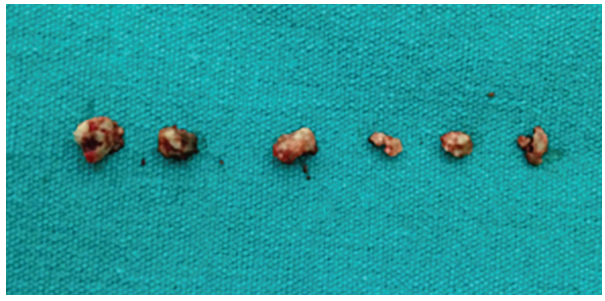

Figure 3. Dacryoliths removed by curettage

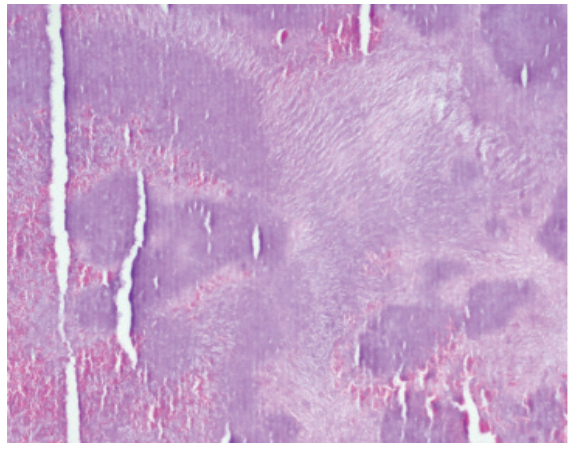

Figure 4. Sulfur granules associated with *Actinomyces*

antibiotics and massage therapy.[2,15] This is because dacryoliths and debris in the lacrimal system cause tear stasis and prevent sufficient antibiotic penetration. Lin et al.[4] treated 25 patients with surgery (canaliculotomy) and 9 patients with medical (local and/or systemic antibiotic) treatment and reported recurrence rates of 33% in the medically treated group and 16% in the surgically treated group. Male sex and the presence of dacryoliths were identified as the main risk factors for recurrence.

In order to increase the effectiveness of conservative therapy and reduce the need for surgery, studies evaluating lacrimal duct irrigation with antibiotics have been conducted. This was intended to enable drugs to better reach the target organism. Mohan et al.[17] reported improvement in all patients treated with intracanalicular antibiotic irrigation and proposed that this method could provide an alternative to surgery. In another study in which some patients had antibiotic and steroid canalicular irrigation and some underwent surgery, success was achieved in 68% of the irrigated patients and 100% of the surgery group. The authors reported that although surgery was more effective, canalicular irrigation could reduce the need for surgery.[5]

Surgery with topical and/or systemic antibiotic therapy has a high success rate and is considered the gold standard for treatment of canaliculitis. Surgical treatment involves performing curettage after punctum dilatation, punctoplasty, canaliculotomy, or punctum-sparing canaliculotomy. Regardless of which technique is used, complete removal of the canalicular contents is of key importance. Canaliculotomy and punctoplasty enable better removal of canalicular content and generally heal without complications.[2,7,13,18] However, complications such as narrowing of the canaliculus, lacrimal pump dysfunction, and lacrimal fistulae may occur in rare cases and lead to epiphora in the long term. Kim et al.[19] reported epiphora in 8.7% of the patients they treated with three-snip punctoplasty and curettage and followed for a mean of 11 months. Due to the risks associated with punctoplasty and canaliculotomy, there has been a recent focus on punctum-sparing surgeries. Buttanri et al.[20] performed punctum dilation and removed the dacryoliths by applying pressure along the canaliculus from immediately distal to the common canaliculus to the punctum using forceps or a cotton-tipped applicator. Then they completely cleared the canaliculus using a chalazion curette and irrigated with an antibiotic solution. No recurrence was observed in any of the patients during at least 3 months of follow-up. Khu and Mancini[21] created a horizontal incision along the canaliculus starting 2 mm from the punctum; after removing the dacryoliths, they placed a monocanalicular silicone tube and the incision was left to heal by secondary intention. All of the patients recovered with no complications.

In conclusion, canaliculitis is a recurrent condition that can be easily clinically diagnosed but, because it is encountered so infrequently, is commonly misdiagnosed and inadequately treated for long periods. Although conservative treatment can be effective in some patients, the method is best accepted and has the highest success rate is surgery. The condition is more common in the middle-aged and older age groups. However, it should not be forgotten that, although rare, it can also occur in pediatric patients like ours.

Ethics

Informed Consent: Written informed consent was taken from the parents for reporting this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Elif Eraslan Yusufoğlu, Concept: Elif Eraslan Yusufoğlu, Design: Elif Eraslan Yusufoğlu, Data Collection or Processing: Elif Eraslan Yusufoğlu, Sabiha Güngör Kobat, Analysis or Interpretation: Elif Eraslan Yusufoğlu, Sabiha Güngör Kobat, Literature Search: Elif Eraslan Yusufoğlu, Sabiha Güngör Kobat, Writing: Elif Eraslan Yusufoğlu.

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

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

References

1. Freedman JR, Markert MS, Cohen AJ. Primary and secondary lacrimal canaliculitis: a review of literature. Surv Ophthalmol. 2011;56:336-347.
2. Vecsei VP, Huber-Spitzy V, Arocker-Mettinger E, Steinkogler FJ. Canaliculitis: Difficulties in diagnosis, differential diagnosis and comparison between conservative and surgical treatment. Ophthalmologica. 1994;208:314-317.
3. Kaliki S, Ali MJ, Honavar SG, Chandrasekhar G, Naik MN. Primary canaliculitis: clinical features, microbiological profile, and management outcome. Ophthal Plast Reconstr Surg. 2012;28:355-360.
4. Lin SC, Kao SC, Tsai CC, Cheng CY, Kau HC, Hsu WM, Lee SM. Clinical characteristics and factors associated the outcome of lacrimal canaliculitis. Acta Ophthalmol. 2011;89:759-763.
5. Xu J, Liu Z, Mashaghi A, Sun X, Lu Y, Li Y, Wu D, Yang Y, Wei A, Zhao Y, Lu C, Hong J. Novel Therapy for Primary Canaliculitis: A Pilot Study of Intracanalicular Ophthalmic Corticosteroid/Antibiotic Combination Ointment Infiltration. Medicine (Baltimore). 2015;94:e1611.
6. Park A, Morgenstern KE, Kahwash SB, Foster JA. Pediatric canaliculitis and stone formation. Ophthalmic Plast Reconstr Surg. 2004;20:243-246.
7. Yaman A, Özbek Z, Öztürk AT, Lebe B, Söylev MF. Kronik kanalikülit olgularında kanalikülotomi ile kanalikül küretajı. Türkiye Klinikleri J Ophthalmol. 2009;18:1-6.
8. Yılmaz MB, Şen E, Evren E, Elgin U, Yılmazbaş P. Kanalikülit farkındalığı. Turk J Ophthalmol. 2016;46:25-9
9. Nair AG, Potdar NA, Gore SS, Ganvir AY, Apte MK, Marathe TR, Kumar CA, Shinde CA. Actinomycetes canaliculitis complicating congenital nasolacrimal duct obstruction in an infant. Indian J Ophthalmol. 2018;66:574-577.
10. Ding J, Sun H, Li D. Persistent pediatric primary canaliculitis associated with congenital lacrimal fistula. Can J Ophthalmol. 2017;52:161-163.
11. Hussain I, Bonshek RE, Loudon K, Armstrong M, Tullo AB. Canalicular infection caused by Actinomyces. Eye (Lond). 1993;7:542-544.
12. Richards WW. Actinomycotic lacrimal canaliculitis. Am J Ophthalmol. 1973;75:155-157.
13. Çiftçi FÖ, Karadayı K, Yıldız TF, Akın T, Yıldıray Y. Süpüratif kanalikülit tedavisinde küretaj, punktoplasti ve monokanaliküler silikon stent. Turk J Ophthalmol. 2004;33:324-332.

14. Zaldivar RA, Bradley EA. Primary canaliculitis. Ophthalmic Plast Reconstr Surg.2009;25:481-484.
15. Anand S, Hollingworth K, Kumar V, Sandramouli S. Canaliculitis: the incidence of long-term epiphora following canaliculotomy. Orbit. 2004;23:19-26.
16. Perumal B, Carlson JA, Meyer DR. A Pathological Analysis of Canaliculitis Concretions: More Than Just Actinomyces. Scientifica (Cairo). 2016;2016:6313070.
17. Mohan ER, Kabra S, Udhay P, Madhavan HN. Intracanalicular antibiotics may obviate the need for surgical management of chronic suppurative canaliculitis. Indian J Ophthalmol. 2008;56:338-340.
18. Stucki VC, Demolli P, Kniestedt C, Frimmel S. Long-term Follow-up of Canaliculotomies after Canaliculitis. Klin Monbl Augenheilkd. 2018;235:392-397.
19. Kim UR, Wadwekar B, Prajna L. Primary canaliculitis: The incidence, clinical features, outcome and long-term epiphora after snip-punctoplasty and curettage. Saudi J Ophthalmol. 2015;29:274-277.
20. Buttanri IB, Serin D, Akbaba M, Karslioğlu S. Incision-sparing management of canaliculitis. Orbit. 2014;33:356-358.
21. Khu J, Mancini R. Punctum-sparing canaliculotomy for the treatment of canaliculitis. Ophthalmic Plast Reconstr Surg. 2012;28:63-65.

DOI: 10.4274/tjo.galenos.2018.90768
Turk J Ophthalmol 2019;49:106-108

Case Report

Swept-source Optical Coherence Tomography Angiography in a Patient with Bietti Crystalline Dystrophy Followed for Ten Years

Şefik Can İpek*, Ziya Ayhan*, Sibel Kadayıfçılar**, Ali Osman Saatci*

*Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

A woman with Bietti's crystalline dystrophy (BCD) was first examined when she was 27 years of age and has been followed for 10 more years. The disease course was monitored initially with spectral domain-optical coherence tomography and then with swept-source optical coherence tomography angiography (OCTA). OCTA analysis showed that choroidal vessels could be visualized at the outer retinal layer segmentation due to retinal pigment epithelial atrophy and blood flow was reduced at the level of choroidal segmentation. OCTA can play a major role in the follow-up of BCD patients by analyzing changes in choroidal flow.

Keywords: Bietti crystalline dystrophy, optical coherence tomography, optical coherence tomography angiography, retinal dystrophy

Introduction

Bietti crystalline dystrophy (BCD) is a retinal dystrophy characterized by shiny yellow crystalline deposits in the retina and sometimes the limbus with progressive chorioretinal atrophy starting in the posterior pole.[1] Mutations in the *CYP4V2* gene have been detected in patients with BCD.[2]

Indocyanine green angiography, one of the conventional imaging methods, shows extensive areas of hypofluorescence due to choriocapillaris atrophy as the disease progresses in posterior pole.[3] Optical coherence tomography has demonstrated reduced central foveal and subfoveal thickness, hyperreflective spots in all retinal layers and even within the choroid, outer retinal tubulations, and hyperreflective plaques in the retinal pigment epithelium (RPE)-Bruch's membrane complex.[4]

Compared to conventional methods, there are fewer reports of findings associated with BCD in optical coherence tomography angiography (OCTA), which is a very new imaging modality. In this case report, we describe the clinical entities and OCTA characteristics of a woman with BCD who was followed for 10 years.

Case Report

A 27-year-old woman presented to our clinic in 2008 with progressive visual impairment in both eyes. On ophthalmologic examination, her best corrected visual acuity (BCVA) on Snellen chart was 0.3 (-4.50) in the right eye and 0.2 (-4.50) in the left eye. Slit-lamp examination showed clear cornea, calm anterior chamber, and transparent lens in both eyes. Deposits were not observed in the corneal limbus of either eye. The optic discs appeared normal on fundus examination. Extensive shiny white-yellow deposits were observed in the posterior pole and mid-peripheral retina (Figures 1A and B). Based on these findings, a clinical diagnosis of BCD was made and the patient was scheduled for follow-up.

Upon retrospective analysis of her records, we noticed that patient did not undergo OCT in 2008. OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) performed in 2014 revealed central macular thickness was 194 µm in the right eye and 198 µm in the left eye. Hyperreflective intraretinal spots were observed in the sensorial retina and hyperreflective plaque-

Address for Correspondence: Ali Osman Saatci MD, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
E-mail: osman.saatci@yahoo.com **ORCID-ID:** orcid.org/0000-0001-6848-7239
Received: 19.05.2018 **Accepted:** 07.09.2018

like deposits were identified at the RPE-Bruch's membrane junction. Intraretinal cystic spaces were observed in some of the sections. Outer retinal tubulation was noted in the outer retinal layers. Choriocapillaris atrophy and subsequent enhanced visibility of the large choroidal vessels was noted in enhanced depth imaging mode, which provides better visualization of the choroid. Complete obliteration of the choroidal vasculature was observed in some places. Choroidal hyperreflective foci were noted around the choroidal vessels (Figures 2A and B). Swept-source OCT (SS-OCT) performed in 2018 showed a relative reduction in the intraretinal hyperreflective spots and hyperreflective plaque-like deposits at the RPE–Bruch's membrane detected in 2014 (Figure 2C and D).

On examination in 2018, BCVA was 0.1 (-4.50) in both eyes. There were still no signs of corneal pathology on slit-lamp examination. Fundus examination revealed retinal crystalline deposits and extensive areas of retinal and choroidal atrophy in both eyes (Figure 1C and D). In SS-OCTA (Topcon DRI OCT Triton, Topcon, Japan), the choroidal vessels were visible in the area of outer retinal layer projection due to increased permeability resulting from diffuse RPE atrophy; in the area corresponding to the choriocapillaris projection, no flow associated with the choriocapillaris was observed and vessels belonging to the deeper choroidal layers were apparent in this area (Figure 3A, B, C, and D [right eye]; E, F, G, and H [left eye]).

Discussion

Hirashima et al.[5] used SS-OCTA to evaluate 9 eyes of 9 patients with BCD, 16 eyes of 16 retinitis pigmentosa patients with *EYS* mutation, and 16 eyes of 16 control subjects. The outer choroidal vascular area was 43.34±5.76% in eyes with BCD, 53.73±4.92% in eyes with *EYS* mutation/retinitis pigmentosa, and 52.80±4.10% in healthy subjects, with the value in BCD being significantly lower. Thinning in the outer choroidal vascular area in eyes with BCD was associated with thinning of the subfoveal choroid, and interestingly, the inner choroidal vessels could not be identified in 8 of the 9 BCD eyes.

Miyata et al.[6] analyzed 13 eyes of 13 patients with BCD using Optovue OCTA (RTVue XR, Avanti-AngioVue, Optovue, Freemont, CA, USA) and demonstrated reduced choriocapillaris flow in 12 (92%) of the 13 eyes. The authors reported that subfoveal choriocapillaris thickness was correlated with visual acuity.

In our patient, after 10 years of follow-up, we observed a slight decline in vision, which was already poor at baseline,

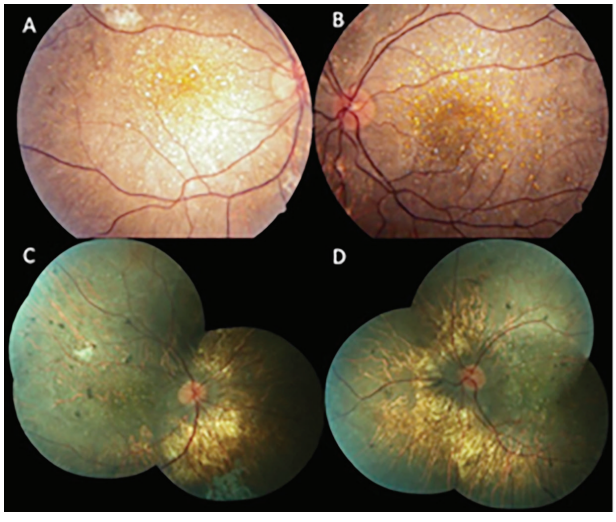

Figure 1. Color fundus images: In 2008, extensive intraretinal crystals concentrated around the posterior pole and relatively little chorioretinal atrophy were observed in the right (A) and left (B) eyes; In 2018, there was a marked decrease the number of crystalline deposits and increase in chorioretinal atrophy in the right (C) and left (D) eyes

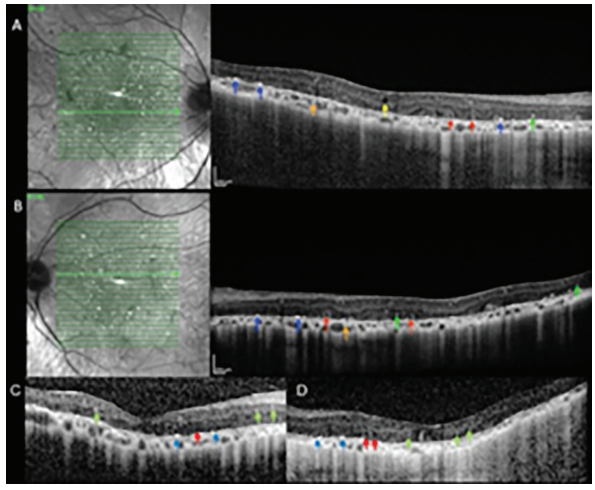

Figure 2. Enhanced depth imaging spectral domain-optical coherence tomography images from 2014, right (A) and left (B) eye. Red arrows: Outer retinal tubulations; Blue arrows: Hyperreflective plaque-like deposits in the retinal pigment epithelium (RPE)-Bruch's membrane; Green arrows: Intraretinal hyperreflective spots; Orange arrows: Choroidal hyperreflective spots; Yellow arrow: Intraretinal cystic space. Swept-source optical coherence tomography images from 2018, right (C) and left (D) eye. Hyperreflective plaque-like accumulations on the RPE-Bruch's membrane (blue arrow), outer retinal tubulations (red arrow), and hyperreflective intraretinal spots (green arrow)

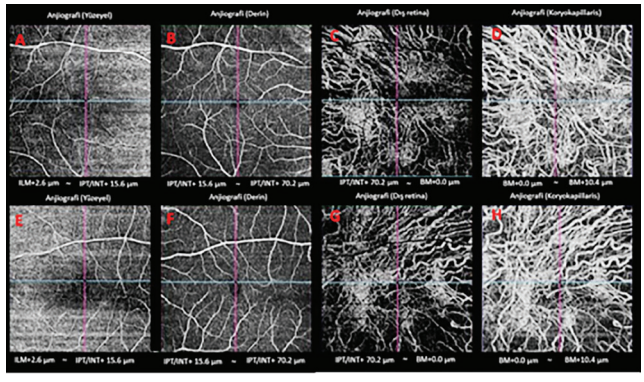

Figure 3. Spectral domain-optical coherence tomography angiography images, 2018: from left to right, projections of the superficial, deep, outer retinal, and choriocapillaris in the right (A-D) and left (E-H) eye. The choroidal vasculature is evident in the area of the outer retina layer projection due to increased permeability secondary to retinal pigment epithelium atrophy, but no flow associated with the choriocapillaris can be seen in the region corresponding to the choriocapillaris projection

reduction of intraretinal crystals, and substantial progression of chorioretinal atrophy. Consistent with the publications cited above, we noted a significant decrease in choriocapillaris flow in SS-OCTA performed 10 years after the first examination.

We believe that OCTA will become an important adjunctive examination in the follow-up of choroidal blood flow and changes in the choroidal vasculature in BCD, a disease that causes progressive vision loss.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ali Osman Saatci, Concept: Ali Osman Saatci, Design: Ali Osman Saatci, Data Collection or Processing: Sefik Can İpek, Ziya Ayhan, Analysis or Interpretation: Ali Osman Saatci, Sibel Kadayıfcılar, Literature Search: Sefik Can İpek, Ziya Ayhan, Writing: Şefik Can İpek, Ali Osman Saatci.

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

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

References

1. Saatci AO, Can Doruk H. An Overview of Rare and Unusual Clinical Features of Bietti's Crystalline Dystrophy. Med hypothesis Discov Innov Ophthalmol. 2014;3:51-56.
2. Ng DS, Lai TY, Ng TK, Pang CP. Genetics of Bietti Crystalline Dystrophy. Asia Pacific J Ophthalmol (Phila). 2016;5:245-252.
3. Saatci AO, Yaman A, Oner FH, Ergin MH, Cingil G. Indocyanine green angiography in Bietti's crystalline retinopathy. Can J Ophthalmol. 2002;37:346-351.
4. Saatci AO, Doruk HC, Yaman A, Oner FH. Spectral domain optical coherence tomographic findings of bietti crystalline dystrophy. J Ophthalmol. 2014;2014:739271.
5. Hirashima T, Miyata M, Ishihara K, Hasegawa T, Sugahara M, Ogino K, Yoshikawa M, Hata M, Kuroda Y, Muraoka Y, Ooto S, Yoshimura N. Choroidal vasculature in bietti crystalline dystrophy with CYP4V2 mutations and in retinitis pigmentosa with EYS mutations. Investig Ophthalmol Vis Sci. 2017;58:3871-3878.
6. Miyata M, Oishi A, Hasegawa T, Ishihara K, Oishi M, Ogino K, Sugahara M, Hirashima T, Hata M, Yoshikawa M, Tsujikawa A. Choriocapillaris flow deficit in Bietti crystalline dystrophy detected using optical coherence tomography angiography. Br J Ophthalmol. 2018;102:1208-1212.

DOI: 10.4274/tjo.galenos.2018.79577
Turk J Ophthalmol 2019;49:109-113

Case Report

Vitreomacular Traction and Outer Retinal Structural Changes

Şeyda Yıldırım*, Jale Menteş**, Mine Barış***

*Adıyaman University Training and Research Hospital, Ophthalmology Clinic, Adıyaman, Turkey
**Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
***Buca Seyfi Demirsoy State Hospital, Ophthalmology Clinic, İzmir, Turkey

Abstract

In this case report we aimed to present the outer retinal structural changes secondary to vitreomacular traction (VMT). Outer retinal structural changes occurring secondary to VMT due to incomplete posterior vitreous detachment were described retrospectively with spectral-domain optical coherence tomography in 3 eyes of 3 patients. The patients ranged in age from 58 to 65 years and best corrected visual acuity in the 3 eyes was 4/10, 8/10, and 9/10. All of the patients were symptomatic and exhibited outer retinal microholes at the fovea extending from the retinal pigment epithelium to outer limiting membrane, with an overlying operculum on the detached posterior hyaloid membrane over the macula following spontaneous resolution of VMT. In the mean follow-up period of 32 months, the outer retinal microholes decreased in size but did not completely resolve. As demonstrated in these cases, VMT can cause small outer retinal layer defects without signs of full-thickness macular hole. These lesions can cause symptoms and affect visual function, and may be permanent structural changes.

Keywords: Vitreomacular traction, outer retinal microhole, optical coherence tomography

Introduction

Posterior vitreous detachment (PVD) is the separation of the posterior vitreous cortex from the internal limiting membrane due to liquefaction of the vitreous gel and weakened vitreoretinal adhesion. This detachment process occurs in four stages. Stage 1 involves perifoveal separation of the vitreous with adhesion to the fovea, midperipheral retina, and optic disc. Stage 2 is characterized by complete vitreofoveal separation with persistent adhesion to the midperipheral retina and optic disc. In Stage 3, there is vitreous detachment from the midperipheral retina with persistent adhesion to the optic disc. In Stage 4, also known as complete PVD, the vitreous is completely detached from the optic disc as well.

Various clinical manifestations may be encountered as a result of tractional interactions between the vitreous and retina during progression of PVD. One of these is vitreomacular traction (VMT) syndrome. Vitreomacular traction during the PVD process can cause structural defects such as cysts in the inner and/or outer retinal layers, full-thickness macular hole, and schisis, or can regress spontaneously without causing any structural changes in the retinal layers.[1] In VMT syndrome, visual symptoms such as metamorphopsia, scotoma, and decreased visual acuity may arise due to anteroposterior traction exerted on the macula. Although the pathogenesis of the disease has not been fully elucidated, the ability to visualize the retina and vitreoretinal interface in high resolution with spectral domain optic coherence tomography (SD-OCT) has provided a better understanding of the effects of tractional forces on the retina and macular surface.[1]

In this article, we present three eyes of three patients with microdefects that developed secondary to VMT in the outer retinal layers only, without causing any anatomic abnormality in the inner retinal layers, together with their follow-up results.

Address for Correspondence: Şeyda Yıldırım MD, Adıyaman University Training and Research Hospital, Ophthalmology Clinic, Adıyaman, Turkey
Phone: +90 536 817 81 67 E-mail: seydayildirim@hotmail.com **ORCID-ID:** orcid.org/0000-0003-1473-9001
Received: 02.02.2018 **Accepted:** 15.09.2018

Case Reports

Case 1

A 58-year-old woman presented with complaints of decreased visual acuity and metamorphopsia in her left eye. Her history was unremarkable and full ophthalmological examination was normal. Color fundus and red-free fundus images (Topcon SD-OCT; Topcon Medical Systems, Paramus, New Jersey, USA) were normal (Figure 1). Best corrected visual acuity (BCVA) of her left eye was 8/10 and SD-OCT (Topcon SD-OCT; Topcon Medical Systems, Paramus, NJ, USA) revealed incomplete PVD and VMT. There was puckering and disorganization of the inner retinal layers due to anteroposterior traction, irregular foveal contour, and a defect approximately 140 microns wide in the external limiting membrane (ELM) and photoreceptor inner segment–outer segment (IS/OS) layers (Figure 2).

After 5 months of follow-up, the VMT spontaneously regressed, after which the patient's metamorphopsia resolved suddenly, BCVA in that eye increased to 9/10, and SD-OCT revealed complete normalization of the foveal contour as well as regression of the irregularities in the inner retinal folds. In addition, an operculum was observed over the macula attached to the residual posterior hyaloid membrane, and a defect 90 microns in diameter persisted in the ELM and IS/OS layers (Figure 3). At 46-month follow-up, the patient was asymptomatic and the defect in the outer retinal layers was found to persist at a size of 68 microns. The operculum on the detached posterior hyaloid membrane over the macula was also visualized using three-dimensional (3D) SD-OCT (Figure 4).

Case 2

A 65-year-old woman presented due to sudden-onset metamorphopsia in her left eye. BCVA was 4/10 in the affected eye and color fundus and red-free fundus images (Topcon SD-OCT; Topcon Medical Systems, Paramus, New Jersey, USA) were normal (Figure 5). Examination of the left eye with SD-OCT (Topcon SD-OCT; Topcon Medical Systems, Paramus, NJ, USA) revealed grade 3 PVD and an operculum over the macula, as well as a 156-micron outer retinal defect in the ELM and IS/OS (Figure 6). The operculum on the residual posterior hyaloid membrane over the macula was also observed in 3D SD-OCT (Figure 7).

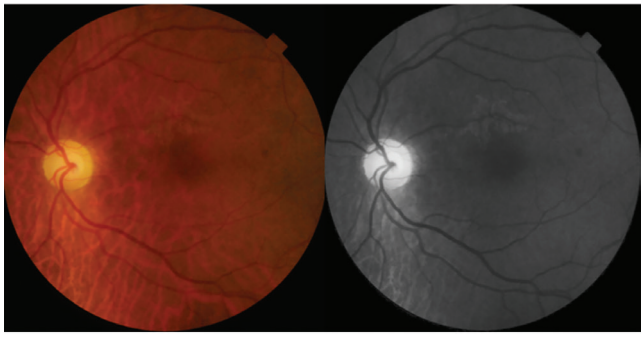

Figure 1. Case 1: Color fundus and red-free fundus images

At 42-month follow-up, BCVA in the affected eye was 6/10 and a 90-micron defect persisted in the ELM and IS/OS (Figure 8).

Case 3

A 59-year-old man presented due to central scotoma that had recently developed in his right eye. BCVA was 8/10 and infrared fundus images (Heidelberg Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) showed a dark spot in the fovea (Figure 9). SD-OCT (Heidelberg Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) revealed grade 3 PVD with an operculum attached to the posterior hyaloid membrane remnants overlying the macula, and a 122-micron defect in the ELM and IS/OS layers (Figure 10).

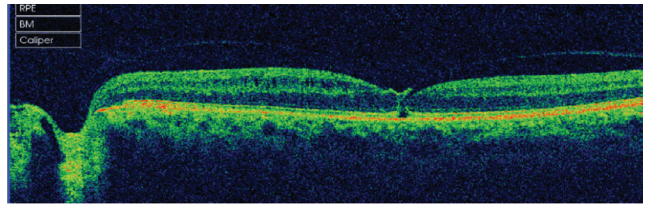

Figure 2. Case 1: Spectral domain optical coherence tomography shows a microdefect in the outer retinal layers at the fovea due to vitreomacular traction

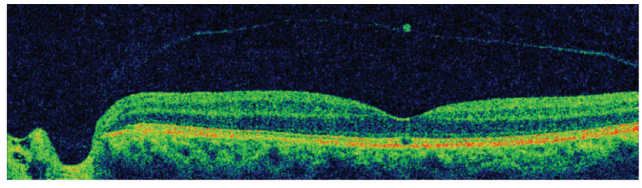

Figure 3. Patient 1: At 5-month follow-up, spectral domain optical coherence tomography shows a defect in the external limiting membrane and inner segment/outer segment line and an operculum on the detached posterior hyaloid membrane

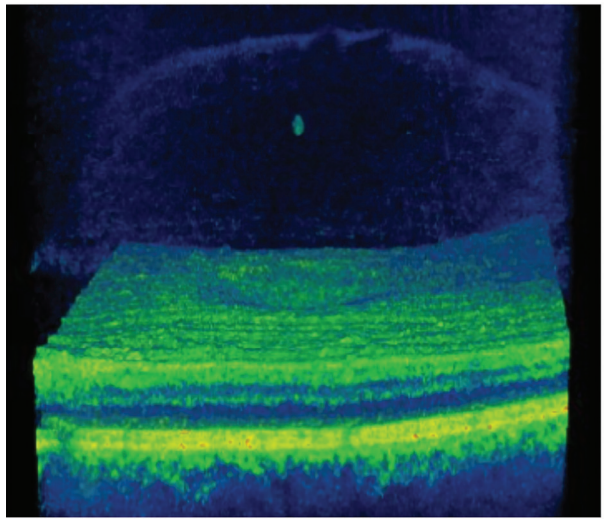

Figure 4. Patient 1: Three-dimensional spectral domain optical coherence tomography shows operculum over the macula on the detached posterior hyaloid membrane

After a 10-month follow-up period, the patient had BCVA of 9/10, persistent central scotoma, and the outer retinal defect was unchanged (Figure 11).

Discussion

In this paper, we present outer lamellar microdefects appearing as disruptions in the continuity of the ELM and IS/OS layers of the retina in OCT in three eyes, two of which were detected after the regression of VMT and the other that was observed both concurrently with and after regression of VMT, as well as their outcomes over a mean follow-up period of 32 months.

Although VMT associated with incomplete PVD is known to frequently cause changes in the inner retinal folds, it was also reported to lead to the development of a rectangular outer retinal defect in the outer macular layers, and these microdefects were referred to as microholes. These outer retinal microholes are defects extending from the inner boundary of the retinal pigment epithelium (RPE) to the outer limiting membrane, including the photoreceptor IS/OS junction.[2] Emerson et al.[3] claimed that the term "microhole", which was coined before OCT, was not accurate to the actual anatomy of these lesions, and that "microcyst" would be a more appropriate term for these small defects of the outer retinal layer at the fovea. In the following years, there was an increase in the number of case

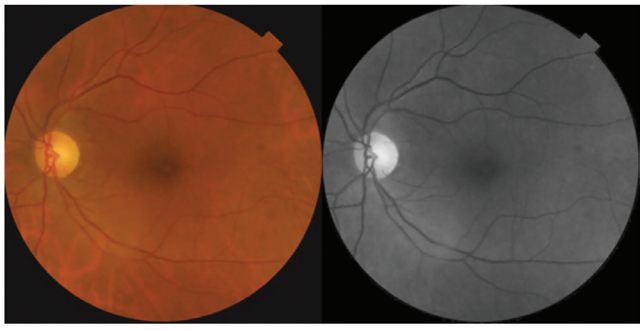

Figure 5. Patient 2: Color fundus and red-free fundus images

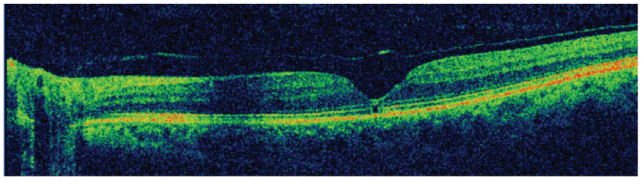

Figure 6. Patient 2: Spectral domain optical coherence tomography shows a microdefect in the external limiting membrane and inner segment/outer segment line and an operculum on the detached posterior hyaloid membrane

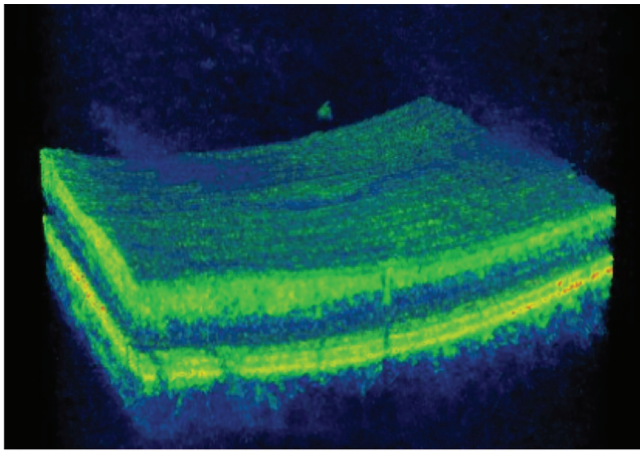

Figure 7. Patient 2: Three-dimensional spectral domain optical coherence tomography shows operculum over the macula on the detached posterior hyaloid membrane

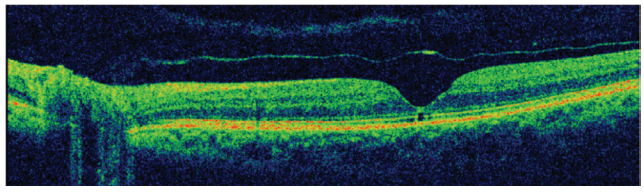

Figure 8. Patient 2: At 42-month follow-up, spectral domain optical coherence tomography showed a microdefect at the external limiting membrane and inner segment/outer segment line

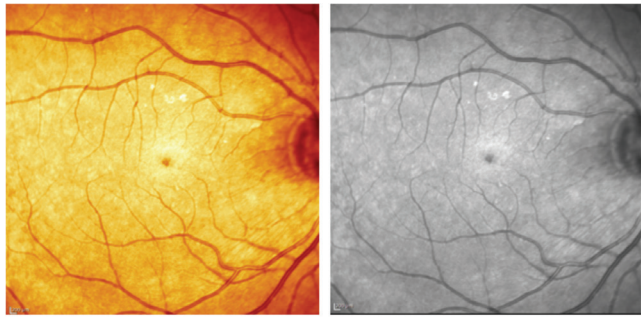

Figure 9. Patient 3: Infrared images

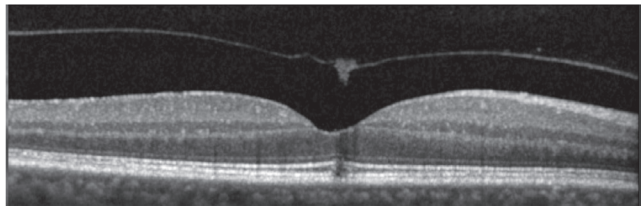

Figure 10. Patient 3: Spectral domain optical coherence tomography shows a microdefect in the external limiting membrane and inner segment/outer segment line and an operculum on the detached posterior hyaloid membrane

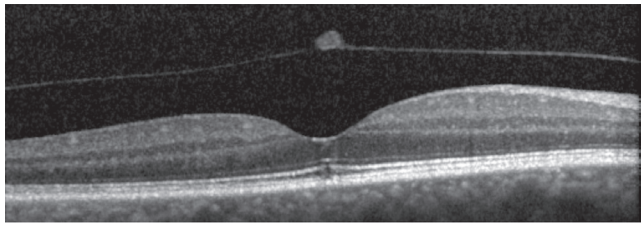

Figure 11. Patient 3: At 10-month follow-up, spectral domain optical coherence tomography shows the persistent microdefect in the external limiting membrane and inner segment/outer segment line

reports and studies attempting to explain the etiology of the new clinical entity of outer lamellar microholes.

Although vitreofoveal traction and trauma are known to trigger the formation of microholes, we have yet to identify all of the etiologic factors.[4] Various studies have reported that they can occur either with or without vitreomacular tractional interactions. In their study investigating 14 macular microholes, Ooto et al.[5] reported that 64% of the eyes (9 eyes) exhibited complete or incomplete PVD, while 36% (5 eyes) showed no signs of PVD or vitreous traction. They suggested the possibility of a primary pathology in this group of microholes that may arise in the photoreceptor layer. Other authors have reported that outer retinal holes may occur as a result of vitreomacular traction as well as a wide range of other conditions such as trauma, solar maculopathy, welder's and tamoxifen maculopathy, juxtafoveal macular telangiectasia, achromatopsia, alkyl nitrate abuse, acute retinal pigment epithelitis, and early Stargardt's disease.[2]

In their report of a single case, Lai et al.[6] detected a full-thickness macular microhole 137 microns in diameter in a patient who had PVD with an operculum on the detached posterior hyaloid membrane, and suggested that this microhole formed when a small piece detached from the fovea due to acute anteroposterior vitreous traction. At 3-week follow-up, they observed apposition of the full-thickness defect in the inner retinal layers, while a small defect persisted in the outer retina at the IS/OS border. Thus the authors reported that outer lamellar microdefects can be seen during the spontaneous resolution of full-thickness defects.

Yu et al.[7] demonstrated oblique traction exerted on the fovea by incomplete PVD using swept-source OCT, and presented the multimodal imaging characteristics of a 38-micron defect in the continuity of the outer retinal layers in the photoreceptor region of the fovea. They used the term "foveal red spot syndrome" to describe this lesion.

Takahashi et al.[8] reported that photoreceptor layer elevation associated with perifoveal PVD can cause the formation of outer retinal microholes.

In all three of our cases, VMT was determined to be the cause of the microdefects in the outer retinal layers. This conclusion was supported by our observations of puckering in all retinal layers and irregular foveal contour due to traction as well as the microdefect that appeared in the ELM and IS/OS layers during our 5-month follow-up of the VMT process in our first case. We believe that the opercula that appeared directly over the fovea on the floating posterior hyaloid membrane after VMT regression and persisted throughout follow-up were formed by detachment of a piece of the outer retinal layer.

Of the publications in the literature describing the characteristics of microdefects (microholes) in the outer retinal layers after VMT, only two have mentioned the presence of foveal operculum, in one case each.[9,10] Similar opercula are known to form over the fovea in full-thickness macular holes caused by VMT, and histopathological examination of samples showed that these opercula include photoreceptor cells.[9,10]

In addition to OCT studies on microholes, there are also microperimetry studies in the literature. Gella et al.[11] evaluated OCT and microperimetry in 12 eyes with defects in the photoreceptor layer at the IS/OS line. They reported that the mean diameter of microholes was 163±99 µm, retinal sensitivity was reduced in the area corresponding to the hole and had a mean of 13.79±4.6 dB, and that microhole diameter was negatively correlated with retinal sensitivity.

With advances in technology, more studies will provide increasingly detailed information. Especially with the widespread use of high-resolution OCT devices, it has been shown that microdefects involving only the outer retinal layers can develop in the fovea. These defects, which appear on OCT as a discontinuity in the ELM and IS/OS layers of the outer retina under the fovea (outer retinal microholes), can arise both during VMT and after resolution of VMT, as seen in our cases. We believe that future studies on these microholes will yield more information on the etiology and natural history of the disease.

Ethics

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Jale Menteş, Şeyda Yıldırım, Mine Barış, Concept: Jale Menteş,Design: Jale Menteş, Data Collection or Processing: Jale Menteş, Şeyda Yıldırım, Mine Barış, Analysis or Interpretation: Jale Menteş, Şeyda Yıldırım, Mine Barış, Literature Search: Seyda Yıldırım, Jale Menteş, Writing: Seyda Yıldırım, Jale Menteş, Mine Barış.

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

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

References

1. Di Antonio L, Toto L, Aharrh-Gnama A, Ciciarelli V, Mastropasqua A, Carpineto P. Retinal structral changes in a case of spontaneous resolution of vitreomacular traction sendrom:multimodal retinal imaging approach. Eur J Ophthalmol. 2015;25:68-72.
2. Comander J, Gardiner M, Lowenstein J. High-Resolution Optical Coherence Tomography Findings in Solar Maculopathy and the Differential Diagnosis of Outer Retinal Holes. Am J Ophthalmol. 2011;152:413-419.
3. Emerson GG, Spencer GR, Klein ML. Macular Microholes. Retina. 2007;27:595-600.
4. Vaishnavi BP, Nair U, Soman M, Nair KG, Spectral domain optical coherence tomography study of macular microhole morphology and its correlation with vitreomacular interface abnormalities. Int Ophthalmol. 2014;34:493-499.
5. Ooto S, Hangai M, Takayama K, Ueda-Arakawa N, Makiyama Y, Hanebuchi M, Yoshimura N. High-resolution imaging of photoreceptors in macular microholes. Invest Ophthalmol Vis Sci. 2014;55:5932-5943.
6. Lai MM, Bressler SB, Haller JA. Spontaneous resolution of macular microhole. Am J Ophthalmol. 2006;141:210-212.

7. Yu S, Bellone D, Lee SE, Yannuzzi LA. Multimodal imaging in foveal red spot syndrome. Retin Cases Brief Rep. 2015;9:97-101.
8. Takahashi A, Ishiko S, Nagaoka T, Kato Y, Kameyama D, Yoshida A. Macular Microhole of the Outer Retinal Defect with a Perifoveal Posterior Vitreous Detachment. Ophthalmic Surg Lasers Imaging. 2010:1-4.
9. Reddy CV, Folk JC, Feist RM. Microholes of the Macula. Arch Ophthalmol. 1996;114:413-416.
10. Grinton ME, Sandinha MT, Stell DH. Photoreceptor Outer Segment on Internal Limiting Membrane after Macular Hole Surgery: Implications for Pathogenesis. Case Rep Ophthalmol. 2015;6:339-344.
11. Gella L, Raman R, Pal SS, Nittala MG, Sharma T. Morphological and functional changes in spectral domain optical coherence tomography and microperimetry in macular microhole variants: spectral domain optical coherence tomographyand microperimetry correlation. Indian J Ophthalmol. 2012;60:53-56.

DOI: 10.4274/tjo.galenos.2018.67670
Turk J Ophthalmol 2019;49:114-116

Case Report

Purtscher-Like Retinopathy Associated with Synthetic Cannabinoid (Bonzai) Use

Zafer Onaran*, Yaprak Akbulut**, Serkan Tursun**, Tevfik Oğurel**, Nesrin Gökçınar**, Ayşegül Alpcan**

*Kırıkkale University Faculty of Medicine, Department of Ophthalmology, Kırıkkale, Turkey
**Kırıkkale University Faculty of Medicine, Department of Pediatrics, Kırıkkale, Turkey

Abstract

Purtscher's retinopathy is a microvascular occlusive disease initially described as retinal edema, cotton wool-like exudation, and hemorrhages occurring after severe head trauma. A similar clinical presentation called Purtscher-like retinopathy is associated with systemic diseases instead of trauma. In the present case, ophthalmic eksamination of a patient with complaints of blurred vision related to substance (Bonzai) use revealed bilateral cotton-wool spots. Purtscher-like retinopathy was diagnosed based on fluorescein angiography and optical coherence tomography findings. This is the first case of Purtscher-like retinopathy associated with Bonzai use described in the literature.

Keywords: Cannabinoid, substance abuse, Purtscher-like retinopathy

Introduction

Synthetic cannabinoids are drugs similar to the active ingredient of cannabis and in recent years their use has increased worldwide, including in Turkey, because they are cheap and easy to obtain. Known as Bonzai and Jamaica in Turkey, these substances affect the central nervous system by binding to cannabinoid 1 and 2 receptors and induce behavioral changes.[1]

Purtscher's retinopathy is a microvascular obstructive disease first described as a result of severe head trauma and characterized by retinal findings of cotton-wool spots and hemorrhage.[2] Purtscher-like retinopathy refers to a similar nontraumatic clinical presentation seen in a wide spectrum of illness including pancreatic disease, hematologic disorders, renal pathologies, and pregnancy-related conditions. Here, we present a case of Purtscher-like retinopathy and severe visual impairment together with serious systemic disorders in an adolescent with a history of synthetic cannabinoid use.

Case Report

A 16-year-old patient with no known diseases presented to the pediatric outpatient clinic with muscle weakness, fatigue, nausea, vomiting, and clouding of consciousness. The patient had signs of meningeal irritation and laboratory test results showed marked elevation in aspartate aminotransferase: 2650 U/L, alanine transaminase: 1110 U/L, creatine phosphokinase: 6765 U/L, amylase: 167 U/L, and lipase: 909 U/L. Based on these results, the patient was admitted for further testing and treatment and was referred to our department due to complaints of vision loss for two days. On examination, visual acuity was 0.05 in the right eye and 0.4 in the left eye. Intraocular pressure, pupillary light reflexes, eye movements, and anterior segment examination were normal. Fundus examination revealed extensive retinal lesions consistent with the appearance of cotton-wool spots in both eyes (Figure 1). Optical coherence tomography (OCT) revealed subretinal fluid and macular edema in both eyes, and fundus fluorescein angiography showed hypofluorescent

Address for Correspondence: Zafer Onaran MD, Kırıkkale University Faculty of Medicine, Department of Ophthalmology, Kırıkkale, Turkey
Phone: +90 533 359 30 75 E-mail: drzaferonaran@yahoo.com **ORCID-ID:** orcid.org/0000-0001-8603-601x
Received: 27.04.2018 **Accepted:** 13.08.2018

areas due to blockage and leakage from the retinal vessels in the late phase (Figures 2 and 3). Provisional diagnoses included Guillain-Barre, toxic hepatitis, hepatic encephalopathy, influenza, rhabdomyolysis, dermatomyositis, and muscular dystrophy. Detection of tetrahydrocannabinol in urinalysis and the patient's reported use of Bonzai when questioned suggested that it was a drug-related condition. Significant abnormalities were detected in coagulation tests: complement factor C3: 41 mg/dL (↓), platelet count: 33,000 (↓), activated partial thromboplastin time: 37.5 s (↑), d-dimer: 14.9 µg/mL (↑), fibrinogen: 160 mg/dL (↑). Evaluation of the patient's ocular findings together with the systemic presentation led to a diagnosis of Purtscher-like retinopathy. In follow-up examination 5 days later, the patient's visual acuity had decreased further (0.05 in the right eye, 0.2 in the left eye) and macular edema showed progression in OCT. Three days after being diagnosed with retinopathy, the patient was started on megadose steroid therapy (1 g/day intravenous for 5 days) due to systemic problems, but was admitted to intensive care due to multiple organ failure and died one week later.

Discussion

After Purtscher's retinopathy was first described in a patient with head trauma in 1910 by Othmar Purtscher, similar clinical presentations observed in nontraumatic conditions became known as Purtscher-like retinopathy. Purtscher-like retinopathy is characterized by severe angiopathy starting within a few hours or days of the onset of systemic disease, with cotton-wool spots in the fundus, intraretinal hemorrhage, and Purtscher flecken in the acute phase. Purtscher flecken are polygonal areas of whitening in the inner retina between the retinal arterioles and venules. These lesions are pathognomonic for the disease but occur in only half of patients.[3] Retinal edema or macular atrophy can be seen on OCT. However, OCT may be normal in some patients. Retinal ischemia, early hyperfluorescence, late leakage, peripapillary staining, and precapillary occlusion are observed on fluorescein angiography.[4] Diagnosis is based on the patient's history, clinical findings, and laboratory tests. Most cases are asymmetrical and bilateral, although unilateral cases are also seen.[2,5]

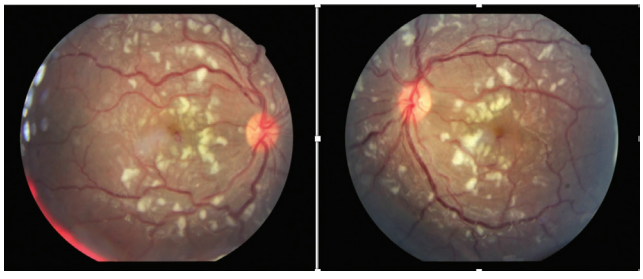

Figure 1. Bilateral cotton-wool spots concentrated in the posterior pole

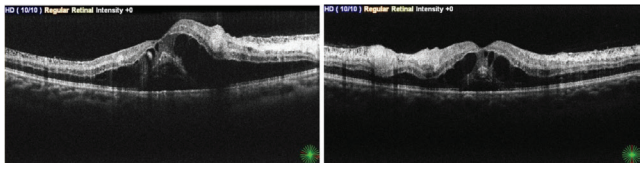

Figure 2. Optical coherence tomography revealed subretinal fluid, cystic macular edema, and hyperreflectivity in the ganglion cell layer corresponding to areas of soft exudate

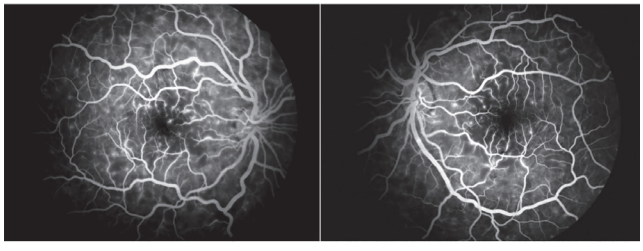

Figure 3. Fundus fluorescein angiography shows hyperfluorescent spots and hypofluorescent areas in regions corresponding to soft exudates

While Purtscher-like retinopathy can occur in acute pancreatitis, systemic lupus erythematosus, hemolysis, elevated liver enzymes, low platelet syndrome, kidney disease, and pancreatic adenocarcinoma, it has also been associated with injection of the filler polymethyl methacrylate.[6,7]

Although there are theories regarding the pathophysiology of Purtscher-like retinopathy based on some underlying systemic diseases, it remains uncertain. The main cause is believed to be arteriole occlusion and ischemia. In patients with acute pancreatitis, proteolytic enzymes released into the systemic circulation due to pancreatic damage may induce the complement cascade and cause the formation of leukocyte, platelet, and fibrin aggregates.[8] The elevated liver, pancreas, and muscle enzymes and abnormal coagulation parameters in our patient may explain the probable arteriolar occlusion implicated in the development of retinopathy.

There is no effective treatment specific for Purtscher's or Purtscher-like retinopathy. Monitoring and treatment of the underlying etiology may be the most rational therapeutic option.[5] Although there are publications on the use of megadose steroid therapy, hyperbaric oxygen therapy, and oral indomethacin in treatment, they do not provide sufficient evidence for a disease that can be self-limiting.[9] While the benefit of intravitreal bevacizumab was reported in the treatment of macular edema associated with Purtscher-like retinopathy, the complete regression of macular edema at 3 months after injection raised questions about its effectiveness.[10]

Negative prognostic factors include choroidal hypoperfusion and involvement of the outer retinal layers, optic disc edema and leakage on angiography, history of a similar attack, and severity of systemic disease; nevertheless, vision recovers to varying degrees without any specific treatment in most cases.[2]

In the literature, conditions such as epileptic seizures, rhabdomyolysis, and liver and pancreas failure have been reported due to synthetic cannabinoids such as Bonzai. This is the first report describing the association between Purtscher-like retinopathy and substance (Bonzai) abuse, and it is important to include Bonzai use in the differential diagnosis of this disease.

Ethics

Informed Consent: Written informed consent was taken from the parents for reporting this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zafer Onaran, Serkan Tursun, Ayşegül Alpcan, Concept: Zafer Onaran, Design: Zafer Onaran, Yaprak Akbulut, Nesrin Gökçınar, Data Collection or Processing: Yaprak Akbulut, Serkan Tursun, Tevfik Oğurel, Ayşegül Alpcan, Analysis or Interpretation: Zafer Onaran, Serkan Tursun, Tevfik Oğurel, Nesrin Gökçınar, Literature Search: Zafer Onaran, Yaprak Akbulut, Writing: Zafer Onaran, Yaprak Akbulut.

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

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

References

1. Ergül DF, Ekemen S, Yelken BB. Synthetic Cannabinoid 'Bonzai' Intoxication: Six Case Series. Turk J Anaesthesiol Reanim. 2015;43:347-351.
2. Agrawal A, McKibbin MA. Purtscher's and Purtscher-like retinopathies: A review. Surv Ophthalmol. 2006;51:129-136.
3. Proença Pina J, Ssi-Yan-Kai K, de Monchy I, Charpentier B, Offret H, Labetoulle M. "Purtscher-like retinopathy: case report and review of the literatüre. J Fr Ophtalmol. 2008;31:609-613.
4. Miguel AI, Henriques F, Azevedo LF, Loureiro AJ, Maberley DA. Systematic review of Purtscher's and Purtscher-like retinopathies. Eye (Lond). 2013;27:1-13.
5. Sarı ES, Kutlutürk I, Yazıcı A, Tıskaoğlu N. A Case of Unilateral Purtscher Like Retinopathy After Spinal Surgery. Turkiye Klinikleri J Ophthalmol. 2018;27:65-67.
6. Chebil A, Mammouri R, Abdallah MB, El Matri L. Purtscher-like Retinopathy as a Rare Presentation of Cryoglobulinemia. Middle East Afr J Ophthalmol. 2016;23:219-221.
7. Khatibi A. Brazilian booty retınopathy: Purtscher-like retinopathy wıth paracentral acute middle maculopathy associated wıth PMMA injection into buttocks. Retin Cases Brief Rep. 2018;12:17-20.
8. Campo SM, Gasparri V, Catarinelli G, Sepe M. Acute pancreatitis with Purtscher's retinopathy: case report and review of the literature. Dig Liver Dis. 2000;32:729-732.
9. Nor-Masniwati S, Azhany Y, Zunaina E. Purtscher-like retinopathy following valsalva maneuver effect: Case report. J Med Case Rep. 2011;5:338.
10. Nesmith BL, Bitar MS, Schaal S. The anatomical and functional benefit of bevacizumab in the treatment of macular edema associated with Purtscher-like retinopathy. Eye (Lond). 2014;28:1038-1040.