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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/);

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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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Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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Original research articles should have the following sections:

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EDITORIAL

2018 Issue 6 at a Glance:

The Turkish Journal of Ophthalmology brings you its sixth issue of 2018 with six original studies, a review, four case reports, and a letter to an editor.

Subaşı et al. share their *in vivo* confocal microscopy evaluation of adenoviral keratoconjunctivitis, the most common viral conjunctivitis. Even in eyes that exhibit no corneal signs on biomicroscopic examination and are considered to be in the prodromal phase, *in vivo* confocal microscopy reveals an increase in the number of dendritic cells and may be a functional early diagnostic tool (see pages 276-280).

Thymoquinone (a compound found in the plant *Nigella sativa*, also known as black seed, black cumin, and fennel flower) has been shown to have anti-oxidant, anti-inflammatory, and even anti-neoplastic effects *in vivo* and *in vitro*. In a study funded by the Scientific and Technological Research Council of Turkey (TÜBİTAK), Kocatürk et al. evaluated the ability of thymoquinone to reduce inflammation in an experimental dry eye model. They report that although thymoquinone had a beneficial effect on inflammatory cell density, it was not as effective as steroids in the inhibition of inflammatory mediators (see pages 281-287).

Şengör et al. present fascinating information about contact lens users in their survey analysis of responses to 836 questionnaires. One-third of respondents reported seeing an eye doctor regularly, while two-thirds said they see an eye doctor only when they have a problem. Another remarkable finding is that only 55.5% of contact lens users were educated in proper lens use by an ophthalmologist. The main message of this study is that mass media, including social media, should be used to increase the proportion of contact lens users who are educated by ophthalmologists (see pages 288-294).

Elgin et al. compared refractive status and anterior segment parameters in 25 patients with juvenile open-angle glaucoma (JOAG) and 24 healthy control subjects. They report that myopia and refractive parameters associated with myopia (long axial length, thin cornea, deep anterior chamber) were more common among JOAG patients. Exploring causality in the relationship between JOAG and myopia seems to be a good research topic for future studies (see pages 295-298).

Despite the many medical and filtering surgical options available, refractory glaucoma still occurs. In a refractory glaucoma series consisting of 30 eyes, Bezci Aygün et al. report that 180-degree ciliary body ablation by transscleral diode laser cyclophotocoagulation (TSCPC) was effective after the first session in 66.6% and after repeated sessions in 86.7% of the eyes. In addition, the procedure resulted in reduced visual acuity in only 6.6% of the eyes, leading the authors to conclude that TSCPC is a valuable last resort in refractory cases (see pages 299-303).

Bingöl Kızıltunç and Şermet evaluated fundus autofluorescence (FAF) patterns in 150 eyes with age-related maculopathy (AMD) and found that the reticular pattern was the most common and was associated with changes in both early and late AMD. The authors indicated that these findings may be useful in monitoring disease progression in early AMD (see pages 304-308).

Researchers Cem Şimşek, Murat Doğru, Takashi Kojima, and Kazuo Tsubota from the Tokyo-Keio University Department of Ophthalmology did not leave our request for an invited review unanswered, and addressed this hot topic under the title "Current Management and Treatment of Dry Eye Disease." Their review presents an extremely comprehensive as well as easily comprehensible table detailing recommended treatment methods for dry eye disease which will surely be an important bedside reference. In addition, the Japan Dry Eye Society's Tear Film-Oriented Treatment scheme is an example of a new systematic approach (see pages 309-313).

For the first time in the medical literature, Gedar Totuk et al. describe in this issue of our journal a patient with sectoral ciliary body agenesis, an embryonic ocular developmental disorder, associated with complicated cataract detected by ultrasound biomicroscopy (see pages 314-316).

Sül and Karalezli bring attention to the issue of intracameral antibiotic therapy in complicated eyes with a case that illustrates how intracameral cefuroxime injection, which is recommended routinely to reduce the incidence of

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endophthalmitis, can cause retinal infarction due to deterioration of the barrier between the anterior and posterior segments in complicated surgeries (see pages 317-319).

Gönül et al. raise our awareness of spontaneous lens absorption in hypermature cataract with their case report in which capsular remnants in the vitreous of an eye with Fuchs Uveitis Syndrome (FUS) misleadingly appeared in examination as crystalline lens luxation (see pages 320-322).

Sızmaz et al. report a case of bilateral panuveitis that was induced by and regressed with cessation of vemurafenib, a strong oral BRAFV600 inhibitor, given after nodular melanoma surgery. The authors provide an example of a serious unintended effect of targeted agents used in cancer treatment (see pages 323-325).

We believe that our colleagues will greatly benefit both from the important awareness-raising studies and case reports in this issue and from the review, which will serve as a valuable bedside reference for dry eye.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

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Turk J Ophthalmol 2018;48:276-280

Original Article

In Vivo Confocal Microscopy Analysis of the Corneal Layers in Adenoviral Epidemic Keratoconjunctivitis

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Abstract

Objectives: To describe the clinical features and microstructural characteristics assessed by *in vivo* confocal microscopy (IVCM) in patients with adenoviral epidemic keratoconjunctivitis (EKC).

Materials and Methods: The study included 20 eyes of 12 patients who presented to the Kocaeli University Medical Faculty, Department of Ophthalmology with complaints of watering, crusting, and stinging, were clinically diagnosed EKC, and were examined by slit-lamp biomicroscopy and IVCM during the prodromal phase and the punctate keratitis, deep epithelial keratitis, and subepithelial infiltration stages of EKC.

Results: While biomicroscopic examination findings were normal during the prodromal period of EKC, IVCM showed an increase in Langerhans cell numbers in the subbasal plexus. After onset of clinical EKC, the punctate epithelial keratitis stage was characterized by findings of hyperreflective cell clusters in the basal epithelium layer, increased accumulation of Langerhans cells in Bowman's layer, and hyperreflectivity in the anterior stromal layers. In the deep epithelial keratitis stage, the basal epithelial cells displayed peripheral hyperreflectivity and the hyperreflectivity of the anterior stromal surface increased and became more rounded. In the subepithelial keratitis stage, these findings persisted in addition to increased anterior stromal surface hyperreflectivity and focal round plaques.

Conclusion: This study shows that the inflammatory process in the cornea starts in the prodromal period of EKC. Massive inflammation of the epithelium and stroma was observed in the active phase and focal changes were observed on the anterior stromal surface starting in the subepithelial infiltration period.

Keywords: Adenovirus, epidemic keratoconjunctivitis, epithelial keratitis, confocal microscopy, subepithelial infiltrates

Introduction

The most common cause of viral conjunctivitis is adenoviruses. Adenoviral conjunctivitis can manifest clinically as acute follicular conjunctivitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis (EKC), or chronic conjunctivitis. EKC caused by adenovirus serotypes 8, 19, and 37 occurs in epidemics, particularly in the summer months, presents with keratitis in 80% of cases, and shows the most severe clinical course.[1]

EKC is one of the viral diseases that cause severe ocular surface inflammation. After a prodromal period of 7-10 days, unilateral or bilateral follicular conjunctivitis develops; within 2-4 days after onset of conjunctivitis, diffuse epithelial keratitis appears, followed by focal epithelial keratitis. A subepithelial infiltration period begins in the third week, and this clinical presentation may last for weeks or even months.[2,3,4]

In vivo confocal microscopy (IVCM) is a non-contact imaging method that enables evaluation of the cornea at the cellular level.[5] In addition to having a well established place in the

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diagnosis and follow-up of many corneal diseases, studies including IVCM findings have also shown corneal changes in the various stages of EKC. These studies described changes starting at the basal epithelium level and extending into the midstroma, while images targeting the subepithelial infiltration period showed focal inflammatory foci.[6,7] In this study we sought to use IVCM to elucidate corneal alterations that begin in the prodromal period of EKC, evaluate findings seen in the clinical course of the disease, and discuss our results within the context of the literature.

Materials and Methods

The study included 20 eyes of 12 patients (6 males, 6 females) who presented with complaints of burning, watering, and discharge from the eyes and were clinically diagnosed with EKC in the ophthalmology outpatient clinic of the Kocaeli University School of Medicine. Ethical approval was obtained from the university ethics committee, and informed consent was obtained from all participants prior to examination.

Following clinical assessment with biomicroscopy, patients underwent IVCM (Rostock Cornea Module/Heidelberg Retina Tomography 3, Heidelberg Engineering GmBH, Germany) examination under topical anesthesia (0.5% proparacaine Hydrochloride; Alcaine®; Alcon Laboratories, Fort Worth, TX, USA). A new sterile polymethylmethacrylate cap (Tomocap®; Heidelberg Engineering GmBH, Germany) was placed over the objective lens for each patient. Gel (Viscotears®; Carbomer 980, 0.2%; Novartis, North Ryde, Australia) was applied to the cap at the start of imaging. The distance between the cornea and objective was monitored on the camera display as imaging was initiated. After visualizing the surface epithelium on the screen, the objective lens was manually focused to acquire images of the corneal layers sequentially until reaching the endothelium.[8]

At initial examination, patients underwent IVCM both in the eye diagnosed with EKC and the eye with no clinical signs. IVCM imaging was done in the patients' healthy, non-EKC eyes at each follow-up visit in order to capture images in the prodromal period. For the patients whose healthy eyes developed clinical EKC during follow-up, eyes imaged by IVCM within the 7-10 days prior to the appearance of EKC signs were evaluated as prodromal (4 eyes), while eyes that did not develop clinical EKC and remained healthy throughout follow-up were evaluated as the control group (4 eyes). Of the imaged eyes with clinical disease, the routine ophthalmologic examination findings, anterior segment photographs, and IVCM findings of 4 eyes with punctate epithelial keratitis, 4 eyes with deep corneal keratitis, and 4 eyes with subepithelial infiltration were evaluated. Slit-lamp microscopy findings and disease stages were recorded. IVCM findings were scored as 0 (same as control), + (slight increase compared to control), ++ (moderate increase compared to control), and +++ (extreme increase compared to control).[6] All assessments were done at different stages in different patients; disease stages in which patients were examined are shown in Table 1. Patients with history of any ocular disease or with any chronic systemic disease were not included in the study. All eyes with active clinical EKC were treated with topical 0.3% tobramycin (Tobrased, Bilim İlaç, İstanbul, Turkey) 6 times a day and preservative-free artificial tears (Tears Naturale Free, Alcon) 8 times a day. None of the patients in the study were treated with steroids. All treatment except preservative-free tears was discontinued when clinical symptoms had resolved, after about 14 days of treatment.

Results

Clinical features, disease stages, slit-lamp examination findings, and IVCM findings of the patients are given in Table 1. In eyes examined in the prodromal period before the onset of clinical EKC, the epithelial, Bowman's, and stromal layers appeared normal in IVCM, while the subbasal plexus showed an increased number of Langerhans cells (Figure 1).

Clinical EKC eyes evaluated during the punctate epithelial keratitis stage showed cell clusters surrounded by inflammatory cell infiltration in the basal epithelium. An increased number of branching dendritic cells were observed in Bowman's layer. Hyperreflective cells were noted in the anterior stroma (Figure 2).

Eyes in the deep epithelial keratitis stage showed basal epithelial cells with peripheral hyperreflectivity in keratitis foci, inflammatory cells in the form of punctate hyperreflectivity, and the hyperreflective areas in the anterior stroma had acquired round focal borders. The increase in Langerhans cells in the subbasal plexus continued (Figure 3).

In the subepithelial infiltrate period, the basal epithelium still exhibited hyperreflective foci and inflammatory cells, but the areas of anterior stromal hyperreflectivity formed more distinct round hyperreflective plaques. The eyes exhibited no changes in the deep stromal layers or endothelium during the course of EKC (Figure 4).

Discussion

The cornea is the most densely innervated tissue in the body, and this innervation provides corneal sensitivity. Many diseases disrupt corneal sensitivity, including ocular infections, herpetic eye disease, dry eye syndrome, and diabetes.[9,10,11,12,13,14] Animal studies have shown a correlation between corneal inflammation and innervation.[15,16] Hamrah et al.[17] and Liu et al.[18] demonstrated that immature dendritic cells in the cornea had matured after inflammation and transplantations. In noninflammatory, quiet conditions, dendritic cells are found in the central corneal epithelium and anterior stroma, whereas during inflammation they infiltrate the entire cornea, thus preparing it to respond to pathogens.[19] With IVCM enabling *in vivo* visualization of these cells, it has become possible to document their increase in immune active situations.

Corneal involvement occurs during the course of EKC, and various corneal findings can be observed in the different disease stages. Corneal involvement leads to symptoms such as dry eye, glare, blurry or low vision, and irregular astigmatism.[20] No

Table 1. The patients' clinical, slit-lamp microscopy, and *in vivo* confocal microscopy evaluations

				Slit-lamp microscopy			Confocal microscopy		
Patient/ Eye	**Age/ Sex**	**Examination time**	**BCVA**	**Punctate keratitis**	**Deep epithelial keratitis**	**Subepithelial infiltrate**	**Dendritic cells**	**Basal epithelial hyperreflectivity**	**Anterior stromal hyperreflectivity**
1/OD	28/M	Day 7	0.9	+			++	++	+
1/OS		P	1.0				+	0	0
2/OD	40/F	Day 5	0.9	+			+	++	++
3/OS	37/M	Day 6	0.8	+			++	+++	+
4/OS	44/F	Day 4	1.0	+			++	+++	+
5/OD	29/M	Day 10	1.0		+		++	++	++
5/OS		P	1.0				+	0	0
6/OD	65/E	P	1.0				+	0	0
6/OS		Day 12	0.8		+		+++	++	++
7/OD	53/F	Day 14	0.9		+		++	++	++
7/OS		P	1.0				+	0	0
8/OD	42/M	Day 10	1.0	+	+		++	++	+++
9/OD	44/M	Day 20	0.9			+	++	+	++
9/OS		C	1.0				0	0	0
10/OD	38/F	Day 22	0.9			+	+++	+	++
10/OS		C	1.0				0	0	0
11/OD	28/M	C	1.0				0	0	0
11/OS		Day 21	0.8			+	+++	++	+++
12/OD	50/F	C	1.0				0	0	0
12/OS		Day 20	0.9			+	++	++	+++

BCVA: Best corrected visual acuity, OD: Right eye, OS: Left eye, P: Prodromal, C: Control, Scoring is described in the Materials and Methods section. The fellow eyes of patients 2, 3, 4, and 8 were not included in the study

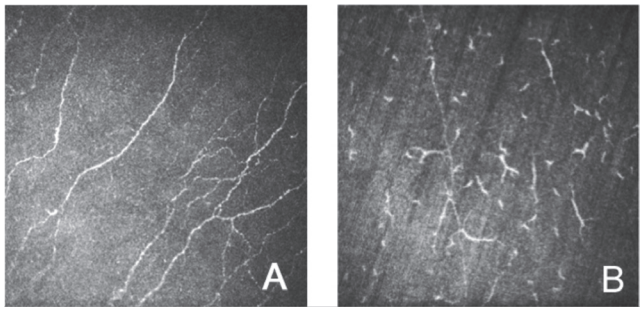

Figure 1. Appearance of subbasal plexus in healthy cornea (A) and increased Langerhans cells in the subbasal plexus in the prodromal period (B)

corneal and conjunctival findings occur in the prodromal period, but clinical signs of conjunctivitis appear within 7-10 days after this period. Despite apparently normal biomicroscopic and clinical findings during the prodromal period, IVCM revealed a marked increase in Langerhans cells in the subbasal plexus in our study, indicating that inflammation has already started. These findings suggest an active prodromal process in the healthy eye that precedes clinical disease.

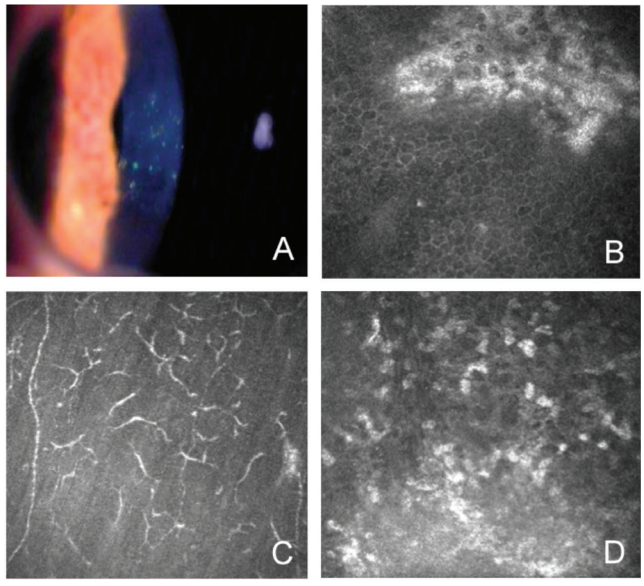

Figure 2. Fluorescein-stained foci of punctate keratitis in the cornea (A); cell clusters in the basal epithelial layer (B); increased Langerhans cells (C); and hyperreflectivity in the anterior stroma (D)

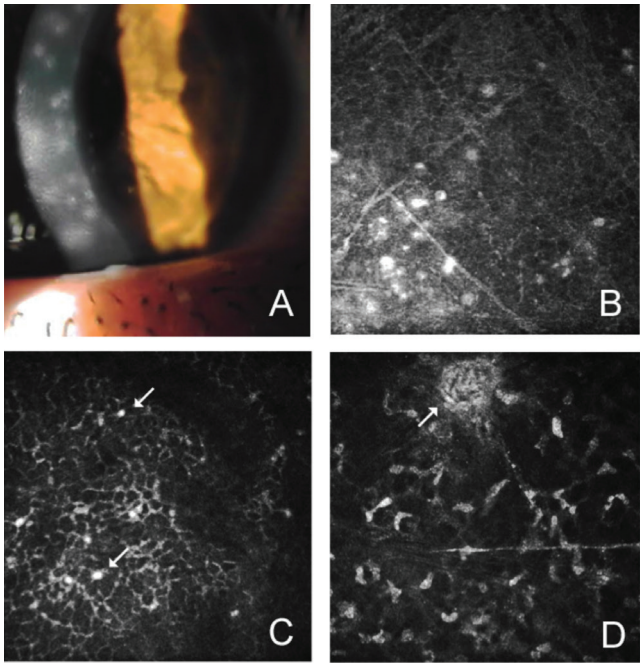

Figure 3. Foci of deep epithelial keratitis (A); hyperreflective inflammatory cells between the basal epithelium and anterior stromal surface (B); basal epithelial cells and inflammatory cells (arrows) with peripheral hyperreflectivity (C); and inflammatory focus in the anterior stroma (arrow) (D)

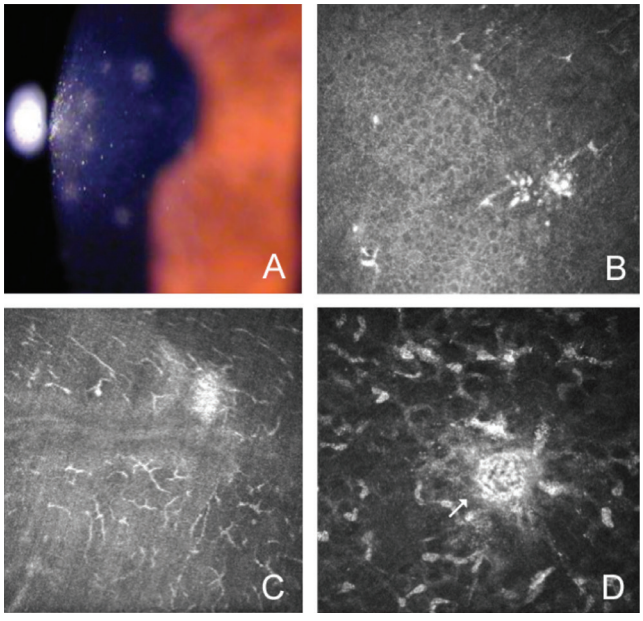

Figure 4. Areas of subepithelial infiltration (A); focus of hyperreflective keratitis in the basal epithelium (B); Langerhans cell connections in the subbasal plexus (C); and focal hyperreflective plaque with round border in the anterior stroma (arrow) (D)

The active follicular conjunctivitis phase is characterized by the formation of corneal punctate epithelial keratitis, followed by a long-term inflammatory process with subepithelial infiltration, believed to be a result of type 4 hypersensitivity reaction. In EKC, inflammatory cell infiltration in the basal epithelium and anterior stromal surfaces has been demonstrated by the higher concentration of dendritic cells observed in IVCM.[6,7,21]

The increase in dendritic cells in the subbasal plexus is considered an important IVCM finding in EKC and herpes simplex keratitis. Öztürk et al.[22] reported that herpetic keratoconjunctivitis can often be confused with adenoviral EKC due to similarities in their clinical course and common IVCM findings. In addition, a temporary reduction in corneal sensitivity has been observed following inflammatory cell activation in 74% of patients with EKC.[22]

In the subepithelial infiltration phase, an increase in inflammatory cells is observed in addition to inflammatory foci in the stroma. Dosso and Rungger-Brandle[6] reported that Langerhans cells were reduced in more advanced disease stages. However, our study encompassed the earlier subepithelial infiltrate stage and showed an increase in Langerhans cells, consistent with the literature.

Conclusion

Our study demonstrates based on IVCM findings that corneal involvement in EKC begins not in the clinical disease stage but in the prodromal phase, with an increase of Langerhans cells. In clinical disease stages, findings such as increased dendritic cells accompanying the development of epithelial keratitis, and hyperreflective plaques in the basal epithelial layer and anterior stromal surface are seen on IVCM. In the subepithelial infiltration phase, lesions become more focal and persist without extension to the posterior stromal surface. Based on our findings, we suggest that corneal findings in IVCM signal the development of clinical EKC starting in the prodromal period.

Ethics

Ethics Committee Approval: Obtained (Project number: KÜ GOKAEK 2016/237).

Informed Consent: Obtained.

Peer-review: Internally peer-reviewed.

Author contributions

Concept: Nurşen Yüksel, Design: Sevgi Subaşı, Nurşen Yüksel, Data Collection and Processing: Sevgi Subaşı, Müge Toprak, Analysis and Interpretation: Nurşen Yüksel, Sevgi Subaşı, Müge Toprak, Büşra Yılmaz Tuğan, Literature Search: Sevgi Subaşı, Writing: Sevgi Subaşı.

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

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Original Article

Effects of Topical Thymoquinone in an Experimental Dry Eye Model

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Abstract

Objectives: To comparatively evaluate the effects of thymoquinone (TQ), the biologically active main component of volatile oil derived from *Nigella sativa* seeds, in an experimental dry eye model.

Materials and Methods: A total of 36 BALB/c mice 10 weeks of age were used in the study. The mice were divided into 6 groups of 6 mice. Two groups were negative and positive controls, and the other 4 groups were treated with balanced salt solution, fluorometholone (FML), TQ, or vehicle (Tween80). After 1 week of treatment, the mice were killed and the eyes removed for histopathologic examination and cytokine analysis. Interleukin (IL)-1α tumor necrosis factor-α, interferon-γ, IL-2, IL-6, IL-10, and lactoferrin levels in the conjunctival tissue were measured by multiplex immunobead assay. The presence of inflammatory cells in ocular tissue samples were investigated by hematoxylin-eosin and periodic acid-Schiff staining. Inflammatory T cells containing CXT receptor in the conjunctiva were determined by flow cytometry.

Results: FLML and TQ groups had less inflammatory cell density and more goblet cells compared to the other groups. High levels of IL-1α and IL-2 were found in the TQ group.

Conclusion: TQ treatment was associated with reduced inflammation in pathological examination, but did not significant lower cytokine levels.

Keywords: Black seed oil, dry eye, thymoquinone

Introduction

Dry eye is a chronic and common eye problem that affects millions of people due to various reasons.[1] Various factors including age, hormone deficiencies, medications, surgery, and systemic autoimmune diseases cause damage to lacrimal functional units and create surface inflammation, which can lead to dry eye symptoms.[2]

Chronic immune-mediated inflammatory processes in the lacrimal gland and conjunctival epithelium gradually cause dysfunction leading to destruction and are involved in the pathogenesis of dry eye. Increased levels of inflammatory

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cytokines, particularly interleukin 6 (IL-6), have been found in the lacrimal gland and conjunctival epithelium and/or in the patient's tear fluid.[3,4,5,6,7] Surface inflammation occurs due to functional lacrimal unit dysfunction and alterations in tear film composition and stability, leading to dry eye disease. Decreased tear production and removal creates a chronic ongoing inflammation cycle.[3]

There is currently no ideal treatment for dry eye disease. Artificial tears containing preservatives or tear support are the main treatment options, but they are palliative measures. Anti-inflammatory treatments for dry eye target mediators or pathways associated with dry eye.[8,9] The use of topical preservative-free corticosteroids or cyclosporine may alleviate dry eye symptoms and provide normalization of the ocular surface.[10,11,12,13,14,15,16] However, current treatment options are limited due to undesired side effects and low effectiveness. Possible side effects of immunosuppressive agents have not been fully established.

Thymoquinone (TQ) is the biologically active main constituent of volatile oil derived from black seed (*Nigella sativa*, also known as black cumin, fennel flower, and various other names), which is popular in Middle Eastern countries. It possesses strong antioxidant properties against oxidative damage induced by a variety of free radical-generating agents. The anti-inflammatory,[17,18] antioxidant,[19,20] and antineoplastic[21] effects of TQ have been demonstrated both *in vivo* and *in vitro*.[22] TQ appears to inhibit PGE_2 production in arachidonic acid metabolism catalyzed by COX-2 more strongly than indomethacin.[18,23]

TQ is proposed to disrupt the pathogenetic mechanisms of dry eye disease through its anti-inflammatory effects. It may also theoretically have a lower side effect profile compared to other agents used in dry eye disease, such as steroids. There is no information available about the therapeutic potential of TQ in ocular tissues.

This research is a pioneer study on TQ and dry eye treatment. The study aimed to comparatively investigate the possible therapeutic efficacy and side effects of black seed oil, which naturally contains high levels of TQ and is easily accessible by the public, in dry eye disease.

Materials and Methods

This study was approved by Institutional Animal Ethics Committee. The project was supported by the Scientific and Technological Research Council of Turkey (Türkiye Bilimsel ve Teknolojik Araştırma Kurumu [TÜBİTAK]; program code: 1002, project number: 214S539). A total of 36 male BALB/c mice approximately 10 weeks of age were used. The mice were randomly assigned to 6 equal groups. One group was a normal control group, while the experimental dry eye (EDE) model was applied in the other 5 groups. The mice in the 6 groups were subjected to the following EDE/treatment conditions: Group 1 (negative control group): no EDE + no treatment; Group 2 (positive control group): EDE + no treatment; Group 3: EDE + sterile Balanced Salt Solution (BSS) (Alcon, Fort Worth, TX, USA); Group 4: EDE + topical 0.1% fluorometholone (FML) (FML®, Allergan, Westport, County Mayo, Ireland); Group 5: EDE + TQ[8]; Group 6 (vehicle group): EDE + topical 0.8% Tween80 (vehicle). Following induction of EDE, approximately 2 µL eye drops were instilled twice daily for 1 week. After this treatment period, the mice were assessed by Schirmer test and tear break-up time (TBUT) assessment to measure tear production and stability, respectively. The mice were then killed; from each animal, one eye was prepared for flow cytometry and multiplex immunobead assay applications and the other for histopathological examination.

Experimental Dry Eye Induction

EDE was induced in the mice by administering 0.2% benzalkonium chloride (BAC) topically to the eyes for 7 days.[24,25]

Preparation of TQ

TQ powder (274666-1G, 2-isopropyl-5-methylbenzoquinone the Sigma-Aldrich, St. Louis, MO) was dissolved in 0.8% Tween80 at a dose of 0.4% and applied topically twice a day to the eyes of mice.[8] Erdurmuş et al.[8] reported that 0.4% TQ was as effective as triamcinolone acetonide.

Tear Volume Measurement

Tear measurement was performed using a modified Schirmer I test. The lower eyelid was pulled down and Whatman 41 filter paper (trimmed by about ¼ to fit mouse eyes) was placed in the palpebral conjunctiva of the lower fornix (at the junction between the middle and temporal thirds). Distance wetted (mm) was measured at 15-second intervals while the eyes remained open. The measurement was repeated 3 times and the average was recorded.

Tear Break-up Time Measurement

TBUT was measured as the time (s) from the first blink after instilling 1 µL sodium fluorescein in the lower conjunctival fornix to the appearance of the first dry spot on the cornea. Measurements were repeated three times and mean values were recorded.

Tissue Collection

The mice were killed under ketamine (50 mg/kg) and xylazine (10 mg/kg) anesthesia. The right eyes were removed and fixed in 10% neutral buffered formalin (NBF) for histopathologic examination. The left eyes were obtained for multiplex immune bead assay and flow cytometry; they were homogenized and used for cytokine analysis.

Histopathological Studies

Bulbar conjunctiva, palpebral conjunctiva, and lacrimal gland samples were examined histologically for inflammatory cells and goblet cells using hematoxylin and eosin stain and periodic acid-Schiff slides. The samples were evaluated in terms of presence of inflammatory cells and goblet cell density in the upper and the lower conjunctival regions.

Enzyme-linked Immunosorbent Assay

The bulbar and the palpebral conjunctival tissue samples were lysed by incubating in radioimmunoprecipitation assay

lysis buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 1% NP-40, and 0.1% sodium deoxycholate 1 µg/mL aprotinin, 1 µg/mL leupeptin) for 30 minutes. After centrifugation the obtained cell extracts and supernatants were stored at -80 °C until analysis. Related pro-inflammatory cytokine levels in the samples were assessed by ELISA using commercial kits (E-Bioscience, Platinium ELISA, Vienna, Austria) as per the manufacturers' recommended protocol.

The supernatants were assessed for levels of IL-1α, tumor necrosis factor-alpha (TNF-α), IL-6, IL-2, lactoferrin, IL-10, and interferon-gamma (INF-γ). The basic 3-step working principle of the assay is as follows: An anti-mouse cytokine antibody was adsorbed onto microwells. Mouse cytokine present in the sample bound to the antibodies coating the microwell. A biotin-conjugated anti-mouse cytokine antibody was added to bind to the mouse cytokine captured by the first antibody (first incubation). Following incubation, unbound biotin-conjugated anti-mouse cytokine antibody was removed during a wash step. Streptavidin horseradish peroxidase (HRP) was added to bind to the biotin-conjugated anti-mouse cytokine antibody (second incubation). Following this incubation, unbound Streptavidin HRP was removed with a wash step, and a substrate solution reactive with HRP was added to the wells (third incubation). A colored product was formed in proportion to the amount of mouse cytokine present in the sample. The reaction was terminated by addition of acid and absorbance was measured at 450 nm. A standard curve was prepared from 7 mouse cytokine standard dilutions and the concentration of mouse cytokine in the sample was determined.

Flow Cytometry

The amount of CD4+ inflammatory T cells containing CXC receptor 3 ligands in the bulbar and palpebral conjunctiva were determined by flow cytometry. In these cells, CD4, CD8, CD45, CD25, CD16, CD56, and CD3 were evaluated by flow cytometry using commercial kits (FITC, LS-C140363).

Statistical Analysis

The data were analyzed using ANOVA. Tukey's test was used for *post hoc* analysis.

Results

The data obtained are summarized in Tables 1 and 2. Figure 1 shows examples of the microscopic findings in each group.

Tear Production

Table 1 summarizes the average tear production before and after treatment. There was a statistically significant difference between the results of Schirmer tests performed before and after the treatment ($p<0.001$). Repeated measures ANOVA confirmed the effect of time for the right eye ($p=0.019$), but the effect of time in the left eye was not statistically significant ($p=0.084$, $f=3.190$). In addition, the interaction between time and interventions was significant for both eyes ($p<0.001$). Within-subject test confirmed the effect of time and its interaction with interventions for the right eye ($p=0.019$ and $p<0.001$, respectively), but not for the left eye ($p=0.084$, $f=3.190$). *Post hoc* tests revealed that the differences were usually due to the control group. The average tear production of the negative control group was significantly greater than that of all other groups.

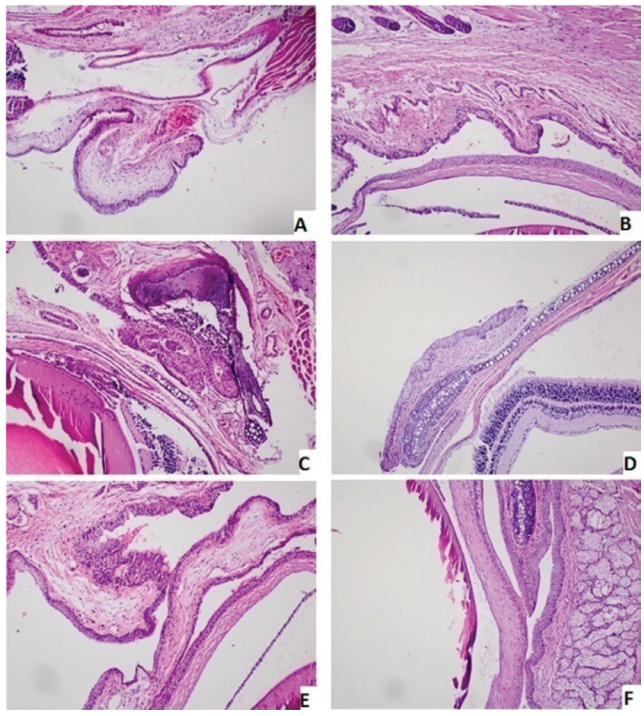

Figure 1. Histopathological findings (x100, H&E): A) Control: A few inflammatory cells and edema; B) EDE Control: Focal mild chronic inflammation; C) EDE+BSS: Intense chronic inflammation; D) EDE+FML: Focal mild chronic inflammation; E) EDE+TQ: Focal mild inflammation; F) EDE+Tween80: Slight to moderate inflammation
EDE: Experimental dry eye, BSS: Balanced salt solution, TQ: Thymoquinone, FML: Fluorometholone, SD: Standard deviation

Pathology

Tissue samples taken from the upper and lower conjunctiva and lacrimal gland were stained with hematoxylin and eosin and periodic acid-Schiff and evaluated in terms of inflammatory cell density and goblet cell numbers. The EDE control group had more inflammatory cells and fewer goblet cells. Among the treatment groups, the FML and TQ groups had lower inflammatory cell density and more goblet cells compared to the other groups. However, the differences were not significant.

Pro-inflammatory Cytokines

Conjunctival IL-1α, TNF-α, IFN-γ, IL-2, IL-6, IL-10, and lactoferrin levels are summarized in Table 2.

Statistical analysis of the data indicated that interventions had a significant impact on IL-1α and IL-2 levels ($p<0.001$). However, their effect on IL-10 level was not statistically confirmed ($p=0.065$, $f=2.353$). *Post hoc* analysis showed that differences usually arose from the EDE+Tween80 and EDE+TQ groups. Especially in the EDE+TQ group, IL-1α levels were significantly higher compared to the other groups. The average IL-1α levels of the EDE+TQ group were higher when

compared to the negative control, EDE control, EDE+BSS, and EDE+FML groups (p<0.001, p<0.001, p=0.026, and p=0.001, respectively). Similarly, the EDE+Tween80 group had higher mean IL-1α levels than the negative control, EDE control, and EDE+FML groups (p<0.001, p=0.001, and p=0.003, respectively). However, compared with EDE+BSS group, the increase in mean IL-1α levels of EDE+Tween80 group was not confirmed statistically (p=0.058, 95% CI: -742.4975-71973.7275).

The difference in IL-2 levels also originated from the EDE+Tween80 and EDE+TQ groups. Tween80 administration caused an important increase in IL-2 levels compared to the control group and FML group (p=0.005 and p=0.046, respectively). However, the difference in mean IL-2 level between the BSS and Tween80 groups was not statistically significant (p=0.055; 95% CI: -27.049-3637.399). There was no significant difference in mean IL-2 levels between the EDE+Tween80 and control groups (p>0.05). However, similar to that of IL-1α, TQ application resulted in a significant increase in mean IL-2 levels compared to the negative control, EDE control, EDE+BSS, and EDE+FML groups (p=0.001, p=0.044, p=0.008, and p=0.006, respectively).

IL-6, INF-γ, and lactoferrin levels were also affected by the intervention, but nonsignificantly (p>0.05). When compared to the control group, Tween80 application also caused an increase in IL-6 values, but it was not statistically significant (p=0.063, 95% CI: -31.626-1,793.493).

Because flow cytometry values for most of the animals in each group were "out of range", the data could not be evaluated statistically.

Table 1. Mean tear production before and after treatment measured by Schirmer I test

Groups	Schirmer I test results (mm) Mean ± SD (minimum - maximum)		
	Pre-treatment	Post-treatment	p values
Right eye			
Negative control	6.0±1.0 (5.0-7.0)		
EDE control	1.2±0.2 (1.0-1.5)	1.0±0.0 (1.0-1.0)	0.175
EDE + BSS	1.0±0.4 (1.0-2.0)	2.1±0.4 (1.5-2.5)	0.002
EDE + FML	1.0±0.5 (0.5-2.0)	2.0±0.5 (1.5-3.0)	0.015
EDE + TQ	1.4±0.4 (1.0-2.0)	2.9±0.8 (2.0-4.0)	0.002
EDE + Tween80	1.2±0.2 (1.0-1.5)	1.8±0.3 (1.5-2.0)	0.141
Left eye			
Negative control	6.0±1.0 (5.0-7.0)		
EDE control	1.3±0.4 (1.0-2.0)	1.0±0.2 (0.5-1.0)	0.102
EDE + BSS	1.3±0.4 (1.0-2.0)	2.0±0.3 (1.5-2.5)	0.030
EDE + FML	1.1±0.2 (1.0-1.5)	2.0±0.7 (1.0-3.0)	0.020
EDE+ TQ	1.2±0.2 (1.0-1.5)	2.8±0.7 (2.0-4.0)	0.003
EDE +Tween80	1.1±0.2 (1.0-1.5)	1.9±0.6 (1.0-2.5)	0.076

BSS: Balanced salt solution, EDE: Experimental dry eye, FML: Fluorometholone, SD: Standard deviation, TQ: Thymoquinone

Discussion

Dry eye disease is a common health problem in the vast majority of society. It occurs in older adults and in autoimmune disorders including Sjögren's syndrome, and can also be seen after keratoplasty and chemotherapy. There are no curative treatment options besides temporary and palliative efforts. Therefore, the search for a permanent and continuous treatment option is ongoing. We investigated the possible therapeutic effects of TQ in an EDE model.

There are alternative measurement techniques to evaluate tear film volume, such as fluorescein staining, rose Bengal staining, phenol red thread test, Schirmer test, tear meniscus height, and TBUT.[26] Clinically, no single test is capable of reliably differentiating individuals with and without dry eye. The Schirmer test is the most common test used in clinical practice to measure the quantity of aqueous tear production. Besides clinical workup, it is also used for experimental studies involving humans and animals.

Studies evaluating the effects of topical *Buddleja officinalis* extract on tear production in a castration-induced dry eye model

Table 2. Mean levels of proinflammatory cytokines

Groups	Mean pro-inflammatory cytokine levels (mean ± SD)					
	IL-1α (pg/mL)	IL-2 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)	Lactoferrin (ng/mL)
Negative control	2903±21	1825±420	710±284	519±340	4418±868	307±35
EDE control	6295±3902	2825±1040	1311±913	578±445	4235±1975	479±223
EDE + BSS	27846±3229	2401±542	987±327	520±543	3567±932	408±122
EDE + FML	13568±1887	2353±459	1204±463	1706±1272	3797±727	367±43
EDE + TQ	67470±1843	4689±1301	1279±263	1104±902	4147±909	378±31
EDE + Tween80	63461±34348	4206±1754	1591±561	1407±986	4491±1637	432±125

EDE: Experimental dry eye, BSS: Balanced salt solution, TQ: Thymoquinone, FML: Fluorometholone, SD: Standard deviation, IL: Interleukin

in male Wistar rats[20] and Victory rabbits[27] revealed a significant increase in Schirmer values compared to untreated controls. Moreover, *B. officinalis* extract instillation decreased TNF-α expression in the lacrimal glands, while there was a significant increase in TGF-1β expression. In other words, *B. officinalis* extract also possesses anti-inflammatory effects.[27]

Corneal bioavailability may be another issue regarding the unexpectedly low effect of TQ on inflammatory cytokines. Topical administration in the eye is the most common and acceptable treatment route for various ocular diseases. However, the major problem of ophthalmic drug delivery is rapid elimination from the pre-ocular area due to anatomical constraints, such as lacrimal secretion, nasolacrimal drainage, and poor corneal permeability. Consequently, only a small amount of drug (1%-10%) permeates through the cornea into the intraocular tissues.[28] TQ is known to be a lipophilic substance. In order to achieve rapid and adequate penetration, a drug must have an optimal lipophilic/hydrophilic balance in molecular structure.[28] We used Tween80 as a solvent to enhance the corneal penetration of TQ.

Among the most popular drug delivery systems for ophthalmic application, lipid nanoparticles have recently received substantial attention. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), regarded as the first and second generation of lipid nanoparticles, respectively, have emerged as promising approaches to deliver drugs due to their ability to prolong the residence time of dosage forms, reduce systemic absorption and administration frequency, and enhance the bioavailability of drugs.[28] Instead of Tween80, SLNs or NLCs might have increased the efficacy of TQ by enhancing its bioavailability.

One study showed that TQ had an inhibitory effect comparable to corticosteroids in a rat model of corneal neovascularization.[8] This inhibition was dose-dependent and its mechanism, although not exactly known, may arise through antioxidant, anti-inflammatory, and immune regulatory factors.

In this study, Tween80 was used to dissolve powdered TQ to facilitate its passage through the corneal tissue. We prepared the TQ-Tween80 suspension as described previously by Erdurmuş et al.[8] Different environmental factors, such as contamination with other chemicals, humidity, and temperature, may alter the concentration and purity of the TQ-Tween80 suspension. Impurity of the suspension may have resulted in unexpectedly low anti-inflammatory effects of TQ. Moreover, this impurity may have caused irritation on the ocular surface and altered the levels of inflammatory and anti-inflammatory cytokine levels as well. We used a concentration of 0.4%, the same as Erdurmuş et al.[8] used for the treatment of corneal neovascularization. The dosage used in our study might have been excessive for the treatment of DED and resulted in adverse toxic and inflammatory effects.

Different animal models[29] have been developed to imitate the pathophysiologic mechanisms involved in dry eye. Each has unique features and limitations, but none exactly matches the pathogenesis of human dry eye. BAC is a well-known preservative commonly used in eye drops and has long been recognized as a potential risk factor for dry eye syndrome because it causes serious ocular surface inflammation. As the major role of inflammation in dry eye is well known, the BAC-induced mouse model seems to be especially appropriate for studies evaluating the therapeutic effects of anti-inflammatory agents on ocular surface inflammation. We preferred to use the 0.2% BAC-induced dry eye model described by Xiong et al.[25]

Onizuka et al.[30] conducted a study to examine the ophthalmic additives responsible for modulating acute corneal epithelial toxicity induced by BAC.[30] Rabbit corneal epithelial cells were examined using the cell proliferation assay. Corneal damage was assessed using scanning electron microscopy. Among the tested additives, only Tween80 prevented BAC-induced cytotoxicity. Corneal epithelial barrier function disorder caused by 0.02% BAC was significantly alleviated by Tween80. In our study, only the group treated with Tween80 showed better results than the TQ group. Excessive TQ concentration or contamination from the environment might have caused the unexpected results in the TQ group. However, we found low levels of inflammatory cytokines, which supported Onizuka et al.'s[30] results.

Despite the positive effect of Tween80 on corneal epithelial cells mentioned above, there are also some reports of anaphylactoid reactions caused by Tween80. Although a drug-induced anaphylactoid reaction is difficult to assay *in vitro* and in conventional animal models, Yang et al.[31] developed a microplate-based quantitative *in vivo* zebra fish assay for assessing anaphylactoid reaction, and quantitatively measured live whole zebra fish mast cell tryptase activity. They concluded that impurity due to oxidized fatty acid residues in Tween80 samples, but not Tween80 itself, may induce anaphylactoid reaction.[31]

IL-6 is a mediator in inflammatory and allergic pathways. When challenged with conjunctival provocation with airborne allergens, atopic keratoconjunctivitis patients showed significant increases in IFN-γ, IL-6, and IL-10 in the tear fluid at 48 hours after provocation.[32] Our results also showed marked elevation in IL-6 levels in the Tween80 group compared to the other groups. However, Tween80 application did not cause a statistically significant increase in IL-6 values when compared to the control group (p=0.063, 95% CI: -31.6266-1,793.4933).

Based on the well-known anti-inflammatory[17,18] and antioxidant[19,20] effects of TQ, positive effects on local inflammation and tear secretion were expected. The effects of TQ on dry eye and related inflammatory conditions were evaluated with biochemical and histopathological methods.

According to our data, artificial tear interventions had a partial positive effect when tear production was taken into account. In pathological examination, a reduction in inflammation was observed with TQ treatment; however, when compared to controls for the variables in the cascade of inflammation, high levels of IL-1α and IL-2 were seen in the TQ group, which may indicate systemic inflammation.[33] One of the reasons for these findings may be inappropriateness of the substance for use on the ocular surface. When carefully examined, similar findings can be seen with Tween80. The TQ or Tween80 used in this study may not be pure enough to use in the eye; pyrogens in the solution

may have triggered inflammation, thus limiting improvement in tear secretion caused by TQ. Another reason may be that TQ was administered at a lower dose than needed. Topical application of TQ helped reduce inflammation pathologically, but might not have been enough to reduce systemic inflammation. This study can serve as a basis for further studies examining these relationships.

Conclusion

The method used in this study effectively induced EDE in BALB/c mice. Our pathological findings confirmed that groups treated with FML and TQ had lower inflammatory cell density, suggesting an anti-inflammatory effect of TQ on the eye. However, TQ was not associated with significant reduction in cytokine levels.

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The study was conducted in Adnan Menderes University, the laboratory tests were also performed in the laboratories of Adnan Menderes University.

Ethics

Ethics Committee Approval: This study was approved by Institutional Animal Ethics Committee.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Tolga Kocatürk, Design: Tolga Kocatürk, Erol Erkan, Muharrem Balkaya, Data Collection or Processing: Tolga Kocatürk, Erol Erkan, İbrahim Meteoğlu, Mehmet Ekici, Aslıhan Karul Büyüköztürk, İrfan Yavaşoğlu, Harun Çakmak, Volkan Dayanır, Muharrem Balkaya, Analysis or Interpretation: Tolga Kocatürk, Erol Erkan, İbrahim Meteoğlu, Mehmet Ekici, Aslıhan Karul Büyüköztürk, İrfan Yavaşoğlu, Harun Çakmak, Volkan Dayanır, Muharrem Balkaya, Literature Search: Tolga Kocatürk, Erol Erkan, İbrahim Meteoğlu, Mehmet Ekici, Aslıhan Karul Büyüköztürk, İrfan Yavaşoğlu, Harun Çakmak, Volkan Dayanır, Muharrem Balkaya, Writing: Tolga Kocatürk, Erol Erkan, Muharrem Balkaya.

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Original Article

Survey to Determine Perceptions and Practices in Contact Lens Use and Identify Key Features of Safe Use Education

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Abstract

Objectives: To identify consumers' tendencies regarding contact lens (CL) use in order to develop recommendations for messages to include in education for safe CL use and in public awareness campaigns.

Materials and Methods: Subjects living in Ankara, Turkey who used eyeglasses and/or contact lenses due to refractive error were included in the study. CL users' reasons for choosing CLs for vision correction, CL-related problems they encountered, and their perceptions regarding safe CL use education and regular ophthalmologic follow-up visits were evaluated using a survey completed by 917 participants.

Results: In total, 836 survey forms were included in the analysis. Most of the participants were female (59.6%), university students (91.4%), and 18-30 years old (68.9%). According to the survey results, 64.6% of eyeglass users stated that they had never tried CLs, while 17.7% reported using CLs regularly. Most of the participants (61.7%) said they visit an ophthalmologist only when they needed, while 33.1% claimed to attend regular follow-up. When all participants were considered, the level of satisfaction with glasses was 3.11 out of 5, while CL users reported satisfaction of 4.15 out of 5. Most (78.6%) of the CL users said they started using CL by their own initiative, most commonly due to a dislike of eyeglasses. The most frequent complaint from CL users was dry eye and discomfort in the evening. The most common source of CL use education was ophthalmologists (55.5% of the participants), followed by opticians (28.2%).

Conclusion: Incorrect and inappropriate information on CL usage may lead to problems that can threaten eye health. The results of our study suggest that providing accurate information through concise messages in physician-supervised education and raising awareness through the media may be beneficial to public health. Therefore, we identified messages about CL usage and quality of life, safety, and the rules for proper use.

Keywords: Contact lens consumer trends, education, message contents, public health

Introduction

Contact lenses (CLs) are temporary prostheses placed on the eye for optical, aesthetic, or therapeutic purposes. Glasses have been the most widely used tool for correcting refractive errors throughout human history. In terms of optical properties, because the lens sits 10-12 mm in front of the eye, glasses have a limiting effect on field of vision and may cause alterations in image size and deviations that reduce the quality of vision, particularly at high diopters. Unlike glasses, CLs correct refractive errors at the ocular surface, which helps widen field of vision, reduce spheric and chromatic aberrations and distortions compared to glasses, improve image quality, and eliminate the esthetic issues associated with glasses. CLs are especially preferred by younger populations because of this optical and esthetic superiority.[1,2,3]

Numerous studies have shown that CLs can lead to serious problems that threaten ocular health if certain basic guidelines of use are not observed, particularly those concerned with

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cleaning.[4,5,6,7,8] It is crucial to raise social awareness regarding the health problems that may be caused by CLs that are purchased without a prescription and used without the proper examination, practical training, and trial provided by an ophthalmologist.[9,10] In the present study, quantitative and qualitative research methods were used in the target population to conduct a detailed analysis of this public health issue, and the results were used to create key messages that can be used in physician-delivered user education and to raise social awareness through mass media.

Materials and Methods

Ethics committee approval was obtained and the study was conducted in compliance with the ethical rules for human research set forth in the Declaration of Helsinki. All participants included in the survey provided written informed consent.

This study was exploratory research employing both quantitative and qualitative research methods to identify user tendencies related to CL use.[9,10]

In the first phase of the study, survey preparation, 35 randomly selected CL users were interviewed in 6 focus groups. For each focus group, the interview was planned to last at least 1 hour. The survey questions were prepared based on the information obtained from these interviews.

For the survey, a sample group representative of the general population was selected from among the residents of the district of Çankaya in Ankara, Turkey who used glasses and/or CLs for refractive correction. A total of 917 people participated in the survey. Participants who had undergone ocular surgery in the previous 3 months or were found to have any active eye disease were excluded from the study. As a result, 836 survey forms were included in the analysis.

Statistical Analysis

Descriptive statistics (percentage, mean, standard deviation) were used to evaluate the data collected. Based on the calculated mean values, we evaluated concepts such as level of satisfaction or concern about the use of CLs and glasses and the CL-related problems encountered by CL users. Weighted total values were calculated and interpreted using rank data in order to determine the relative significance of the reasons for CL avoidance and non-CL users' concerns regarding CL use.

Results

The study findings are presented below under two headings.

1. Focus Group Interviews

A focus group interview is a carefully planned form of discussion/interview performed with a small group led by a moderator in order to obtain detailed information and elicit opinions about a topic defined by the researcher.[11]

A questioning route was used, with all questions prepared in full prior to the interviews. After conducting 6 focus group interviews with a total of 35 glasses/CL users, the frequency and repetition rates of the participants' answers were used to restructure the response options for the survey questions.

2. Survey Results

The respondents' demographic features, duration and status of glasses and CL use, and frequency of ophthalmologist visits were evaluated (Table 1). Of the survey respondents, 59.6% were women and 40.4% were men, and most were high school graduates and university students (91.4%). The majority (68.9%) of participants were 18-30 years old; most had a middle to high income level.

Duration of glasses use was >1 year for the majority of respondents and >10 years in 26.6% of the respondents. Nearly two-thirds (64.6%) of the respondents said they had never used CLs, while 17.7% used CLs continuously, 10.8% used CLs intermittently, and 6.9% had used CLs previously but since stopped. Many (61.7%) of the respondents reported visiting an ophthalmologist when necessary, whereas 33.1% stated that they attended regular follow-up.

When respondents were asked to rate their satisfaction with the use of glasses and CLs (on a scale of 1 to 5), mean satisfaction among the entire group was slightly above neutral for glasses (3.11±1.18), while CL users reported a much higher mean satisfaction level for CLs (4.15±0.73) (Table 2).

Table 1. Demographic and contact lens-related data of the study participants

Characteristic n		Sample	
		n	(%)
Gender	Female	498	59.6
	Male	338	40.4
Age	<18 years	23	2.8
	18-30	577	68.9
	31-40	88	10.6
	41-50	74	8.7
	51-60	50	5.9
	61 years and above	24	3.1
Education level	Primary school	72	8.6
	High school	388	46.4
	University	376	45.0
Income level (monthly)	<890 TL	28	3.3
	891-1600 TL	108	12.9
	1601-3000 TL	258	30.9
	3001-5000 TL	268	32.1
	>5001 TL	174	20.8
Duration using glasses	<1 year	70	8.4
	1-5 years	283	33.9
	6-10 years	260	31.1
	>10	223	26.6
Contact lens use	Continuous wear	148	17.7
	Intermittent use	90	10.8
	Used previously but not currently	58	6.9
	Never used	540	64.6
Visits ophthalmologist	Regularly	277	33.1
	When necessary	516	61.7
	When I need to buy contact lenses	26	3.1
	Other	17	2.0

Table 2. Satisfaction levels of participants using glasses and contact lenses

	Not at all satisfied (1)	Not satisfied (2)	Neutral (3)	Satisfied (4)	Completely satisfied (5)		
	n (%)	n (%)	n (%)	n (%)	n (%)	Mean	Standard deviation
Satisfaction with using glasses (n=836)	91 (10.9)	185 (22.1)	179 (21.4)	297 (35.5)	84 (10.0)	3.11	1.18
Satisfaction with using contact lenses (n=238)	1 (0.4)	5 (2.1)	28 (11.8)	127 (53.4)	77 (32.4)	4.15	0.73

Table 3. Satisfaction levels of participants using glasses and contact lenses according to their contact lens use

	Continuous wear		Intermittent use		Previous use		Never used	
	n	Mean	n	Mean	n	Mean	n	Mean
Satisfaction with using glasses	148	2.3514	90	2.9222	58	3.1379	540	3.3574
Satisfaction with using contact lenses	148	4.3851	90	3.7667				

Table 4. Levels of importance of participants' reasons for contact lens avoidance

	Degree of Importance			Weight		Order of importance
	1	2	3	Total	%	
Using CLs is difficult	255	139	99	1142	34.03	**1**
Using glasses is comfortable	128	168	103	823	24.52	**2**
Using CLs is harmful to the eye	104	140	142	734	21.87	**3**
My ophthalmologist does not recommend CLs	55	44	63	316	9.42	4
CLs are expensive	32	26	82	230	6.85	5
Other	25	10	16	111	3.31	6
Total	599	527	505	3356	100	

*Weighted total: (1st degree frequency x 3) + (2nd degree frequency x 2) + (3rd degree frequency x 1)

When evaluated separately based on CL use, the group with no CL experience was more satisfied with glasses. In contrast, the respondents who reported continuous CL use were least satisfied with glasses, as expected. Degree of satisfaction with CL use also differed between continuous and intermittent users, with continuous users reporting greater satisfaction (Table 3).

The survey included a question for non-CL users (both those who used them previously and those who never used them) regarding their reasons for avoiding CL use. Table 4 shows the importance levels of the possible causes determined according to the focus group interviews. The most important reason for avoiding CL use was the belief that CL use is difficult. The second and third reasons were the convenience of wearing glasses, and the opinion that CLs harm the eyes.

All of the non-CL users were also asked to indicate their level of concern about the difficulties that can be experienced while using CLs. The potential difficulties that have been or may be experienced while using CLs were identified and listed after the focus group interviews (Table 5). Mean values indicate that the biggest concern is the possibility of eye infection due to CL use. Other major problems included fear of the lens sticking to the eye or experiencing a stinging/foreign body sensation. Another potential problem mentioned during the focus group interviews was difficulty with near vision while wearing CLs, but this was not a concern for the non-CL users. Similarly, the beliefs that CLs may lead to refractive error progression, cause cataracts, and prevent laser eye surgery in the future caused less concern than the mean value of 3.284.

Finally, non-CL users were asked to state the source of their concerns about CL use and rank the information sources identified in the focus group interviews based on their importance. The most important source of concerns related to CL use was personal observations, followed by information obtained from immediate social circles, and news in the printed/visual media (Table 6).

The next section of the questionnaire consisted of questions for CL users. Lens users (continuous and intermittent users) were first asked about how/why they started wearing CLs. The response options for this question were based on findings from the focus group interviews. Accordingly, most of the participants (78.6%) stated that they began wearing lenses by their own initiative and 9.2% started following recommendations from others (Table 7).

The participants were asked to rank the factors that influenced their decision to wear CLs in order of importance. The most influential reason was that they disliked and were tired of glasses. Other reasons included esthetic concerns and the inconveniences of glasses (limited vision, fogging, getting wet in the rain, etc.) (Table 8).

When asked about the difficulties they experienced, CL users' most common problem was dry eye, followed by discomfort and stinging in the eye in the evenings as a result of wearing CLs all day long. The least common problems were ocular surface scratches, problems with near vision, and blurred vision. Eye infection, which was the biggest concern of non-CL users, had never occurred in 54.6% of the CL users. Similarly, the fear that

Table 5. Concerns related to contact lens use among participants who did not use contact lenses

Problems	Not at all concerned (1)	Not very concerned (2)	Neutral (3)	Somewhat concerned (4)	Very concerned (5)	Mean	Standard deviation
	n (%)	n (%)	n (%)	n (%)	n (%)		
Problem with near vision	331 (55.4)	91 (15.2)	89 (14.9)	41 (6.9)	46 (7.7)	**1.96**	1.29
Increased refractive error	217 (36.3)	102 (17.1)	129 (21.6)	77 (12.9)	73 (12.2)	**2.47**	1.40
Infection	39 (6.5)	38 (6.4)	93 (15.6)	124 (20.7)	304 (50.8)	4.03	1.22
Itching	35 (5.9)	55 (9.2)	118 (19.7)	156 (26.1)	234 (39.1)	3.83	1.20
Lens sticking to the eye	45 (7.5)	42 (7.0)	100 (16.7)	124 (20.7)	287 (48.0)	3.94	1.26
Lens decentration	45 (7.5)	37 (6.2)	114 (19.1)	144 (24.1)	258 (43.1)	3.89	1.23
Stinging	38 (6.4)	39 (6.5)	127 (21.2)	134 (22.4)	260 (43.5)	3.90	1.21
Burning	42 (7.0)	45 (7.5)	126 (21.1)	143 (23.9)	242 (40.5)	3.83	1.23
Redness	40 (6.7)	57 (9.5)	136 (22.7)	132 (22.1)	233 (39.0)	3.77	1.24
Blurred vision	160 (26.8)	106 (17.7)	123 (20.6)	94 (15.7)	115 (19.2)	**2.82**	1.46
Ocular surface scratches	130 (21.7)	79 (13.2)	106 (17.7)	98 (16.4)	185 (30.9)	**3.21**	1.53
Discharge	146 (24.4)	112 (18.7)	139 (23.2)	84 (14.0)	117 (19.6)	**2.85**	1.43
Evening discomfort	76 (12.7)	69 (11.5)	118 (19.7)	136 (22.7)	199 (33.3)	3.52	1.38
Dryness	70 (11.7)	67 (11.2)	119 (19.9)	129 (21.6)	213 (35.6)	3.58	1.37
Cataract development	199 (33.3)	95 (15.9)	103 (17.2)	68 (11.4)	133 (22.2)	**2.73**	1.55
Prevents future laser surgery	218 (36.5)	73 (12.2)	87 (14.5)	62 (10.4)	158 (26.4)	**2.78**	1.64
Eye loss	242 (40.5)	77 (12.9)	56 (9.4)	44 (7.4)	179 (29.9)	**2.73**	1.71

Values below the overall mean (3.284) are shown in bold

Table 6. Source of concerns about contact lens use

	Degree of importance			Weight		Order of importance
	1	2	3	Total	%	
Personal observations	276	123	79	1153	35.65	1
Immediate social circle (family, friends)	148	200	106	950	29.38	2
Information from ophthalmologist	71	67	95	442	13.67	4
Print/visual media	54	91	152	496	15.34	3
Not concerned	42	10	17	163	5.04	5
Other	6	3	6	30	0.92	6
Total				3234	100	

*Weighted total: (1st degree frequency x 3) + (2nd degree frequency x 2) + (3rd degree frequency x 1)

Table 7. How the participants started using contact lenses

	n	(%)
I started on my own volition	187	78.6
I started based on doctor recommendation	16	6.7
I started based on advice from others	22	9.2
I started to emulate others (friends, celebrities, etc.)	9	3.8
Other	4	1.7

a lens may adhere to the eye was shown to be a misconception that should be dispelled, as most CL users did not experience this problem (Table 9).

When the CL users were asked where they obtained information about how to use CLs, 55.5% reported getting the information from ophthalmologists, and the second most common source was opticians (Table 10).

Discussion

CLs are temporary prostheses placed on the eye for optical, esthetic, or therapeutic reasons and are considered optically and esthetically superior to glasses. Similarly, our results showed that among all participants, the mean level of satisfaction was 3.11/5 for users of glasses and higher in CL users, at 4.15/5.

In spite of their advantages, preference for CLs may not be as high as expected in Turkey. In fact, 64.6% of the participants in our study said they had never tried CLs, while only 17.7% reported using CLs regularly. Based on the inclinations of the group that did not prefer CLs, their main reason for avoidance was the belief that CL use is difficult, and their main concern

Table 8. Importance of reasons influencing the decision to start using contact lenses						
	Degree of importance			Weight		Order of importance
	1	2	3	Total	%	
Disliked/tired of wearing glasses	96	30	30	378	26.05	**1**
Physical discomfort (weight on face, headache, etc.) or necessity (facial structure, eye structure, etc.)	26	32	24	166	11.44	4
Esthetic/visual concerns	40	46	35	293	20.19	**2**
Comments and suggestions from others	8	6	14	50	3.45	7
Emulation of others	5	13	9	50	3.45	8
Disliked/tired of wearing glasses	41	56	43	278	19.16	**3**
Inability to use glasses regularly (difficulties forgetting or carrying, etc.)	5	23	25	86	5.93	6
Refractive error progression	3	6	18	39	2.69	9
Limitation of movement (wearing glasses inconvenient while working/professional reasons, sports, etc.)	13	20	32	111	7.64	5
Total				1451		
*Weighted total: (1st degree frequency x 3) + (2nd degree frequency x 2) + (3rd degree frequency x 1)						

Table 9. Frequency of contact lens-related problems experienced by contact lens users							
Problems	**Never experienced (1)**	**(2)**	**(3)**	**(4)**	**Experience all the time (5)**		
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**Mean**	**Standard deviation**
Difficulty with near vision	152 (63.9)	49 (20.6)	21 (8.8)	8 (3.4)	8 (3.4)	1.62	1.01
Increased refractive error	115 (48.3)	62 (26.1)	37 (15.5)	18 (7.6)	6 (2.5)	1.90	1.08
Infection/keratitis	130 (54.6)	45 (18.9)	39 (16.4)	14 (5.9)	10 (4.2)	1.86	1.14
Itching	58 (24.4)	69 (29.0)	59 (24.8)	30 (12.6)	22 (9.2)	2.53	1.24
Lens sticking to the eye	104 (43.7)	54 (22.7)	39 (16.4)	26 (10.9)	15 (6.3)	2.13	1.26
Lens decentration	58 (24.4)	63 (26.5)	45 (18.9)	40 (16.8)	32 (13.4)	2.68	1.36
Stinging	30 (12.6)	55 (23.1)	66 (27.7)	51 (21.4)	36 (15.1)	**3.03**	1.25
Burning	58 (24.4)	66 (27.7)	50 (21.0)	41 (17.2)	23 (9.7)	2.60	1.29
Redness	68 (28.6)	57 (23.9)	51 (21.4)	36 (15.1)	26 (10.9)	2.56	1.34
Blurred vision	103 (43.3)	52 (21.8)	47 (19.7)	24 (10.1)	12 (5.0)	2.12	1.22
Ocular surface scratches	201 (84.5)	14 (5.9)	16 (6.7)	2 (0.8)	5 (2.1)	1.30	0.81
Discharge	134 (56.3)	55 (23.1)	23 (9.7)	16 (6.7)	10 (4.2)	1.79	1.13
Evening discomfort	52 (21.8)	33 (13.9)	53 (22.3)	49 (20.6)	51 (21.4)	**3.06**	1.44
Dryness	29 (12.2)	53 (22.3)	56 (23.5)	44 (18.5)	56 (23.5)	**3.19**	1.34

was the possibility of eye infection while using CLs. The fact that these well-educated participants' primary source of concern about CL use was information acquired through their own observations or from their immediate social circles suggests a lack of access to sufficient and reliable information through proper and effective channels.

Among the CL users, 78.6% said that they started using CLs on their own initiative, mainly due to disliking glasses and wanting to stop wearing them. Other reasons included esthetic concerns about wearing glasses and the related

Table 10. Source of information about contact lens use		
	n	**(%)**
Ophthalmologist	132	55.5
Optician	67	28.2
Social circles	22	9.2
No such information was given	3	1.3
Other	4	1.7
Ophthalmologist and optician	10	4.2

discomfort (limited vision, fogging, getting wet in the rain, etc.).

On the other hand, CLs are in direct contact with corneal surface and eyelids. Each CL user differs in terms of occupation, environmental conditions, tear film properties, corneal gradient and diameter, and anatomical features such as interpalpebral distance and eyelid shape. Therefore, CLs should be prescribed by an ophthalmologist who can select suitable materials, surface and edge designs, and curvature radius based on variable environmental conditions and eye anatomy and physiology. In best practice, the ophthalmologist chooses a lens according to these individual variables and allows the patient to wear it for a time in order to evaluate compatibility with the ocular surface and eyelids and confirm the refractory power of the lens. After this trial period, the patient is provided a basic theoretical and practical training focusing heavily on cleaning, and finally the lens is prescribed. If CLs are used without the supervision and education provided by ophthalmologists, these important steps are neglected, which greatly increases the likelihood of complications that threaten ocular health, such as corneal ulcers.[4,5,6,7,8] Thus, legislation governing the health care system (Law and Regulation number 5193) states that CL examination must only be done by ophthalmologist, and forbids opticians from selling CLs without a prescription. However, available data indicate that CLs are being sold without prescription and used inappropriately in Turkey.[9,10]

A survey of 443 university students conducted by Dinç et al.[9] revealed that 47.3% of the participants received basic information about CLs from an ophthalmologist, while the rest learned this information from various sources. In addition, only 43.9% of the participants visited the ophthalmologist regularly while using CLs. Similarly, many of the participants in our study (61.7%) reported seeing an ophthalmologist only when needed, while 33.1% visited regularly. The remarkably low rates of regular follow-up in both studies indicate an important deficit.

Donshik et al.[12] noted that nonadherence to guidelines for safe CL wear is still a major contributor to CL-related complications and discontinuation of CL use. They also emphasized that lack of information, bad habits, misconceptions, and the inadequacy of available information sources all play a role in this noncompliance.

Wu et al.[13] evaluated noncompliant behaviors in 210 CL users and identified hand hygiene, improper lens care, and inability to remember follow-up appointments as the main problems, noting that the ability to purchase CLs online results in unawareness regarding follow-up examinations.

As for education in CL use, we also found that only 56% of the participants in our study had received information about how to use CLs from their ophthalmologist, while the other half reported getting that information from people without adequate knowledge and authority. Consistent with previous reports, our study shows that CL users' adherence to basic guidelines, such as attending regular follow-up and receiving practical education in CL use directly from an ophthalmologist, is far below necessary levels. These findings indicate that the public is not adequately informed and aware of these issues.

Ensuring appropriate CL use is a matter of protecting public health and enhancing social awareness. To ensure appropriate CL use, it is key to promote users' awareness of important evidence-based and legally regulated issues related to the examination, procurement, and usage of CLs. To achieve the greatest benefit from this awareness raising, concise messages conveyed in physician-delivered education and via mass media have an important impact on the perceptions of CL users.

Based on this and the findings of our study, the main elements to be emphasized in public awareness and user education are summarized as follows: CLs improve quality of life; CLs are not harmful to the eyes when guidelines for safe use are followed; cleaning and disinfecting are essential; dryness and stinging are common but easily solved problems; and CLs should be used under ophthalmologist supervision. To the same end, initiatives to raise public awareness were implemented by the Turkish Ophthalmological Association Contact Lens Unit as part of the Contact Lens Information Project. Using slogans of "Did you consult your eye doctor?" and "Do you follow the rules?", the campaign yielded positive results, which is promising for the promotion of public awareness in Turkey.

Conclusion

In conclusion, incorrect and inadequate information about CL use may result in problems that threaten eye health. Our findings suggest that disseminating accurate information and proper guidelines through concise messages in physician-provided education and raising awareness via mass media will help protect public health. Therefore, we identified message content about CL usage and quality of life, safety, and rules for proper use.

However, a noteworthy limitation of our study is that data were not collected regarding the participants' refractive error, CL type, and whether they purchased CLs by prescription or online. Subsequent research among CL users that utilizes a survey including these details will further raise awareness of this issue.

Ethics

Ethics Committee Approval: Fatih Sultan Mehmet Traning and Research Hospital 2017/32.

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Sanem Alkibay, Tomris Şengör, Design: Tomris Şengör, Sanem Alkibay, Data Collection or Processing: Sanem Alkibay, Tomris Şengör, Ayşegül Ermeç Sertoğlu, Sevda Aydın Kurna, Analysis or Interpretation: Tomris Şengör, Sanem Alkibay, Ayşegül Ermeç Sertoğlu, Sevda Aydın Kurna, Literature Search: Tomris Şengör, Sanem Alkibay, Ayşegül Ermeç Sertoğlu, Sevda Aydın Kurna, Writing: Tomris Şengör.

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Original Article

Comparison of Refractive Status and Anterior Segment Parameters of Juvenile Open-Angle Glaucoma and Normal Subjects

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Abstract

Objectives: Our aim was to compare the refractive status and anterior segment parameters of patients with juvenile open-angle glaucoma (JOAG) and normal subjects.

Materials and Methods: Twenty-five recently diagnosed cases of JOAG and 24 normal subjects were included in this prospective controlled clinical trial. Central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), axial length (AL), K1 and K2 keratometry, and white-to-white distance (WTW) measurements were performed with optical biometry (LenStar LS 900, Haag Streit Diagnostics). Spherical equivalent (SE) values and anterior segment parameters were statistically compared by chi-square, Kolmogorov-Smirnov, and independent samples t-tests.

Results: The mean age of the 15 male and 10 female JOAG patients was 11.8±2.78 (8-18) years and the mean age of the 14 male and 10 female normal subjects was 11.58±3.04 (7-16) years (age: p=0.51; sex: p=0.18). Mean intraocular pressure in the JOAG group before treatment was 30.08±4.3 mmHg. The mean SE values of the JOAG and the control group were -1.94±1.86 (+2.35/-5.5) and -0.76±2.03 (+2.25/-4.85) diopters, respectively (p=0.048). JOAG patients had lower mean CCT values (p=0.016) and higher mean AL and ACD values (p=0.049 and p=0.016). There were no significant differences between the groups for LT, WTW, K1, or K2 (p=0.61; p=0.52; p=0.95; p=0.31 respectively).

Conclusion: JOAG patients were found to be more myopic and have lower CCT and greater AL and ACD values than normal subjects. These anterior segment changes may be associated with myopia, which is common in JOAG.

Keywords: Juvenile glaucoma, optical biometry, anterior segment parameters, axial length, spherical equivalent

Introduction

Juvenile open-angle glaucoma (JOAG) is a more aggressive subtype of primary open-angle glaucoma (POAG), with an age at diagnosis between 5 and 35 years.[1,2] It is mostly a hereditary disease and has autosomal dominant inheritance.[3,4] JOAG is known to be associated with higher intraocular pressure (IOP) levels and fluctuations than POAG.[1,2,5,6] Myopic refractive state and male gender have also been reported to be associated with JOAG.[2]

Noncontact biometers can provide some anterior segment measurements using the low-coherence reflectometry method.[7,8] Central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), axial length (AL), K1 and K2 keratometry, and white-to-white distance (WTW) can be measured by optical biometers with the help of diode laser.[7,8]

Because myopia was reported to be associated with JOAG, some differences in anterior segment parameters and AL are expected in these patients. In our study, we aimed to compare

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refractive status and anterior segment parameters in patients with JOAG and normal subjects.

Materials and Methods

This prospective controlled clinical trial included 25 eyes of 25 patients recently diagnosed with JOAG and 24 eyes of 24 normal subjects. The glaucoma patients were examined between December 2015 and December 2017 in the Glaucoma Department of Ulucanlar Eye Research Hospital and the control subjects were recruited from among similarly aged patients who presented to our hospital for routine ophthalmological examination. Our study was approved by the Ethics Committee of Ankara Numune Training Hospital and written informed consent was obtained from the patients' parents.

All patients underwent detailed ophthalmologic examinations including best-corrected visual acuity with Snellen chart, anterior and posterior segment examinations, and intraocular pressure (IOP) measurements with Goldmann applanation tonometer. In addition, central corneal thickness measurements by ultrasonic pachymeter, visual field examinations with Humphrey automated perimeter (Humphrey Field Analyzer; SITA Standard 24-2 strategy, model 750i; Zeiss-Humphrey Instruments, Dublin, CA), gonioscopic examination by Goldmann 3-mirror lens in cooperative patients, and retinal nerve fiber layer (RNFL) analysis by spectral-domain optical coherence tomography (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were also done for the diagnosis of glaucoma. For patients who were not cooperative enough for gonioscopy, the iridocorneal angle was visualized by Scheimpflug imaging system (Pentacam, Oculus, Lynwood, WA).

Diagnosis criteria for JOAG were optic nerve head changes such as cup-to-disc (C/D) ratio ≥0.3 and localized neuroretinal rim defects, IOP ≥22 mmHg, glaucomatous changes of optic disc and retinal nerve fiber layer in OCT analysis, and visual field defects such as nasal step, Seidel, or arcuate scotoma, and abnormal glaucoma hemifield test in cooperative patients. Patients older than 18 years old and those with history of any systemic diseases were excluded from the study, as well as any eyes with history of keratitis, uveitis, congenital ocular disease, contact lens use, and ocular surgery or trauma. In addition, eyes with best-corrected visual acuity worse than 20/30 and high spherical equivalent (SE) values (<-6.0 D or >+3.0 D) were excluded from the study.

Statistical Analysis

CCT, ACD, LT, AL, K1 and K2 keratometry, and WTW measurements were obtained by optical biometer (Haag-Streit LenStar® LS 900 Optical Biometer Switzerland) by the same experienced physician (M.U.) for glaucoma cases and control subjects. The measurements were done before anti-glaucoma treatment in glaucoma cases and also before cycloplegia. Chi-square, Kolmogorov-Smirnov, and independent samples t-tests were used for statistical analysis. The Kolmogorov-Smirnov test was used for testing normal distribution of the data and independent samples t-test was used for comparison of the data. The eyes with higher initial IOP values were included in the glaucoma group. The right eyes were included in the control group.

Results

The mean age of the 15 male (60%) and 10 female (40%) patients with JOAG was 11.8±2.78 (8-18) years and the mean age of the 14 male (58.3%) and 10 female (41.7%) normal subjects was 11.58±3.04 (7-16) years. Differences in age and sex distribution between the groups were not statistically significant (age: p=0.51; sex: p=0.18). Ten (40%) of our JOAG patients had family history of JOAG (Table 1).

The mean IOP before treatment was 30.08±4.3 (22-38) mmHg and the mean IOP in the control group was 16.2±2.4 (10-19) mmHg (p<0.001) (Table 1). On clinical examination, vertical C/D ratio was 0.3-0.5 in 9 eyes, 0.6-0.7 in 13 eyes, and 0.8-0.9 in 3 eyes. The mean SE values of the JOAG and the control group were -1.94±1.86 (+2.35 to -5.5) and -0.76±2.03 (+2.25 to -4.85) diopters, respectively (p=0.048) (Table 1). Reliable visual field results could be obtained for 20 JOAG patients. The mean value of the mean deviation of these 20 eyes was -9.61±4.23 dB (between -4.5 and -18.23 dB). Mean circumpapillary RNFL thickness of the 25 eyes with glaucoma was 76.83±12.6 (60.03-100.02) µm.

JOAG patients had significantly smaller mean CCT values (p=0.016) and larger mean AL and ACD (p=0.049 and p=0.016). There were no significant differences between the groups for LT, WTW, K1 or K2 (p=0.61; p=0.52; p=0.95; p=0.31, respectively) (Table 2).

All JOAG patients had bilateral disease. For the eyes in the study group, treatment was initiated with prostaglandin

Table 1. Demographic characteristics of the patients and the intraocular pressure and the spherical equivalent values of the eyes

	JOAG patients	Control group	p value
Sex (n/%)	15 male (60%) 10 female (40%)	14 male (58.3%) 10 female (41.7%)	p=0.18
Mean age (range)	11.8±2.78 (8-18) years	11.58±3.04 (7-16) years	p=0.51
Mean intraocular pressure (range)	30.08±4.3 (22-38) mmHg	16.2±2.4 (10-19) mmHg	p<0.001
Mean spherical equivalent (range)	-1.94±1.86 (+2.35/-5.5) D	-0.76±2.03 (+2.25 / -4.85) D	p=0.048
Family history of glaucoma (n/%)	10 patients 40%	0%	

JOAG: Juvenile open-angle glaucoma, D: Diopter

Table 2. The anterior segment parameters of patients with juvenile open-angle glaucoma and control subjects

	JOAG cases	Control group	p value
AL (mean ± SD) mm	24.63±0.83	23.09±1.44	0.049*
CCT (mean ± SD) µm	521.32±20.07	549.83±35.09	0.016*
ACD (mean ± SD) mm	3.52±0.25	3.30±0.33	0.016*
LT (mean ± SD) mm	3.41±0.38	3.37±0.21	0.61
K1 (mean ± SD) mm	7.81±0.31	7.82±0.16	0.95
K2 (mean ± SD) mm	7.58±0.27	7.63±0.2	0.31
WTW (mean ± SD) mm	12.11±0.62	12.23±0.56	0.52

JOAG: Juvenile open-angle glaucoma, AL: Axial length, CCT: Central corneal thickness, ACD: Anterior chamber depth, LT: Lens thickness, K1: Flat keratometry value, K2: Steep keratometry value, WTW: White-to-white distance; *Statistically significant

monotherapy for 12 eyes, prostaglandin and brimonidine for 5 eyes, and prostaglandin and brinzolamide for 5 eyes. In 3 eyes, trabeculectomy with mitomycin C was performed in order to control glaucoma.

Discussion

JOAG, a rare form of POAG, is characterized by high IOP and glaucomatous optic disc and RNFL changes with normal ocular structure and open iridocorneal angle (±prominent iris processes) and without any systemic disorders.[1,2] The absence of anterior segment disorders like megalocornea, buphthalmos, and other findings of anterior segment dysgenesis is the main difference between JOAG and other childhood glaucomas.[1,2] Our hypothesis in this study was that patients with JOAG exhibit minor differences in the anterior segment. Therefore, we compared the anterior segment parameters and axial length values of JOAG patients with normal subjects. We included recently-diagnosed JOAG cases in our study and used optical biometry working with low-coherence reflectometry.[7,8] We also compared refractive status between JOAG patients and normal subjects, as the parameters we investigated should be associated with refraction.

All of our patients had bilateral JOAG and 40% had family history of glaucoma. Our results are similar to those reported in a study by Aponte et al.[9] in which they investigated the incidence and clinical characteristics of childhood glaucoma. In total, 13.3% of their patients had JOAG. All JOAG cases were bilateral disease and 50% of their patients had family history of the disease.[9]

Our comparison of refractive status in JOAG patients and normal subjects showed that the JOAG patients were more myopic, though the difference was not statistically significant. Park and Kee[6] reported myopic SE values between -3.5 and -7.5 D and large diurnal variations in IOP in their JOAG patients despite maximum medical treatment. They stated that trabeculectomy was more effective in such cases to prevent glaucoma progression.[6] Kwun et al.[2] retrospectively investigated the clinical characteristics of 125 eyes of 72 JOAG patients. Male predominance and myopia were found to be significantly associated with JOAG in their study.[2] We also determined that 63.6% of the JOAG patients in our study were male, consistent with previous studies. Ko et al.[10] compared the risk factors of JOAG and POAG in their study. Myopic refractive state was significantly more common in JOAG than POAG and they stated that axial myopia might be one of the main factors in the pathogenesis of JOAG.[10] Our findings of significantly longer AL in our JOAG patients are also supportive of Ko et al.'s[10] results, due to the relationship between myopia and long AL.

The mean CCT values of glaucoma patients were found to be significantly lower than those of normal subjects in our study. Urban et al.[11] investigated the CCT and endothelial cell density in adult patients with JOAG under topical anti-glaucoma treatment and compared them with ocular hypertension patients without glaucoma therapy. They found significantly lower endothelial cell density in JOAG patients but no significant differences in CCT. Unlike our study, they investigated adult patients with JOAG, as all of our patients were younger than 18 years old. Furthermore, all of our cases had recently diagnosed glaucoma and none of them had used anti-glaucoma treatment before the measurements. Tai et al.[12] investigated CCT and corneal diameter in childhood glaucoma and found a relationship between a larger corneal diameter and thinner CCT. However, their study included patients with all types of childhood glaucoma. Also, in our study no significant differences in WTW values were found between the glaucoma and control groups. Goel et al.[13] presented cases of keratoconus with JOAG in their study and stated that thin CCT associated with keratoconus may be an independent risk factor for glaucoma. However, none of the patients in our study had keratoconus.

JOAG patients showed deeper anterior chambers than normal subjects in this study. An inverse relationship between age and ACD has been shown in both POAG cases and normal subjects.[14] To the best of our knowledge, there have been no previous reports that compared ACD in JOAG patients and normal subjects. This finding may be explained by the greater myopic shift of our glaucoma patients. Myopic eyes have been shown to have deeper ACD than emmetropic and hyperopic eyes.[15] As no significant correlation between IOP and ACD has been shown among POAG cases before, the higher IOP values of our JOAG cases should not contribute to this ACD difference.[16] No significant differences in LT, K values, or WTW values were detected in our study. We measured these parameters before antiglaucoma treatment and excluded patients with previous anti-glaucoma treatment because these agents may affect the structure of the anterior segment.[17,18]

JOAG patients show more posterior segment alterations than POAG patients. Gupta et al.[19] compared the optic discs of primary congenital glaucoma, JOAG, and POAG cases by scanning laser ophthalmoscopy (Heidelberg Retina Tomograph III, Heidelberg Engineering, Heidelberg, Germany). They observed larger optic discs, greater horizontal C/D ratios and concentric enlargement of the cup in JOAG compared with POAG and stated that this may be related to higher IOP values.[19]

In addition, cupping reversal has been demonstrated in pediatric glaucoma cases, unlike with adults.[20,21] The reversal of cupping was proposed to be a result of increased elasticity of the optic nerve head and lamina cribrosa in childhood.[18,19] These posterior segment differences suggested the possibility of anterior segment alterations in juvenile glaucoma patients. Therefore, we aimed to find these differences in our study.

Conclusion

In conclusion, we observed more myopic shift, longer AL, and thinner CCT values in JOAG compared with normal subjects in our study. To the best of our knowledge, there have been no previous reports comparing the anterior segment morphology of JOAG patients and normal subjects. The main limitation of our study is the small patient number. Further investigations with larger patient groups and different types of childhood glaucoma should be encouraged. Furthermore, a comparison with other imaging systems like rotating Scheimpflug camera system or anterior segment OCT should strengthen the results.

Ethics

Ethics Committee Approval: Ankara Numune Hospital (date: 26.03.2014 number: 207962|9-E-14-111).

Informed Consent: Written informed consent was obtained from patients' parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ufuk Elgin, Emine Şen, Concept: Ufuk Elgin, Emine Şen, Design: Ufuk Elgin, Emine Şen, Data Collection or Processing: Ufuk Elgin, Emine Şen. Murat Uzel, Pelin Yılmazbaş, Analysis or Interpretation: Ufuk Elgin, Literature Search: Murat Uzel, Pelin Yılmazbaş, Writing: Ufuk Elgin.

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Original Article

Efficacy of 180° Cyclodiode Transscleral Photocoagulation for Refractory Glaucoma

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Abstract

Objectives: To evaluate the efficacy and safety of transscleral cyclophotocoagulation (TS-CPC) limited to 180° of ciliary body ablation in patients with various forms of refractory glaucoma.

Materials and Methods: Thirty eyes with refractory glaucoma treated with 180° TS-CPC were retrospectively analyzed for intraocular pressure (IOP) reduction and success rates. Patients' age, gender, type of glaucoma, number of diode laser treatment sessions, postoperative complications, number of hypotensive medications required to control IOP, and best corrected visual acuity (BCVA) were evaluated. The criteria for success were defined as postoperative IOP <21 mmHg or >20% decrease in IOP with or without additional medical treatment.

Results: The mean age of all patients was 51.3±26.9 years (range,1-84 years). The mean postoperative IOP level (23.9±8.5 mmHg) was significantly lower than preoperative IOP (39.2±8.9 mmHg) (p<0.001). The success rate was 66.6% after the first laser treatment and reached 86.7% following repeat laser treatments over an average follow-up period of 22.2±19.9 months. The need for topical hypotensive medications decreased from 2.8±1.0 preoperatively to 2.4±1.3 following TS-CPC (p=0.048). Two patients (6.6%) had a one-line decrease in their BCVA following TS-CPC. Transient hypotony and hyphema developed in 4 patients (13.3%). Total laser energy delivered did not correlate with either preoperative (rho=0.10; p=0.594) or postoperative IOP (rho=0.21; p=0.260).

Conclusion: TS-CPC limited to 180° of ciliary body ablation is associated with a reasonable success rate and low incidence of adverse effects in patients with refractory glaucoma.

Keywords: Cyclophotocoagulation, laser, glaucoma

Introduction

Destruction of the ciliary body using various methods is an option for the management of refractory glaucoma when conventional medical and or surgical modalities fail to adequately control intraocular pressure (IOP).[1,2,3] Transscleral cyclophotocoagulation (TS-CPC) is currently a widely employed method of ciliary body ablation that reduces aqueous humor formation by destroying the ciliary body and ciliary epithelium using a continuous diode laser energy source.[4] In its most common form, TS-CPC employs an 810 nm semiconductor diode laser, the energy of which has been shown to be absorbed by melanin in the ciliary epithelium. During this process, the surrounding tissues including the ciliary body and its vascular supply are destroyed by the resultant thermal energy transfer.[5]

TS-CPC has been established as an alternative therapeutic modality to tube shunt or augmented trabeculectomy for refractory glaucoma, especially in eyes with poor visual potential.[6] Reported IOP reduction for this procedure has varied between 12% and 66% in different studies.[1,2,7,8] The extent of response to TS-CPC differs depending on the underlying glaucoma, with higher success rates attained in primary open-angle glaucoma (POAG), neovascular glaucoma (NVG), and inflammatory glaucomas compared with congenital, juvenile, and traumatic

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glaucoma, and glaucoma following cataract surgery (i.e., aphakic glaucoma).[9]

Despite the widespread use of TS-CPC, published reports reveal that treatment centers vary significantly with respect to their laser energy delivery and postoperative management schemes. Extent of ciliary body treatment, total amount of delivered energy, and use of postoperative anti-inflammatory medications are likely to impact overall efficacy and safety outcomes.[2,3,6] It has been shown that more extensive treatment of the ciliary body and total energy delivery of >80 J are associated with unfavorable outcomes such as hypotony and phthisis.[3] Analysis of data from standardized treatment protocols may help refine the TS-CPC technique with potentially improved outcomes and reduced adverse effects. Thus, the purpose of the current study was to evaluate the efficacy and safety of TS-CPC limited to 180° of ciliary body ablation in patients with various forms of refractory glaucoma.

Materials and Methods

This was a retrospective study undertaken at a single academic institution. The study adhered to the tenets of the Declaration of Helsinki and was undertaken with institutional review board approval from the Institutional Ethics Committee for Human Research.

The clinical records of patients who were diagnosed with glaucoma and underwent TS-CPC between 2006 and 2015 were reviewed. Parameters for the study included type of glaucoma, number and type of anti-glaucoma medications, visual acuity, slit-lamp biomicroscopic examination findings, and IOP measurements. Goldman applanation tonometry (GAT) and Perkins tonometry were used to obtain IOP measurements in adults and children, respectively. Data related to pre- and post-treatment IOP levels, complications, and the need for topical glaucoma medications were extracted for all patients. Treatment details included number of sessions and number of diode laser spots applied per session.

The entire treatment protocol was performed under operating room conditions. The procedures were performed under either general anesthesia or retrobulbar anesthesia (3 cc 2% lidocaine, 2 cc 0.5% bupivacaine hydrochloride). TS-CPC was performed using a transscleral contact fiberoptic G probe attached to the OcuLight SLx semiconductors laser unit (Iris Medical, Mountain View, CA, USA). Laser duration was set at 1,500 ms in all patients. The probe was placed approximately 1.5 mm posterior to the limbus. For each session, an area of 180° around the limbus was treated. The laser power was initially set at 1,500 mW and was increased by 150 mW until the "pop" sound was heard, at which time power was decreased until no audible pops were heard, up to a maximum level of 3,000 mW. Transillumination was used to identify the ciliary body position if uncertain, as in congenital glaucoma or in those with a previous history of intraocular surgery. The laser spots were not applied at the 3 and 9 o'clock positions to avoid potential damage to the ciliary vessels and nerve. Following the procedure, topical anti-inflammatory therapy was initiated. Hypotony was defined as an IOP level of ≤5 mmHg. Patients were followed up at 1 day, 1 week, and 1 month after the procedure and every 3 months thereafter. Patients were not included if they were not followed for at least 3 months. The total cyclodiode energy (J) was calculated by multiplying the number of laser burns by the duration (s) of each burn by the power (W) of each burn. If more than one session was applied, cumulative energy amounts from all sessions were calculated.

The criteria for success included IOP <21 mmHg with or without additional treatment, or a >20% decrease in IOP. Patients who were found to have inadequate IOP control at the 1-month postoperative visit or beyond received additional medical or surgical treatments.

Statistical Analysis

Microsoft Excel software (Office Excel 2013, Microsoft Corporation, Redmond, WA, USA) were used for data collection. Descriptive data were presented as mean ± SD. Data analysis was performed using SPSS 22.0 (Statistical Package for Social Sciences; SPSS Inc. IBM, Armonk, NY) software package. Independent samples t-test was used for comparisons or Wilcoxon signed rank test was used where necessary. The Spearman's Rho test was used in correlation analyses. A p value of <0.05 was accepted as statistically significant.

Results

Thirty eyes of 30 patients (16 males, 14 females) were included in this study. The mean age of all patients was 51.3±26.9 years (range=1-84 years). Types of glaucoma included in the study are summarized in Table 1. Neovascular glaucoma was the most common indication for TS-CPC (30.0%). There was no significant difference in preoperative IOP values between the groups (p=0.282). In total, 66.8% of patients had secondary glaucoma.

The mean postoperative follow-up period was 22.2±19.9 months (range=3-84 months) after the first cyclodiode laser application. There was a significant (30.9%) IOP reduction at the 3-month post-treatment visit (27.1±8.1 mmHg) compared to baseline (39.2±8.9 mmHg) (p<0.001). Successful results were obtained in 20 patients (66.6%) at the 1-month post-laser control. Postoperatively, 80% of patients who underwent laser treatment still required anti-glaucoma eye drops for IOP control. Sustained IOP control for a duration of at least 12 months was achieved in 14 patients (46.6%).

A second TS-CPC session was required in 16 patients (53.3%) whose IOP could not be adequately controlled following a mean interval of 5.4±3.0 months from the initial TS-CPC procedure. In this subset of patients, postoperative success was attained in 50% of cases. Following the second treatment session, an overall successful outcome was achieved in 73.3% of study eyes. Four (13.3%) patients needed a third laser session within 12 months. Repeat treatments were performed in eyes which had congenital, juvenile, and neovascular glaucoma (Table 2). During the course of follow-up, one of the patients refused a

repeat laser treatment and two were lost to follow-up after the first 3 months. The fourth patient with congenital glaucoma did not achieve a successful outcome after the third diode laser application. Overall, a successful IOP reduction was attained in 86.7% of the study patients.

At final evaluation, the mean postoperative IOP level (23.9±8.5 mmHg) was significantly lower than the mean preoperative IOP (39.2±8.9 mmHg) (p<0.001). In patients with successful outcomes, the mean percentage of IOP reduction was 43.8±17.3%, 46.7±17.4%, and 43.9±6.3% respectively after the first, second, and third cyclodiode laser treatment sessions. The number of active medications decreased from 2.8±1.0 to 2.4±1.3 following treatment (p=0.048). Mean IOP levels, number of glaucoma medications, and mean amount of total energy are presented in Table 1. Short-term hypotony lasting for <2 weeks was observed in 2 patients (6.6%), and 1 patient (3.3%) with neovascular glaucoma had transient hyphema. Hyphema resolved within 1 month following treatment with observation. In another patient, hyphema and phthisis bulbi were noted 3 years after the procedure when the patient returned for a follow-up visit, but not within the 3-month postoperative follow-up interval. There were no cases of retinal detachment, uveitis, or sympathetic ophthalmia. Visual acuity was <20/400 in 28 patients (93.3%). In the other 2 patients (6.6%), VA decreased by 1 line following TS-CPC. Four patients (13.3%) had no light perception prior to treatment and diode laser was performed for ocular pain control.

The mean age of the patients who required repeated (≥2) diode laser applications (44.2±30.9 years) was not significantly different than those who received a single laser application (59.5±19.4 years) (p=0.112).

The mean number of treatment sessions was 1.6±0.7. The mean laser energy delivered per treatment session was 35.4±16.6 J. The cumulative laser energy delivered after all treatment sessions was 58.9±34.7 J per patient. There was no correlation between the amount of laser energy delivered per session and preoperative IOP level (rho=0.27; p=0.142), postoperative IOP level (rho=0.07; p=0.698), or patient age (rho=0.35; p=0.527). The number of sessions was positively correlated with total delivered energy (rho=0.54; p=0.002) and negatively correlated with postoperative number of glaucoma medications (rho=-0.39; p=0.030). Total amount of energy delivered did not correlate with preoperative IOP (rho=0.10; p=0.594), postoperative IOP (rho=0.21; p=0.260), number of preoperative (rho=-0.08; p=0.662) or postoperative (rho=-0.07; p=0.695) glaucoma medications, nor with mean IOP reduction (rho=-0.09; p=0.626) following diode laser treatment.

Table 2. Evaluation of need for repeat cyclophotocoagulation application based on glaucoma subtypes

Type of Glaucoma	Second procedure (n=16)	Third procedure (n=4)
Congenital	4 (25%)	2 (50%)
Neovascular	4 (25%)	1 (25%)
Juvenile	2 (12.5%)	1 (25%)
Pseudoexfoliation	2 (12.5%)	-
Aphakic	1 (6.25%)	-
Uveitic	1 (6.25%)	-
Traumatic	1 (6.25%)	-
Post-keratoplasty	1 (6.25%)	-

Table 1. Clinical parameters of the study subjects

Glaucoma type	Number and percentage of patients	Pre-laser IOP (mmHg) (mean ± SD)	Post-laser IOP (mmHg) (mean ± SD)	Total delivered energy (J) (mean ± SD)	Pre-laser number of medications (mean ± SD)	Post-laser number of medications (mean ± SD)
Aphakic	3 (10%)	36.6±11.0	32.0±7.9	40.4±17.8	2.0±2.0	2.0±2.0
Congenital	5 (16.6%)	36.6±4.7	27.4±8.5	53.0±21.5	2.8±1.3	2.0±1.5
NVG	9 (30%)	44.1±9.2	20.5±6.1	70.9±44.5	2.6±1.1	2.3±1.2
Juvenile	2 (6.6%)	45.5±14.8	30±5.6	59.1±35.2	3.0±0.1	1.5±2.1
POAG	3 (10%)	34.0±6.5	22.6±8.9	29.8±11.4	3.0±1.0	3.0±0.1
PXG	3 (10%)	32.0±4.5	19.0±7.9	44.2±26.8	3.6±0.5	4.0±1.0
Traumatic	2 (6.6%)	49.0±9.8	30.0±18.3	106.1±22.7	3.0±1.4	2.5±0.7
Uveitic	1 (3.3%)	34.0	26.0	99.4	3.0	2.0
Anterior segment dysgenesis	1 (3.3%)	32.0	13.0	22.5	3.0	3.0
Post-keratoplasty	1 (3.3%)	35.0	17.0	67.5	2.0	2.0
All eyes	**30 (100%)**	**39.2±8.9**	**23.9±8.5**	**58.9±34.7**	**2.8±1.0**	**2.4±1.3**

IOP: Intraocular pressure, NVG: Neovascular glaucoma, POAG: Primary open-angle glaucoma, PXG: Pseudoexfoliation glaucoma

Discussion

Cyclodiode photocoagulation is frequently employed at a clinical stage where adequate IOP control is not achieved despite repeated surgical interventions and maximum medical therapy in glaucoma patients with severely compromised visual function. Despite its proven efficacy, the utility of this treatment modality in achieving IOP control has often been eclipsed by unpredictable responses as well as its potential adverse effects of persistent hypotony and the dreaded complication of phthisis bulbi. The findings of the current study reveal that limiting the extent of laser treatment to 180 degrees is associated with a low incidence of adverse effects and appears to be relatively safe, with about 67% of eyes achieving satisfactory IOP lowering after a single treatment session.

In a previous study using 270° ciliary body ablation on 27 eyes, the cumulative probability of success of TS-CPC was 72% in the first and 52% in the second postoperative year based on success criteria similar to those used in the current study.[10] Another study by Mistlberger et al.[1] found the success rate of this procedure with a single treatment was 66.7% at 1 year and 49.7% after 2 years. Although long-term follow-up data for patients treated with a single session were not available, we observed that the 1-month success rate of 66.6% fell to 46.6% at the end of the first year. Thus, the findings of the current study as well as those from other studies indicate a time-dependent loss of IOP control following TS-CPC.

In our study, the cumulative percentage of eyes successfully treated with a single treatment session was found to be 46.6% at the end of 1 year, with repeat laser sessions resulting in a higher success rate (86.7%) at the end of an average of 22.2 months of follow-up. Similar results were obtained in another study that had a 58.9% success rate after the first laser session and a significant increase to 81.3% success with a second treatment session.[2] Overall, data available from previous studies support the beneficial effect of repeat treatment sessions for IOP control in patients undergoing TS-CPC. Our study findings show that even 180-degree repeat laser treatment is able to provide additional benefit in refractory glaucoma cases.

In a study by Murphy et al.[2] in which TS-CPC was applied over 270° of the ciliary body, the IOP reduction rate was found to be 52.6% in the first 7 months of follow-up. In a similar study, Singh et al.[11] found the reduction in IOP to be 58.5% at 9 months post-treatment. In the current study, the IOP reduction rate was 30.9% and 39.0% at 3 and 22.2 months, respectively. One plausible explanation for the limited IOP reduction observed may be related to the lesser extent of ciliary ablation (180° versus 270°) performed in the current study.

A second laser session was required in 53.3% of patients in our study. This group consisted predominantly of cases of juvenile glaucoma, congenital glaucoma, and neovascular glaucoma. Although we did not observe a greater need for repeat interventions among younger patients, a previous study by Threlkeld and Johnson[12] showed an increased need for multiple laser treatment in young patients, which the authors believed was potentially attributable to a higher level of baseline aqueous humor production and more vigorous healing response in the younger population.

A previous study by Threlkeld and Johnson[12] demonstrated a significant IOP reduction following TS-CPC in patients with neovascular glaucoma and emphasized caution for post-operative hypotony. In our study, two patients who developed hypotony had either neovascular or juvenile glaucoma. In both patients, preoperative IOP values and mean total energy delivered were higher than the total group average (Table 1). Our findings lend support to the hypothesis that high IOP may cause ciliary body ischemia and increase the risk of hypotony, as was also pointed out by Murphy et al.[2]

Oguri et al.[13] compared the Nd:YAG laser and diode laser techniques in neovascular glaucoma and found diode laser to be more effective in IOP control. Mistlberger et al.[1] found that neovascular glaucoma responded well to TS-CPC in their study, but was associated with a higher rate of hyphema and phthisis bulbi. In our study, the mean preoperative and postoperative IOP levels in patients with neovascular glaucoma were 44.1±9.2 mmHg and 20.5±6.1 mmHg, respectively (p=0.008). Despite an overall adequate IOP reduction in these patients, complications including hypotony and hyphema occurred in 2 cases (6.6%). Thus, it is recommended that hypotony may occur infrequently even with 180 degrees of ciliary body ablation and that vigilant IOP monitoring should be practiced even in patients who undergo limited (i.e., 180°) laser ablation.

Schlote et al.[9] suggested that the success rate of TS-CPC may be related to the type of glaucoma. The authors reported a high success rate in patients with POAG (89.5%), NVG (86.8%), and inflammatory glaucoma (75%) and a lower success rate in traumatic (57.1%), aphakic (57.1%), and congenital or juvenile (62.5%) glaucoma.[9] In our study, patients with NVG achieved a success rate of 55% with one and 100% with repeat laser treatment. All cases with POAG (n=3) achieved long-lasting IOP control with a single treatment session. On the other hand, the success rate was unsatisfactory for patients with congenital and juvenile open-angle glaucoma, who required repeat laser sessions and ultimately were unable to achieve adequate IOP control (Table 2). Poor response to treatment in the congenital and juvenile groups may be due to the good ciliary body epithelial healing response in this younger patient population.[12]

In 6.6% of our patients, visual acuity was decreased by 1 Snellen line due to cyclodiode application. In the study conducted by Mistlberger et al.,[1] reduction of visual acuity by ≥2 Snellen lines was reported in 18.7% of patients. In another study by Spencer and Vernon,[14] at least 2 lines of visual acuity loss was detected in 32% of the patients. The reason for this difference may be the already low preoperative visual acuity of the patients included in the current study as well as the small number of patients in the study, which may preclude direct comparisons across studies.

IOP control can be achieved with the use of multiple glaucoma medications in refractory cases of glaucoma. The total number of active molecules used by the study patients in

the current study prior to TS-CPC application was 2.8±1.0. Following diode treatment(s), this number decreased to 2.4±1.3 (p=0.042). Four patients (13%) could be taken completely off topical hypotensive medications following TS-CPC. Thus, the findings of our study are in agreement with those of previous reports showing a reduced need for glaucoma drops following laser treatment, but the need to continue medical treatment in the majority of patients postoperatively.[6,12,15]

As there is no standardization of the magnitude and extent of laser energy used during TS-CPC, it is difficult to make comparisons between different studies. Certain studies reveal a correlation between total amount of energy and success rate[6,16] while others fail to detect this association.[7,9,11] In our study, no association was found between energy delivered and postoperative IOP. This discrepancy may stem from the fact that there is really no anatomic landmark during TS-CPC to ensure exact placement of the probe tip over the ciliary body and no method available to assess the energy delivered to the ciliary body tissue.

Study Limitations

The limitations of the study include the small sample size and its retrospective nature. However, the strength of our study is the availability of data from patients who underwent a homogenous TS-CPC technique; 180° of ciliary body ablation was documented in all cases.

Conclusion

In conclusion, a reasonable IOP reduction can be achieved with 180° cyclodiode photocoagulation in patients with refractory glaucoma. As such, 180° TS-CPC appears to be a safe alternative to the 360° circumferential technique with very low risk of adverse effects for glaucoma patients with a history of previous failed glaucoma surgeries and limited visual potential. The possibility of repeat treatment sessions and the likely need for postoperative glaucoma medications should be discussed with patients prior to TS-CPC to ensure realistic post-surgery expectations.

Ethics

Ethics Committee Approval: Hacettepe University Non-invasive Clinical Research Ethics Committee, GO16 /134-04.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Cem Mocan, Sibel Kocabeyoğlu, Concept: Mehmet Cem Mocan, Sibel Kocabeyoğlu, Murat İrkeç, Design: Murat İrkeç, Data Collection or Processing: Figen Bezci Aygün, Analysis or Interpretation: Mehmet Cem Mocan, Sibel Kocabeyoğlu, Figen Bezci Aygün, Literature Search: Mehmet Cem Mocan, Figen Bezci Aygün, Writing: Mehmet Cem Mocan, Sibel Kocabeyoğlu, Murat İrkeç, Figen Bezci Aygün.

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Original Article

Fundus Autofluorescence Changes in Age-related Maculopathy

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Abstract

Objectives: The aim of this study was to describe the fundus autofluorescence (FAF) findings of age-related maculopathy and risk patterns associated with FAF changes.

Materials and Methods: FAF images of 150 eyes with age-related maculopathy were evaluated retrospectively. FAF patterns were classified as normal, minimal change, focal increase, patchy, linear, lace-like, reticular, and speckled pattern. Correlation between patterns and visual acuity, pattern associations at initial visit, and focal atrophy development and pattern alterations during follow-up were evaluated.

Results: At initial examination, 33.3% of the eyes showed no FAF pattern. In the other eyes, the most common patterns were reticular, focal increase, and patchy pattern at rates of 18%, 14.7%, and 11.3%, respectively. There was no correlation between pattern and visual acuity at initial visit. Two coexisting patterns were observed in 4.6% eyes, and the most common pattern in these combinations was reticular pattern (85.7%). Pattern alterations were observed in 5.3% of the eyes during follow-up. Half of these alterations involved transformation to reticular pattern or addition of reticular pattern to the initial pattern. In addition, 13.3% of the eyes developed focal atrophy during follow-up. Development of focal atrophy was more common with focal increase and reticular pattern, with rates of 45% and 30%, respectively.

Conclusion: Presence of reticular pattern may be a risk factor for change and progression of FAF findings in age-related maculopathy.

Keywords: Fundus autofluorescence, lipofuscin, reticular drusen, age-related maculopathy

Introduction

Age-related macular degeneration (AMD) is a multifactorial degenerative macular disease that causes severe visual loss in elderly patients in industrialized countries.[1,2] Although the exact mechanism of AMD is unclear, accumulation of lipofuscin and alteration of retinal pigment epithelial (RPE) cells play a role in the early stages of the disease. Focal hyperpigmentation, hypopigmentation, and drusen are the main findings of early AMD. Eventually all retinal layers are affected, especially the RPE and photoreceptor layers.[3,4,5]

Fundus autofluorescence (FAF) imaging is one of the important imaging methods for understanding the pathophysiology and establishing the progression of early AMD, because of the lipofuscin accumulation. Recent studies have described FAF changes in early AMD patients.[6,7] These FAF changes are important to identify eyes at risk of progression to late AMD.

This study was conducted to describe FAF findings in early AMD and evaluate FAF changes in early AMD stage.

Materials and Methods

A total of 150 eyes with early AMD were evaluated. Eyes with at least 2 FAF images taken 6 months apart and no accompanying retinal pathology were included in this study. The records and FAF images of the eyes were retrospectively

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reviewed. Ethical approval was obtained according to the Ankara University Faculty of Medicine Ethics Committee of Clinical Research (number: 10-403-13). The study was conducted in adherence to the Declaration of Helsinki.

FAF imaging was performed using a confocal scanning laser ophthalmoscope; the Heidelberg Retinal Angiography 2 (Heidelberg Engineering, Heidelberg, Germany). Short-wave autofluorescence images were recorded at a wavelength of 488 nm via ≥500 nm barrier filter.

FAF patterns were classified as normal, minimal change, focal increase, patchy, linear, lace-like, reticular, and speckled according to the classification of International Fundus Autofluorescence Classification Group.[7]

It is advised to use at least two imaging methods for the detection of reticular pseudodrusen.[8,9] Therefore, reticular pseudodrusen was identified according to the presence of reticular pattern on FAF image and spectral-domain optical coherence tomography (SD-OCT). On FAF images, this pattern was identified as an isoautofluorescent area surrounded by halos of reduced autofluorescence. On SD-OCT it was identified as accumulation of hyperreflective deposits in the subretinal space between the RPE and the junction between the photoreceptor inner and outer segments.

FAF patterns at initial visit and during follow-up were evaluated. Eyes exhibiting two patterns at the same time were classified according to the dominant pattern. The relationship between coexisting patterns was investigated. Pattern changes observed during the follow-up period were recorded. In addition, the association between patterns and presence or development of focal atrophy was evaluated. Correlation between patterns and visual acuity at initial visit was investigated.

Statistical Analysis

All analyses were conducted with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test t he distribution pattern of continuous variables. The results of normally distributed variables were presented as mean ± standard deviation and abnormally distributed variables were presented as median (minimum-maximum). Categorical variables were presented as number and percentage (%). Independent samples t-test was used to compare the means of two independent groups, and Mann-Whitney U test was used to compare medians. When comparing more than two groups, ANOVA analysis was used for means and Kruskal-Wallis test for medians. Spearman's correlation or Pearson correlation analysis was performed to evaluate relationship between continuous variables according to distribution pattern. P values less than 0.05 were considered statistically significant.

Results

A total of 150 eyes were evaluated. Mean follow-up period was 42.3 (6-156) months. Mean age of the patients was 75 (59-93) years. The frequency of patterns at initial FAF imaging is shown in Table 1. Fifty eyes (33.3%) had normal FAF imaging in the first examination. The most common patterns were reticular, focal increase, and patchy pattern with the rates of 18%, 14.7%, and 11.3%, respectively. Visual acuities of eyes according to pattern are shown in Table 2. There was no correlation between patterns and visual acuities at initial visit (p=0.073). At initial examination, 4.6% of eyes had two patterns simultaneously and reticular pattern was the most frequent among these pattern combinations (85.7%). Eyes with two patterns are presented in Table 3 and Figure 1. In these eyes, the dominant pattern was accepted as the main pattern. Coexistence of reticular pattern in patients with another pattern was statistically significant (p<0.001). During the mean follow-up period, the baseline pattern changed in 5.3% of eyes (Table 4, Figure 2). Transformation to reticular pattern or addition of reticular pattern to the initial pattern was seen in 50% of the altered patterns. This value was statistically significant (p<0.001). Furthermore, focal atrophy developed in 13.3% of the eyes during follow-up (Figure 3). Development of focal atrophy was significantly more common with focal increase and reticular pattern, with rates of 45% and 30%, respectively (p<0.001) (Table 5).

Discussion

As our knowledge about the role of lipofuscin accumulation in AMD pathogenesis has increased, FAF has become a more

Table 1. Frequency of patterns at initial fundus autofluorescence imaging

Patterns of FAF	Number of eyes, n (%)
Normal	50 (33.3%)
Reticular	27 (18%)
Focal increase	22 (14.7%)
Patchy	17 (11.3%)
Linear	14 (9.4%)
Minimal change	10 (6.7%)
Speckled	5 (3.3%)
Lace-like	3 (2%)
Undetermined	2 (1.3%)
Total	150 (100%)

FAF: Fundus autofluorescence

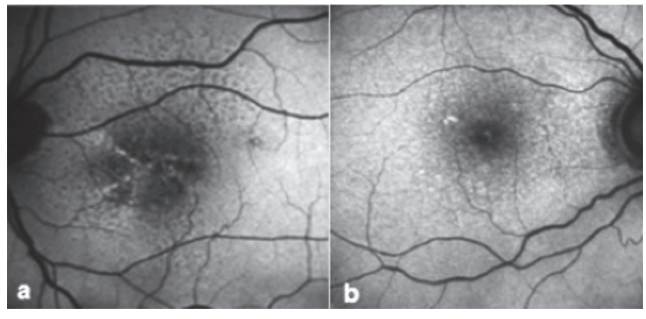

Figure 1. Eyes with two patterns: a) Linear and reticular pattern, b) focal increase and reticular pattern

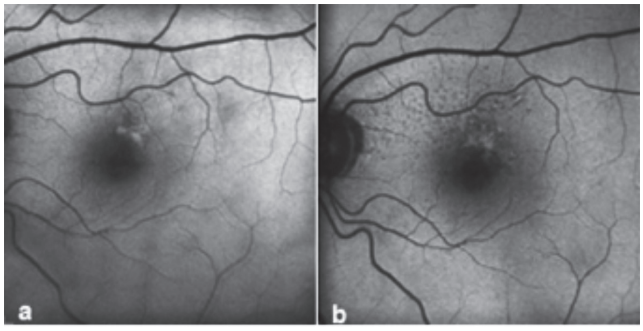

Figure 2. Pattern alteration in fundus autofluorescence imaging: a) Patchy pattern, b) addition of reticular pattern to patchy pattern 64 months later

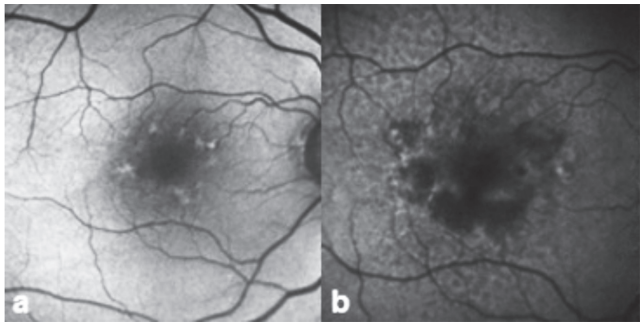

Figure 3. Atrophy development in fundus autofluorescence imaging: a) Linear pattern, b) atrophy and reticular pattern development at 50 months

Table 2. Visual acuities of eyes according to pattern

Patterns of FAF	Number of patients, n	Visual acuity LogMAR (decimal)
Normal	50	0.050 (0.9)
Reticular	27	0.185 (0.63)
Focal increase	22	0.150 (0.7)
Patchy	17	0.150 (0.7)
Linear	14	0.075 (0.9)
Minimal change	10	0.075 (0.9)
Speckled	5	0.300 (0.5)
Lace-like	3	0.00 (1.00)

FAF: Fundus autofluorescence

Table 3. Eyes with two patterns

Patterns of FAF	Dominant pattern	Number of eyes, n (%)
Patchy + reticular	Patchy	1 (14.3%)
Focal plaque + patchy	Patchy	1 (14.3%)
Linear + reticular	Reticular	1 (14.3%)
Linear + reticular	Linear	2 (28.6%)
Focal increase + reticular	Focal increase	2 (28.6%)

FAF: Fundus autofluorescence

Table 4. Pattern alterations observed during follow-up

Initial FAF pattern	Last FAF pattern	Number of eyes, n (%)
Normal	Reticular	1 (12.5%)
Normal	Hyperfluorescence spots	2 (25%)
Focal increase	Patchy	1 (12.5%)
Patchy	Patchy + reticular	1 (12.5%)
Linear	Linear + reticular	2 (25%)
Minimal change	Patchy	1 (12.5%)
Total	-	8 (100%)

FAF: Fundus autofluorescence

Table 5. Patterns that developed focal atrophy

Patterns of FAF	Number of eyes, n (%)
Focal increase	9 (45%)
Reticular	6 (30%)
Linear	2 (10%)
Patchy	2 (10%)
Normal	1 (5%)
Total	20 (100%)

FAF: Fundus autofluorescence

frequently used imaging method for the diagnosis and follow-up of the disease.

Signal alterations shown by FAF imaging do not always correlate with fundus examination findings. Normal fundoscopic findings, drusen, or hyperpigmentation can all be seen in the presence of hyperfluorescence in FAF imaging. This can be explained by the accumulation of different fluorophores located in different retinal cell layers. Delori et al.[6] and Lois et al.[10] evaluated FAF findings in eyes without geographic atrophy and choroidal neovascular membrane and showed that FAF alterations are independent of RPE cell alterations and drusen accumulation. They also showed that alterations of FAF signals are independent of fluorescein angiography (FA) and clinical examination findings. They reported that only foveal large and soft drusen (drusenoid RPE detachment) cause FAF alterations. Kellner et al.[11] showed that in eyes with large drusen (≥125 µm), the main FAF alteration is spots of increased autofluorescence, and that these patients may also exhibit spots of reduced autofluorescence and lines of increased autofluorescence. In addition to detecting different signal alterations in different fundus findings, FAF imaging can also detect changes in areas that appear normal in fundus examination. Therefore, FAF imaging gives more information about the severity and progression of disease in the early stage. All these findings suggest the evaluation of clinical examination and FA findings together with FAF images.

The presence of drusen is a diagnostic criterion for early AMD and also gives information about disease progression. According to the type of drusen, progression to wet AMD can be predicted.[12] Presence of reticular drusen, a variant of soft drusen, is thought to be a risk factor for late AMD.[13,14,15] Previous studies showed that progression to late AMD is more frequent in eyes with reticular drusen than in those without.[16,17] Reticular drusen was also found to be a risk factor for early AMD changes. The Alienor Study showed that the presence of reticular pseudodrusen was significantly associated with an increased risk for early AMD and also that reticular pseudodrusen frequently accompany other signs of early AMD.[18]

Even though fundus examination findings provide information about the progression of AMD, evaluating alterations in lipofuscin accumulation, which plays a role the main mechanism of AMD pathogenesis, has importance in the detection of disease progression. Several studies have demonstrated an association between FAF patterns and progression to late AMD[19,20,21] and reticular pattern was identified as the high-risk pattern for disease progression. Although the association between patterns and progression to late AMD was evaluated in various studies, there is less information about the relationship between patterns and early AMD.[16,18,22,23]

In our study we observed similar patterns to those described in the International Fundus Autofluorescence Classification Group study.[7] Bindewald et al.[7] evaluated FAF patterns in early AMD patients and the most common pattern was speckled pattern (26%) followed by patchy pattern (23%). The frequency of reticular pattern was 15% in their study. In our study, 33.3% of eyes had normal FAF findings. The most common patterns were reticular (18%), focal increase (14.7%), and patchy (11.3%) patterns. In 2 eyes (1.3%) we observed autofluorescence changes that could not be classified according to the International Fundus Autofluorescence Classification scheme. Different studies identified different patterns such as focal confluent,[24] focal plaque-like,[25] and scattered.[24] These patterns' diversity and the undetermined patterns in our study may be due to the clinical variability of AMD. In addition, the prevalence of patterns varies between studies,[7,26,27] which may be attributed to regional variation of AMD patterns.

In early AMD, multiple patterns may be seen at the same time, some patterns may disappear, or a new pattern may emerge in addition to the initial pattern over the course of follow-up. These pattern alterations may give new information about disease progression in the early stage. In our study, we evaluated these pattern alterations and found that reticular pattern was most commonly associated with pattern alterations; 4.6% of eyes had 2 coexisting patterns and 85.7% of these were reticular pattern. We also evaluated the pattern alterations during follow-up, and observed pattern conversion or emergence of a new pattern in 5.3% of eyes, with reticular pattern being the most common. Therefore, reticular pattern is not only associated with late AMD but also early AMD changes. These findings may be helpful for recognizing disease progression in early AMD.

In our study we showed that focal atrophy developed in 13.3% of eyes in the follow-up period. Development of focal atrophy was significantly more common with focal increase (45%) and reticular pattern (30%). Focal atrophy may have an importance in the progression to late AMD.

Conclusion

Presence of reticular pattern in eyes with pattern alterations and focal atrophy development suggest that reticular pattern is also a risky pattern for early AMD progression. Therefore, eyes with reticular pattern should be followed more frequently.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Ethics Committee of Clinical Research (number: 10-403-13).

Informed Consent: Not obtained; retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Figen Şermet, Concept: Figen Şermet, Design: Figen Şermet, Data Collection or Processing: Pınar Bingöl Kızıltunç, Analysis or Interpretation: Pınar Bingöl Kızıltunç, Figen Şermet, Literature Search: Pınar Bingöl Kızıltunç, Writing: Pınar Bingöl Kızıltunç.

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

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Review

Current Management and Treatment of Dry Eye Disease

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Abstract

A better understanding of the pathophysiology and etiology of dry eye disease leads to more efficient management and treatment of the disease process. However, there is substantial variation among both clinicians and countries in terms of dry eye treatment modalities. The latest 2017 International Dry Eye Workshop II report aimed to reduce these differences and emphasized the use of a stepped care algorithm. The algorithm includes treatment forms ranging from artificial tear drops, the primary conventional treatment method, to the latest surgical applications. The aims of the algorithm are to restore homeostasis in the ocular surface, break the vicious cycle of inflammation, and ensure long-term ocular surface comfort.

Keywords: Dry eye, treatment of dry eye, tear film breakup time

Introduction

Dry eye disease (DED) affects hundreds of millions of people worldwide. According to the 2017 International Dry Eye Workshop II (DEWS II) report, dry eye is "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] Typical clinically severe dry eye disease manifests with symptoms such as restriction of daily activities, pain, decreased wellness, and impairment in general health.[2,3,4]

Specifically, the term "multifactorial disease" states that DED is a complex functional disorder involving various findings and symptoms resulting from numerous complicated processes. The term "ocular surface" encompasses the tear film, lacrimal glands, meibomian glands, cornea, conjunctiva, and eyelids. Disruption of homeostasis refers to the tear film and ocular surface imbalances which accompany many symptoms in DED. Tear film instability, hyperosmolarity, inflammation, and damage, which are the main mechanisms contributing to the physiopathological process, were regarded as triggers of the vicious cycle occurring in DED. Additionally, the DEWS II final summary comprehensively emphasized that neuronal involvement and neurosensory abnormalities play an important role in the pathophysiology of DED.[5]

According to the pathophysiological classification, DED has two types, aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE), and this classification is often used to make diagnosis and identify the treatment modality.[6] This review compiles management and treatment options for dry eye disease. The DEWS II and the Asia Dry Eye Society (ADES) reports served as the basis of this review article.

A new treatment strategy developed in line with dry eye identification and diagnosis criteria is discussed in the DEWS II and ADES reports. It was emphasized in these newly published reports that more consideration should be given to etiological distinctions.[7] Determining the necessity of the tear film for a healthy ocular surface and identifying tear film instability as a key factor in the diagnosis of dry eye brought attention to tear film layer stabilization, which led to the development of a new strategy called Tear Film-Oriented Therapy.[8] This review emphasizes major innovations in dry eye treatment according to DEWS II and ADES reports. DED was previously believed to be largely due to tear deficiency, and accordingly, was treated by way of tear replacement, with artificial tears and punctum plugs.[9,10,11,12,13] Recent advances in medical technology and our

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understanding of the pathophysiology, risk factors, and etiology of DED have contributed to an evolution in treatment strategies over time. Table 1 shows the treatment methods used in the management of DED in detail. In the years since publication of the original TFOS DEWS II Management and Therapy Report,[14] there has been a growing realization of the important contribution of meibomian gland dysfunction (MGD) to both the symptoms and signs of DED.[15]

The management of DED is highly complicated because of its multifactorial etiology associated with many mechanisms.[16] Therefore, when making a diagnosis of dry eye, clinicians should clearly determine the underlying etiology, such as EDE or ADDE, which are the mechanisms that cause DED, and/or other ocular surface diseases, and they should administer relevant treatments accordingly.[17,18] In addition, neurotrophic keratopathy accompanied by neuropathic pain and symptoms should definitely be considered in differential diagnosis of patients with intense symptoms despite mild signs.[19] Consequently, determining the main causes behind DED is critical for proper management.

The ultimate goal of DED treatment is to restore homeostasis of the ocular surface and tear film by breaking the vicious cycle of the disease.[20] In addition to short-term therapies, it is also necessary to consider long-term treatment by taking into consideration the sequelae that can occur during the chronic disease process. The sequential treatment algorithm suggested in the DEWS II report should not be applied rigidly, but according to the benefit it will provide the patient. In the majority of DED patients, the general purpose should be to start treatment with the interventions most likely to be beneficial, and use more advanced and specific treatments that target the pathophysiology.

Management algorithms are structured to recommend a series of treatments according to disease stage, but the issue is complicated in DED because the disease often differs from patient to patient in both severity and nature.[21] Treatment planning based on treatment algorithms is done according to disease severity. However, due to the coexistence of many factors in DED, strictly adhering to the algorithm system does not always work. For this reason, a higher stage of treatment can be applied in patients who do not respond to the treatment at the

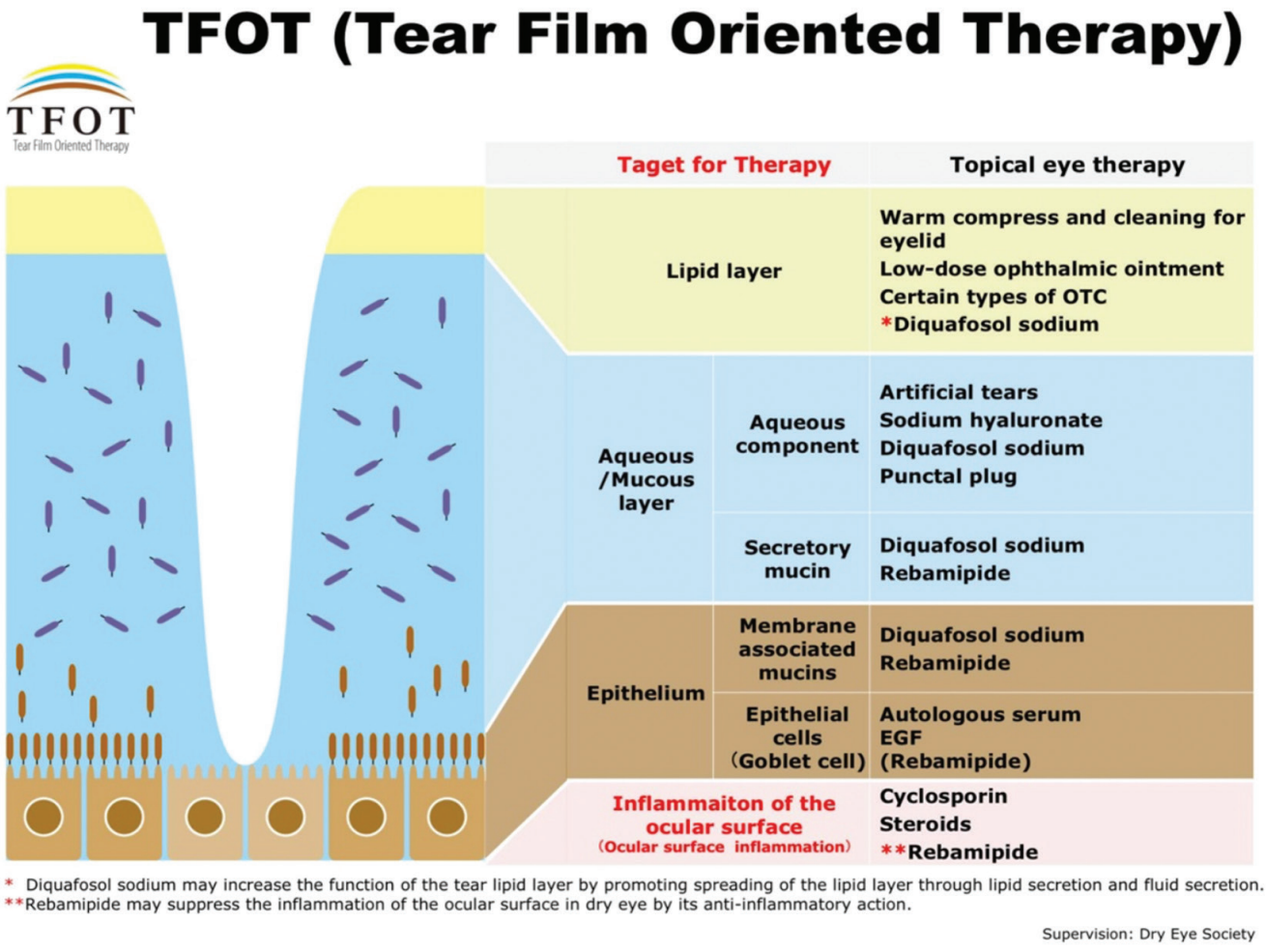

Figure 1. A newly developed treatment strategy for dry eye disease: "tear film-oriented therapy" (used with permission from the Dry Eye Society Japan)

Table 1. Detailed proposed treatment methods of dry eye disease		
1. Treatments for tear insufficiency	**2. Treatments for lid abnormalities**	**4. Surgical approaches**
1.1. Tear replacement approaches	2.1. Anterior blepharitis	4.1. Tarsorrhaphy
1.1.1. Artificial tear substitutes	2.1.1. Lid hygiene	4.2. Surgical treatment for conjunctivochalasis
→ Aqueous supplementation	→ Bacterial overcolonization	4.2. Surgical treatment for conjunctivochalasis
• Viscosity-enhancing agents	• Topical antibiotics	4.4. Lid corrections
◦ Carboxymethyl cellulose (CMC)	→ Demodex infestation	4.4.1. Dermatochalasis surgery
◦ Hydroxypropyl methylcellulose	• Tea tree oil	4.4.2. Blepharoptosis (ptosis)
◦ Hyaluronic acid (HA)	• Ivermectin	4.4.3. Lower lid blepharoplasty
◦ Combination of CMC and HA	2.2. Meibomian gland dysfunction	4.5. Conjunctival surgery and amniotic membrane grafts
◦ Hydroxypropyl-guar (HP-guar)	2.2.1. Ocular lubricants	4.6. Mechanical dacryo-reservoirs
◦ Combination of HA and HP-guar	2.2.2. Warm compresses	4.7. Major salivary gland transplantation
◦ Hydroxypropyl cellulose	→ Blephasteam	4.7.1. Parotid duct transposition
• Osmotic agents	→ MGDRx EyeBag	4.7.2. Microvascular submandibular gland transplantation
• Osmo-protectants	→ EyeGiene mask	4.8. Minor salivary gland auto-transplantation
• Antioxidants	→ Infrared warm compression device	
• Preservatives	2.2.3. Physical treatments	**5. Dietary modifications**
• Inactive agents	→ Forceful expression	5.1. General hydration state
◦ Buffers	→ LipiFlow	5.2. Essential fatty acid (ω-3 and ω-6)
◦ Excipients	→ Intense pulsed light	5.3. Lactoferrin
◦ Electrolytes	→ Intraductal probing	5.4. Other dietary considerations (beta-carotene, vitamins E, C, B, B6, D, zinc and copper)
→ Lipid supplementation	→ Debridement scaling	
• Types and properties of lipids	2.3. Blinking abnormalities and ocular exposure	**6. Local environmental considerations**
1.1.2. Biological tear substitutes	2.3.1. Treatment for corneal exposure	6.1. Chronic topical medications
→ Autologous serum	2.3.2. Entropion and ectropion	6.2. Systemic medications
• Clinical performance	2.3.3. Contact lenses	6.3. Increase blink rate
• Complications and conclusion	→ Therapeutic soft contact lenses (bandage lenses)	6.4. Decrease desiccating conditions and environmental pollutants
→ Adult allogeneic serum	→ Rigid gas permeable scleral lenses	6.5. Contact lens wear
→ Umbilical cord serum		
1.1.3. Other agents	**3. Anti-inflammatory therapy**	**7. Complementary medicines**
→ Mucolytics	3.1. Topical glucocorticoids	7.1. Herbal and natural products
• TRPV1 receptor antagonist	3.2. Non-glucocorticoid immunomodulators	7.2. Honey
1.2. Tear conservation approaches	3.2.1. Cyclosporine A	7.3. Milk
1.2.1. Punctal occlusion	3.2.2. Tacrolimus	7.4. Acupuncture
→ Punctal occlusion with plugs	3.2.3. Non-steroidal anti-inflammatory drugs	
→ Surgical punctal occlusion	3.2.4. Biologics	
1.2.2. Moisture chamber spectacles and humidifiers	→ Recombinant human nerve growth factor	
1.3. Tear stimulation approaches	→ Tumor necrosis factor a-stimulated gene/ protein-6	
1.3.1. Topical secretagogues	→ Interleukin-1 receptor antagonist (IL-1Ra)	
→ Aqueous secretagogues. Diquafosol tetrasodium	→ Anti-tumor necrosis factor-α therapy	
→ Mucin secretagogues	→ Anti interleukin-17 (IL-17) therapy	

Table 1. Continued		
1.3.2. Lipid stimulation	3.2.5. Neuropeptides (Substance P, calcitonin gene-related peptide, neuropeptide Y and vasoactive intestinal peptide	
1.3.3. Oral secretagogues	3.3. Lymphocyte function-associated antigen 1 antagonist	
1.3.4. Nasal neuro-stimulation	3.3.1. Lifitegrast	
1.3.5. Various tear stimulation methods	3.4. Inflammatory modulation with systemic and topical antibiotics	
	3.4.1. Tetracycline therapy	
	3.5. Macrolide therapy	

proposed stage and in patients with severe dry eye, or treatment recommended for the next stage can be added while continuing the previous stage of treatment. Approaches adopting dry eye treatment at home in the early stage can usually be performed with over-the-counter lubricants which are low-risk and easy for patients to obtain, but further advanced treatment options should be considered in advanced patients.[10,21,22,23] In conclusion, the TFOS DEWS II management and therapy report presents a step-wise approach to the treatment of DED. Implementation of the management and therapeutic algorithm according to disease severity can be summarized in four steps.

The first step includes alteration of the local environment, patient education, dietary modifications (including oral essential fatty acid supplementation), identification and potential modification/elimination of offending systemic and topical medications, addition of ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements), lid hygiene, and warm compresses.

If the treatments in the first step are insufficient, the second step is required. Treatments considered in the second step include tea tree oil treatment for Demodex, preservative-free artificial tears (to avoid the toxic effects of preservatives), punctal plugs, moisture chamber devices and goggles to maintain moisture and temperature, overnight ointment application, removing blockages from the meibomian glands using a warming and expression device (such as Lipiflow), intense pulsed light therapy for MGD, and topical administration of drugs such as corticosteroids, antibiotics, secretagogues, non-glucocorticoid immunomodulators (cyclosporine and tacrolimus[24]), LFA-1 antagonist drugs (lifitegrast), and oral macrolide or tetracycline antibiotics.

If the above treatment options are inadequate, oral secretagogues, autologous/allogenic serum eye drops, rigid and soft contact lenses need to be considered in addition as a third-step treatment.

If there is clinical evidence of more severe complications associated with the dry eye presentation, the clinician will need to consider additional treatments in the fourth step, such as application of topical corticosteroid for longer duration, amniotic membrane grafts, surgical punctal occlusion, and other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation).[7]

In summary, dry eye diagnosis and treatment are evolving. The basic mechanism leading to the disease is still not known exactly. Accordingly, a global consensus has not been established in the diagnosis and treatment of the disease. Etiology-oriented treatment has gained importance in the meetings held by ADES and TFOS, and ADES has acknowledged the "Tear Film Layers-Oriented Therapy" protocol. The ADES consensus recommends that the deficient layer of the tear film should be replaced accordingly and the underlying problem should be addressed directly (Figure 1). Since it is very difficult to classify dry eye treatment within strict rules and base it only on evidence-based studies, each patient should be evaluated individually and patient-specific treatment plans should be made.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cem Şimşek, Murat Doğru, Takashi Kojima, Concept: Murat Doğru, Tsubota Kazuo, Design: Takashi Kojima, Cem Şimşek, Kazuo Tsubota, Data Collection or Processing: Cem Şimşek, Murat Doğru, Analysis or Interpretation: Cem Şimşek, Murat Doğru, Literature Search: Cem Şimşek, Murat Doğru, Takashi Kojima, Writing: Cem Şimşek, Murat Doğru.

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Case Report

Sectoral Ciliary Body Agenesis Complicated with Cataract Formation Diagnosed by Ultrasound Biomicroscopy

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Abstract

We aimed to present a novel case of sectoral ciliary body agenesis and complicated cataract as an embryogenic defect of eye development diagnosed by ultrasound biomicroscopy. A 20-year-old male patient presented with a complaint of visual impairment in his left eye since childhood. Slit-lamp examination of the left eye revealed pigment precipitation and focal lens opacities extending from the temporal quadrant through the posterior lens capsule, blocking the central optical axis. On ultrasound biomicroscopy examination, there was a hyperechoic reflection belonging to the rudimentary ciliary body structures between 2-5 o'clock in the temporal quadrant. The zonules could not be visualized in the same location. At all other quadrants of the anterior chamber angle, the ciliary body and zonules were normal. This is a very rare case of sectoral ciliary body agenesis complicated by cataract. Ultrasound biomicroscopy may be useful for detecting rare congenital anomalies of the anterior segment, anterior chamber angle, and ciliary body.

Keywords: Ciliary body agenesis, coloboma, ultrasound biomicroscopy

Introduction

The embryological development of the human eye involves a series of events, beginning with fertilization of the ovum and continuing through the early postnatal period, in three embryonic layers: neural ectoderm, neural crest, and surface ectoderm, with minor contribution from the mesoderm.[1] The lens arises from the surface ectoderm and formation starts with the contact of optic vesicle at about 3 weeks of gestation.[2] The cranial neural crest is the origin of the ciliary body, including pigmented and nonpigmented cells and the ciliary smooth muscle, and it starts to form in the third month as a fold posterior to the progressing edge of the optic cup.[3,4] Developmental defects in embryogenesis cause ocular malformations in a spectrum from congenital cataract to anophthalmia.[5]

In this report, we aimed to present a novel case of sectoral ciliary body agenesis and complicated cataract as an embryogenic defect of eye development diagnosed by ultrasound biomicroscopy (UBM).

Case Report

A 20-year-old male patient presented to our clinic with a complaint of visual impairment in his left eye since his childhood. The patient had no ocular or systemic disease, history of trauma, ophthalmic surgery, or chronic medication. In detailed ophthalmic examination, best corrected visual acuity (BCVA) in the right eye was 10/10 with Snellen chart and anterior and posterior segment evaluation was normal. BCVA in the left eye was limited to hand motions. His eyes were orthophoric in primary position, and there was no restriction of eye movements. Pupillary light reactions were normal. Intraocular pressure measured by applanation tonometry was 13 mmHg in the right eye and 12 mmHg in the left eye.

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Slit-lamp examination of the left eye revealed pigment precipitation and focal lens opacities extending from the temporal quadrant through the posterior lens capsule and blocking the central optical axis (Figure 1a).

On UBM examination, there was a hyperechoic reflection belonging to the rudimentary ciliary body structures between 2-5 o'clock in the temporal quadrant. The zonules could not be visualized in the same location (Figure 1b). In all other quadrants of the anterior chamber angle, the ciliary body and zonules were normal. Media opacities prevented a full fundoscopic examination.

Discussion

Ocular development starts in the third week of gestation. Any error in this process can cause congenital ocular malformations.[6] In terms of ocular developmental chronology, there's no direct connection between formation of the ciliary body and lens other than their location. Embryologically, the ciliary body consists of two different tissue layers. The pigmented and nonpigmented ciliary epithelium derives from the neuroectoderm, while the ciliary muscles and the stroma derive from the neural crest cells. The lens is derived from the surface ectoderm. Similarly, lens formation begins in the third week of gestation as the "lens placode" and initial development concludes in the seventh week. Ciliary body formation starts in the third month of gestation and ends in the fifth month[1]. Apart from their physical proximity, another possible connection is the arrival of growing ciliary processes at the equator and formation of lens zonules in the fourth month. Therefore, it is thought that in our case developmental defect occurred primarily in ciliary body and the lens was affected indirectly.

UBM performed in our patient did not reveal any significant echogenicity belonging to zonules at the defective site. The hypoplastic, rudimentary, underdeveloped ciliary body and lack of connection between the ciliary processes and lens equator, which must have been there since the fourth month of gestation, explains the absence of the zonules.

Other than aqueous humor secretion and accommodation, the ciliary body has another vital function: nutrition of the lens.[7] Interestingly, in our case, only the defect site had focal lens opacities. This may be related to metabolic defects of the lens. However, in that situation, these opacities should be present throughout the entire lens. We also believe that the central pigment precipitation extending through the posterior lens capsule at the defect site might be the more likely reason for formation of these opacities.

Chronologically, the pigmented and nonpigmented ciliary epithelial tissue develop first, followed by the ciliary processes and zonules, and finally the pars plana, ciliary body stroma, and ciliary muscles.[4] This sequence supports the absence of any affected tissue other than the defective ciliary pigment layer in our case.

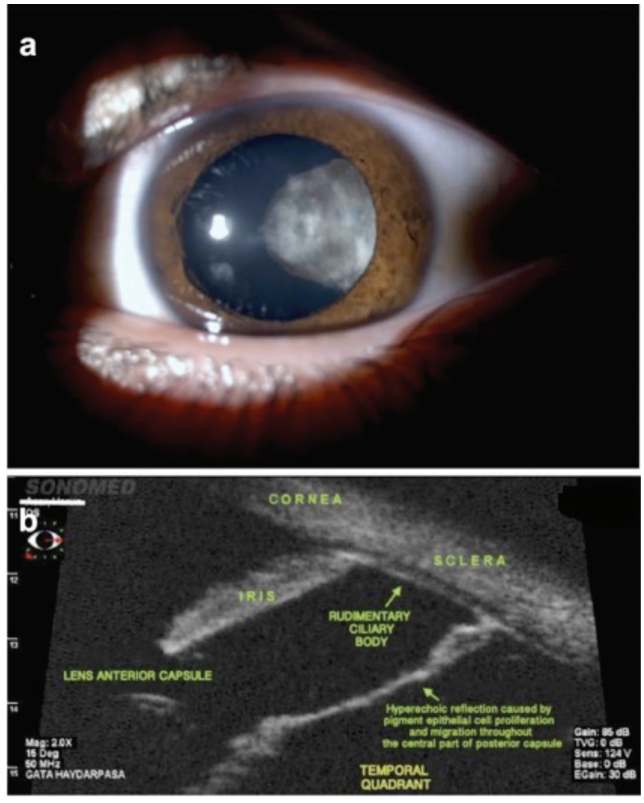

Figure 1. a) Anterior segment photography of the left eye. b) Radial angle image of the temporal quadrant of the left eye on ultrasound biomicroscopy

It is clear that there is a difference between prenatal and postnatal development of nasal and temporal ciliary bodies.[8,9] This difference supports the temporal ciliary body defect site seen in our case. Why the temporal quadrant is affected rather than the nasal quadrant is another pressing question that has yet to be answered.

Because this case was unilateral and the defective ciliary body was not in the closure site of the embryonic fissure, there was a slight possibility of atypical coloboma. However, the presence of normal ocular structures other than the ciliary body reduced this possibility.

UBM is useful in a variety of clinical applications in the diagnosis of eye diseases, providing detailed cross-sectional anterior chamber anatomy with high resolution and reproducible images. In contrast to anterior segment optical coherence tomography and Scheimpflug imaging, which do not penetrate past the iris pigment epithelium to a large degree, UBM can show the exact configuration and position of the iris, ciliary body, and ciliary processes even in the presence of opaque media.[10] In our case, we diagnosed ciliary body sectoral agenesis by means of UBM.

To the best of our knowledge, there is no report similar to our case in the English literature. In the near future it will be possible to evaluate cases like these more reliably due to enhanced imaging techniques, developing technology, and

current embryologic research. Genetic analysis to investigate mutational defects, which might be associated with sectoral ciliary body agenesis, could offer valuable information.

In conclusion, this is the first report of sectoral ciliary body agenesis complicated by cataract in the English literature. UBM may be useful for detecting rare congenital anomalies of the anterior segment, anterior chamber angle, and ciliary body.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İlhami Salcan, Ümit Aykan, Concept: İlhami Salcan, Ümit Aykan, Design: Özgün Melike Gedar Totuk, İlhami Salcan, Data Collection or Processing: İlhami Salcan, Analysis or Interpretation: Özgün Melike Gedar Totuk, Literature Search: Melih Atalay, Writing: Özgün Melike Gedar Totuk.

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Case Report

Development of Retinal Infarct Due to Intracameral Cefuroxime Injection Following Complicated Cataract Surgery

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Abstract

We present the case of a 60-year-old patient who underwent a complicated cataract surgery with cefuroxime injection (1 mg/0.1 mL) into the anterior chamber at the end of surgery. The patient presented to our hospital due to decrease in visual acuity (VA) after surgery. VA was counting fingers (CF) from 4 meters. There was extensive retinal hemorrhages and edema in addition to retinal vascular leakage detected with fluorescein angiography (FA). After negative microbiologic tests, the patient was treated with intravenous pulse and oral corticosteroids. Rheumatologic investigation was also negative. At month 5, VA was CF from 1 meter in addition to disseminated capillary loss in FA and optic nerve atrophy despite corticosteroid treatment. The patient developed retinal infarction due to cefuroxime injection following a complicated cataract surgery. Surgeons and surgical staff should be aware of the possibility of retinal toxicity while using cefuroxime, particularly in complicated cases.

Keywords: Intracameral cefuroxime, retinal toxicity, retinal infarct

Introduction

Bacterial endophthalmitis is the most feared complication of cataract surgery and can cause severe and permanent visual loss.[1] Intracameral antibiotic injection has decreased the incidence of postoperative endophthalmitis.[2] Cefuroxime, moxifloxacin and vancomycin are the preferred antibiotics for cataract surgery.[3,4,5] Cefuroxime has been reported to provide a five-fold decrease in endophthalmitis incidence.[6] A concentration of 1 mg/0.1 mL is the recommended dose for microbial efficacy and tissue safety.[2] However, in the absence of ready-to-use formulations, dilution errors may be overlooked while preparing the desired concentration. Exposure to high-dose cefuroxime can cause retinal toxicity, which can result in retinal and optic nerve infarct.[7] The retinas become more sensitive to the drug doses due to disruption of the barriers between the anterior and posterior segments in complicated surgeries.

Case Report

A 60-year-old patient presented to our hospital due to decreased vision following cataract surgery. The patient underwent a complicated cataract surgery (posterior capsule rupture and anterior vitrectomy) with implantation of a 3-piece foldable IOL in the sulcus and a recommended dose (1 mg/0.1 mL) of cefuroxime was injected into the anterior chamber. Visual acuity (VA) was counting fingers from 4 meters. There were +2 cells in the vitreous, retinal hemorrhages and edema, particularly at the posterior pole (Figure 1A). Fluorescein angiography (FA) revealed extensive vascular leakage (Figure 1B). Foveal thinning and outer segment atrophy were observed in optical coherence tomography (Figure 1C). Microbiologic tests (viral and parasitic antibodies and polymerase chain reaction [PCR] analysis of vitreous samples) were negative. Treatment with 1000 mg intravenous pulse corticosteroid was initiated and continued for 3 days. Medical treatment continued

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with 1 mg/kg oral corticosteroid for 1 month. Meanwhile, rheumatologic etiologies, which can cause retinal vasculitis, were investigated but the results were negative. After 1 month, the retinal hemorrhages had substantially regressed but there were persistent vascular leakage and retinal capillary loss (Figure 2A). At 5 months, VA decreased to counting fingers from 1 meter. Corneal edema, anterior chamber and vitreous cells, and retinal hemorrhages resolved, but the optic nerve was pale and retinal neovascularization developed (Figure 2B). FA showed minimal vascular leakage in addition to extensive retinal infarct (Figure 2C).

Discussion

The patient in this report presented with vitritis, retinal hemorrhages, vascular leakage, and capillary infarct in FA, which were suggestive of obstructive retinal vasculitis due to rheumatologic diseases or viral retinitis. However, the patient did not have a rheumatologic disease history and clinical investigation for rheumatologic diseases (Behçet's disease, systemic lupus erythematosus, inflammatory bowel disease, polyarthritis, multiple sclerosis, sarcoidosis, etc.) was negative. Viral antibodies (particularly to herpes simplex, varicella zoster, or cytomegalovirus) and PCR analysis were also negative.

Aprokam is the ready-to-use formulation of cefuroxime; however, in the absence of the commercial formulation, the recommended cefuroxime concentration is prepared with the surgeons' own dilution procedures. Although the recommended drug concentration can be prepared properly with these procedures, it is nevertheless possible for the surgeon or other personnel to make a mistake during dilution, as shown by previous reports. Çiftçi et al.[7] reported 50 to 70 mg, Qureshi and Clark reported 62.5 mg, Delyfer et al. reported 40 to 50 mg and Olavi reported 10 to 100 mg cefuroxime exposure at the end of surgery.[8,9,10]

Cefuroxime toxicity varies from case to case and the severity of its clinical manifestations is associated with surgical complications as well as drug concentration. In uncomplicated cases, a mild, transient, and reversible retinal toxicity may occur with the recommended dose injection, whereas high-dose exposure can cause severe complications such as macular infarction.[8,11] Furthermore, in complicated cases, more severe complications characterized by extensive retinal edema, hemorrhage, disseminated capillary loss, and optic nerve atrophy can develop after cefuroxime injection.[7] This is due to the absence of a lens capsule barrier limiting the passage of the drug to the posterior segment in complicated cases. The severity of the clinical features in the present case may be associated with posterior capsule rupture, direct retinal exposure to the drug, or breakdown of the blood-retinal barrier due to drug toxicity. Extensive retinal capillary loss and optic atrophy were signs of the retinal and optic nerve infarction, which was previously demonstrated by Çiftci et al.[7] Pars plana vitrectomy might also be considered together with anti-inflammatory treatment to minimize retinal exposure to the toxic agent, particularly in severe cases. In addition, retinal tears and retinal detachment may develop due to retinal infarction. For that reason, patients

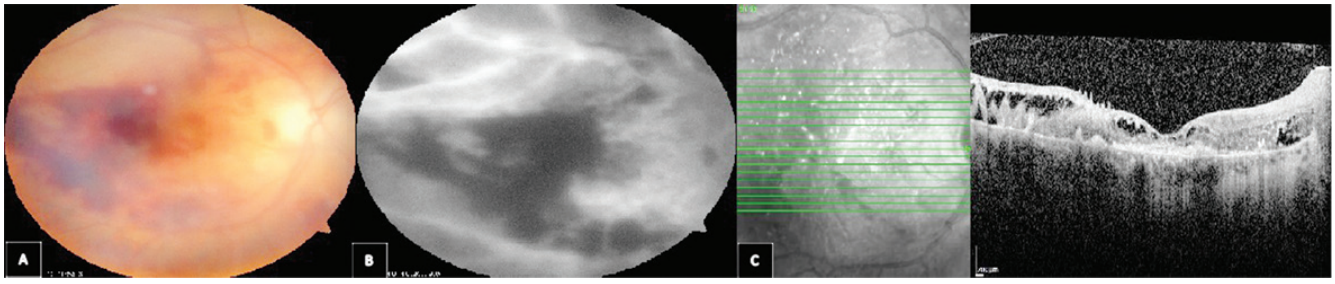

Figure 1. A) Fundus photography of the patient shows retinal hemorrhages particularly at the central retina. B) Fluorescein angiography shows vascular leakage. C) Foveal thinning and outer segment atrophy in optical coherence tomography

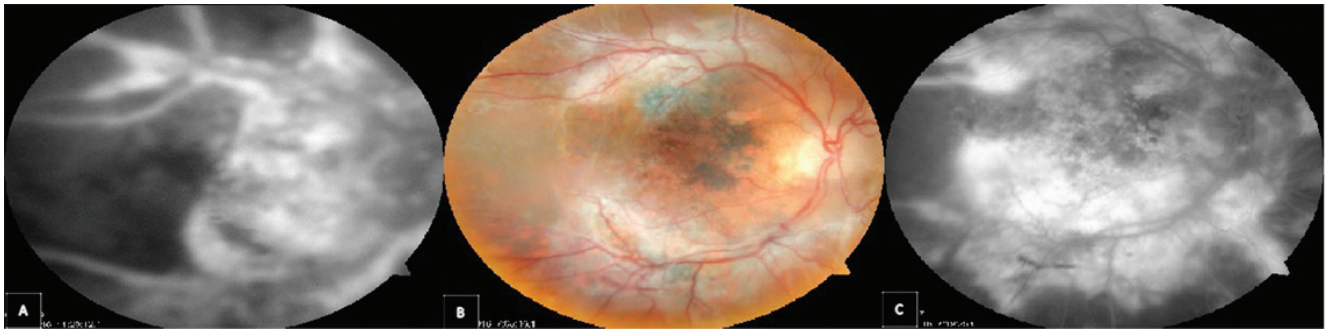

Figure 2. A) At 1 month, hemorrhages were substantially resolved but there was persistent severe vascular leakage and capillary loss in fluorescein angiography despite high-dose anti-inflammatory treatment, B) Fundus photography at 5 months shows neovascular membrane formation, C) Fluorescein angiography shows minimal vascular leakage and extensive retinal infarction

should be followed very closely and argon laser photocoagulation should be considered in these cases during the follow-up period if needed. In our patient, the clinical course did not respond to intensive anti-inflammatory treatment. Therefore, surgeons and staff should adjust the intracameral drug dose accordingly in complicated cataract surgeries to prevent the development of severe complications related to drug toxicity.

In conclusion, retinal toxicity may develop in complicated cases with the recommended cefuroxime concentration. Visual outcome seems to be poor despite high dose anti-inflammatory treatment.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sababahttin Sül, Aylin Karalezli, Concept: Sababahttin Sül, Aylin Karalezli, Design: Sababahttin Sül, Aylin Karalezli, Data Collection or Processing: Sababahttin Sül, Aylin Karalezli, Analysis or Interpretation: Sababahttin Sül, Aylin Karalezli, Literature Search: Sababahttin Sül, Aylin Karalezli, Writing: Sababahttin Sül, Aylin Karalezli.

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

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Case Report

Spontaneous Lens Absorption Initially Misdiagnosed as Crystalline Lens Luxation

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Abstract

Spontaneous lens absorption (SLA) is a rare complication of hypermature cataract. However, this condition has been reported in several cases of hypermature cataracts that were caused by trauma, senility, uveitic disorders such as Fuchs' uveitis syndrome (FUS), and infectious disorders including leptospirosis and rubella. We report a case of spontaneous absorption of a hypermature cataract secondary to FUS. To our knowledge, this is the first report of SLA that was followed by dislocation of the capsular remnants into the vitreous and resulted in a misdiagnosis as crystalline lens luxation.

Keywords: Fuchs' uveitis syndrome, hypermature cataract, spontaneous absorption

Introduction

Spontaneous lens absorption (SLA) is a rare pathology, especially in recent years. It can occur in hypermature and traumatic cataract or in the late stages of some uveitic and infectious diseases.[1,2,3,4,5,6] Recent advances in cataract surgery and the increasing use of surgery have reduced the incidence of hypermature cataracts, thus reducing the prevalence of SLA. In this case report, we present the clinical features of a patient who developed SLA secondary to Fuchs' uveitis syndrome (FUS), a rarely seen entity in our clinical practice.

Case Report

A 63-year-old female patient presented with reduced vision in her right eye. She reported experiencing sudden-onset pain, loss of vision, and redness in her right eye 7 years earlier, but did not seek medical treatment at that time. She had no history of ocular trauma or surgery. Best corrected visual acuity (BCVA) in her right eye was light perception and intraocular pressure was 18 mmHg. Anterior segment examination revealed hypermature cataract. The iris stroma showed diffuse atrophy and appeared hypochromic. Ultrasonography demonstrated retinal attachment. Cataract surgery was recommended, but the patient refused.

At 1-year follow-up examination, the patient stated that her vision had improved. BCVA was 20/25 in the right eye (with +12 D correction) and 20/20 in the left eye. Although her right eye appeared aphakic on anterior segment examination, no surgical scar or signs of trauma were detected. The cornea was clear and the conjunctiva appeared normal. Despite the hyperchromic appearance and stroma atrophy of the iris, there were no findings suggestive of inflammation (keratic precipitates in the corneal endothelium, posterior synechia, or anterior chamber inflammatory cells). The left eye appeared normal (Figure 1). Intraocular pressure was 18 mmHg in the right eye and 16 mmHg in the left eye. The areas that could be visualized in fundus examination were normal. A peripheral retinal scan was done to see the crystalline lens. An ideal evaluation could not be performed because the patient had sunken eyes and incomplete pupil dilation. However, no crystalline lens material was observed in the visualized areas. The absence of crystalline lens material in peripheral retinal examination raised the suspicion of crystalline lens subluxation behind the iris. Ultrasound biomicroscopy (UBM) was performed, but UBM

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images did not show any lens material behind the iris (Figure 2A). B-scan ultrasound revealed a hyperechoic appearance in the inferior peripheral retina suggesting luxation (Figure 2B). Based on these findings, the patient was scheduled for 23-gauge pars plana vitrectomy. Despite intraoperative investigation using 360° scleral depression, there were no signs of the crystalline lens (Figure 3). During the procedure, atrophic holes formed in the peripheral retina. Prophylactic 360° laser was applied to the peripheral retina at the end of the procedure. An intraocular lens was implanted in the posterior chamber by scleral fixation (Figure 4). Postoperatively, the possible etiologies of SLA were investigated. Toxoplasma and leptospirosis tests were negative, while cytomegalovirus, rubella, and herpes simplex virus IgG antibodies were positive. Sedimentation rate, complete blood count, urinalysis, and biochemical tests were within normal limits. The patient was followed for 1 year with no complications.

Discussion

SLA is a rarely encountered pathology in clinical practice. Hypermature cataracts secondary to trauma, advanced age, and certain uveitic and infectious diseases may cause SLA.[1,2,3,4,5,6] The mechanism underlying SLA has not been fully elucidated. In leptospirosis and rubella infection, it is thought to be a response to the agent itself or to antibodies, though the mechanism has not been established.[4] Absorption is unlikely in the presence of an undamaged lens capsule, but may occur following damage to the lens capsule in late hypermature cataract.[1] Similarly, our patient had hypermature cataract. Structural and chemical events associated with FUS also likely facilitated this process.

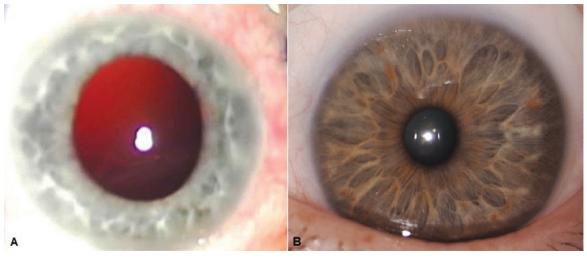

Figure 1. The patient's right eye (A) appears aphakic with iris hypochromia; the left eye (B) shows iris hyperpigmentation

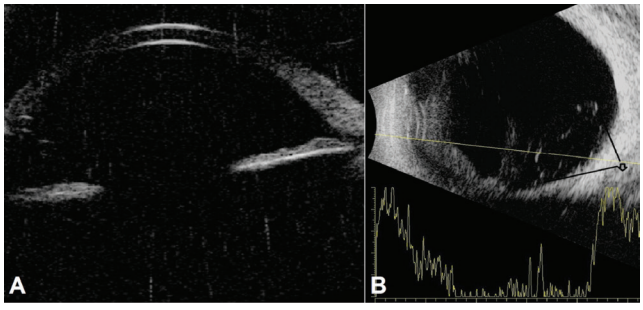

Figure 2. Ultrasound biomicroscopy image of the right eye (A) shows no findings of crystalline lens material posterior of the iris. B-scan ultrasonography (B) shows a hyperechoic area posterior of the iris in the lower quadrant that suggests luxation of the crystalline lens

Before making a clinical diagnosis of SLA, subluxation or lens migration into the vitreous must be ruled out. In addition, the absence of scarring associated with ocular trauma or previous ocular surgery should be confirmed during examination.[1] Our patient had a clear cornea and exhibited no signs of trauma. There were no findings in UBM suggesting lens subluxation. B-scan ultrasound revealed a hyperechoic image thought to be the crystalline lens lumen. Therefore, we suspected lens migration into the vitreous.

In a case of SLA caused by hypermature cataract following FUS, Uemura et al.[3] reported that the presence of capsular remnants in the anterior chamber facilitated the diagnosis. Kobat et al.[7] also presented a case of SLA after hypermature cataract in which capsule pieces found in the anterior chamber provided diagnostic clues. Similarly, Kim et al.[8] discussed capsule remnants in the anterior chamber in their patients with SLA. In our case, however, no such remnants were observed in the anterior chamber. This delayed an accurate diagnosis.

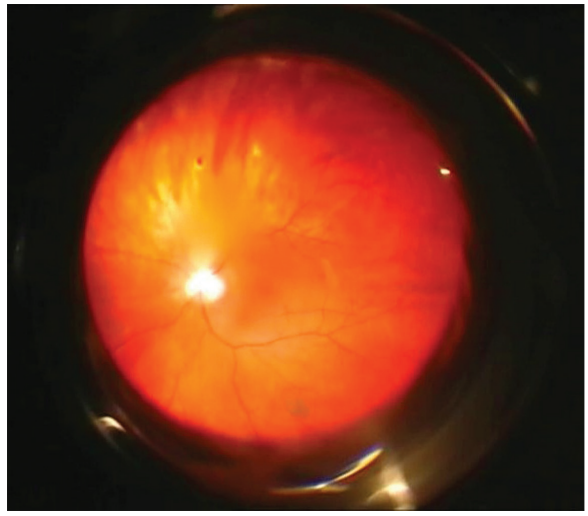

Figure 3. Retinal image obtained during pars plana vitrectomy does not show any crystalline lens material

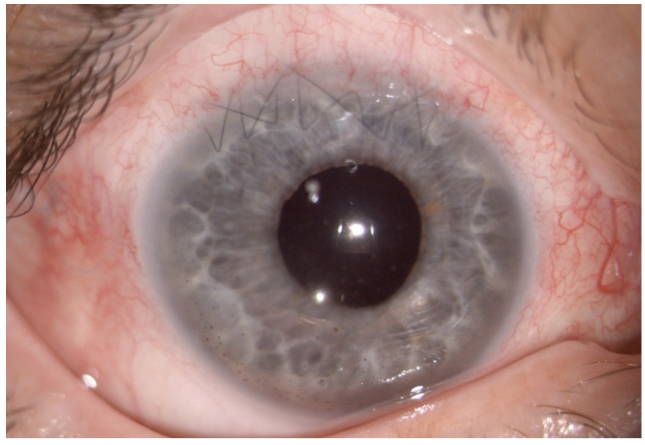

Figure 4. Corneal-scleral sutures, centralized intraocular lens, and clear cornea are seen in postoperative day 1 examination

While the definitive etiopathogenesis of SLA remains unclear, a possible association with infections such as leptospirosis and rubella has been emphasized in several publications.[4,5,6] It has also been reported that FUS may be associated with rubella infection as well as be involved the etiology of SLA.[9,10] Our patient tested positive for rubella IgG. No intraocular sampling of the aqueous humor was done to assess for antibodies to the rubella genome or virus to determine the association between the past rubella infection and both FUS and SLA. For this reason, we were unable to prove a direct causal relationship between FUS, SLA, and her prior rubella infection.

In conclusion, the migration of capsular remnants into the vitreous after SLA is a rare complication of hypermature cataract. This can lead to a misdiagnosis of crystalline lens luxation, especially when conditions for peripheral retinal examination are not ideal. Therefore, SLA should be kept in mind during the clinical evaluation of such patients.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şaban Gönül, Berker Bakbak, Banu Bozkurt, Consept: Şaban Gönül, Ayşe Bozkurt Oflaz, Berker Bakbak, Design: Şaban Gönül, Kamil Yavuzer, Banu Bozkurt, Data Collection or Processing: Şaban Gönül, Kamil Yavuzer, Ayşe Bozkurt Oflaz, Analysis or Interpretation: Şaban Gönül, Banu Bozkurt, Literature Search: Şaban Gönül, Ayşe Bozkurt Oflaz, Berker Bakbak, Writing: Şaban Gönül, Ayşe Bozkurt Oflaz.

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

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

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Case Report

A Rare Cause of Uveitis: Vemurafenib

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Abstract

A 25-year-old female presented with a decrease of vision and redness in both eyes. She had a history of nodular melanoma in her right shoulder, which was excised surgically and she was under oral vemurafenib treatment. She was diagnosed with moderately severe bilateral panuveitis and hospitalized for systemic investigation and workup. The laboratory test results were unremarkable and systemic workup failed to reveal an etiology. The condition was considered vemurafenib-induced uveitis, as the drug is known to be associated with uveitis. After reevaluation with the oncology department, vemurafenib was stopped and topical and systemic corticosteroid therapy was started. The uveitis resolved and her vision returned to normal. No sign of recurrence was detected at 8-month follow-up.

Keywords: Drug-induced uveitis, melanoma, vemurafenib

Introduction

Various drugs, regardless of the route of administration, have been reported to be associated with uveitis, an entity referred to as drug-induced uveitis. While many more drugs have been implicated, the most commonly reported are cidofovir, rifabutin, bisphosphonates, sulfonamides, tumor necrosis factor inhibitors, and fluoroquinolones. The underlying mechanism is proposed to be either inflammatory or toxic.[1,2] Hence, when managing a uveitis patient, the physician should always keep in mind that a drug could be involved in the etiology.

Vemurafenib (Zelboraf, F. Hoffmann-La Roche Ltd, Basel, Switzerland), a potent oral $BRAF^{V600}$ inhibitor, is a new drug shown to be effective against advanced cutaneous melanoma.[3] The drug was found to be more effective than dacarbazine in reducing mortality risk.[4] Reported systemic adverse effects of vemurafenib are arthralgia (53%), alopecia (45%), fatigue (38%), nausea (35%), and photosensitivity (33%).[5] In addition, uveitis was the most commonly reported adverse event related to vemurafenib administration, followed by conjunctivitis and dry eye (4%, 2.8%, and 2%, respectively).[3] Adverse events must be weighed against the potential survival benefit. When it comes to uveitis, steroids were reported to suppress ocular inflammation; however, some authors were in favor of cessation of the therapy.[5]

The aim of this study was to present a case of vemurafenib-induced panuveitis.

Case Report

A 25-year-old woman presented with diminished vision and redness in both eyes. She had a history of resected nodular melanoma in her right shoulder and was under vemurafenib therapy (960 mg/day) initiated at another center, though her family history was unremarkable.

She had 20/200 visual acuity in her right eye which did not improve with correction. Corrected visual acuity was 20/20 in her left eye. Both eyes had normal intraocular pressure readings. Slit-lamp biomicroscopy revealed bilateral 2-3+ cells in the anterior chamber, posterior synechia, and pigment precipitates on the lens, all of which were more severe in the right eye. The fundus was not clear in the right eye due to cells in the vitreous. There were vitreous cells in the left eye; however, the optic nerve, macula, and the peripheral retina seemed normal. On fluorescein angiography, the right eye could not be visualized due to vitreal inflammation; the left eye was normal except peripheral vascular leakage in the late phases of the angiogram. The right eye could not be visualized on optical coherence tomography either; however, in the left eye the retina was normal, with

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clumps of cells in the posterior vitreous (Figure 1). The patient was hospitalized for investigation with the diagnosis of bilateral panuveitis.

The results of diagnostic tests investigating possible etiologies were unremarkable. Systemic workup also failed to lead to a specific diagnosis.

When the patient was questioned in more detail regarding her history, she reported she had had similar symptoms in the past which resolved with cessation of vemurafenib therapy. The patient was evaluated in the oncology department of our hospital and they suggested discontinuing vemurafenib. Oral prednisone 1 mg/kg, topical prednisolone acetate (hourly) and cycloplegic drops (three times daily) were started for both eyes.

Her inflammatory findings subsided and the systemic and topical steroids were tapered. She has been under follow-up for 8 months and has exhibited no signs of recurrence of the uveitis or melanoma.

Discussion

Herein, we report a case of bilateral vemurafenib-induced uveitis. No uveitis was reported in a phase 3 trial of vemurafenib.[6] However, uveitis as an adverse effect of vemurafenib was published in several case reports.[7] Therefore, albeit rare, it is a noteworthy side effect of treatment.

Several mechanisms are believed to be involved in the pathogenesis of vemurafenib-induced uveitis. One is the result of vemurafenib-induced lymphocytic infiltration of subclinical uveal metastases. The second is a possible inflammatory response to antigens shared by melanocytes in the melanoma and the choroid.[3,5] The period between the first administration of vemurafenib treatment and initial uveitis symptoms was reported to vary from 1 to 85 weeks (average of 27).[5]

We attributed uveitis to vemurafenib, as we could detect no potential cause in spite of a thorough etiologic investigation and systemic workup. Moreover, the findings resolved with the cessation of the drug and no recurrence was encountered during a period of 8 months.

Our patient had bilateral panuveitis. Guedj et al.[7] reported 7 cases of bilateral vemurafenib-induced uveitis in patients aged 69-81. Six of their patients had anterior uveitis and one had severe panuveitis. Our patient was very young compared to theirs, and the youngest patient in the literature reported to have vemurafenib-induced uveitis. The course of uveitis might be less severe in the elderly.

Whether to discontinue treatment in cases of drug-induced uveitis is controversial. This should be decided based on each patient's ocular findings and systemic condition, in collaboration with oncologists. In a recent report, Fierz et al.[8] continued vemurafenib despite bilateral anterior uveitis which could be controlled with topical steroids. In one of the very first reports of vemurafenib-induced uveitis, the drug was stopped and the uveitis was controlled with systemic steroid therapy.[9] This was similar to our case.

In conclusion, uveitis is not an uncommon adverse effect of vemurafenib, a successful therapeutic option in metastatic melanoma. As vemurafenib becomes more widely used, clinical variation in cases of uveitis associated with its use will also increase. Mild cases can be controlled with topical steroids; however, severe cases could require cessation of treatment-despite the risk of worsening of the systemic disease-and systemic steroid therapy.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Selçuk Sızmaz, Nuhkan Görkemli, Ebru Esen, Nihal Demircan, Concept: Selçuk Sızmaz, Ebru Esen, Nihal Demircan, Design: Selçuk Sızmaz, Ebru Esen, Nihal Demircan, Data Collection or Processing: Selçuk Sızmaz,

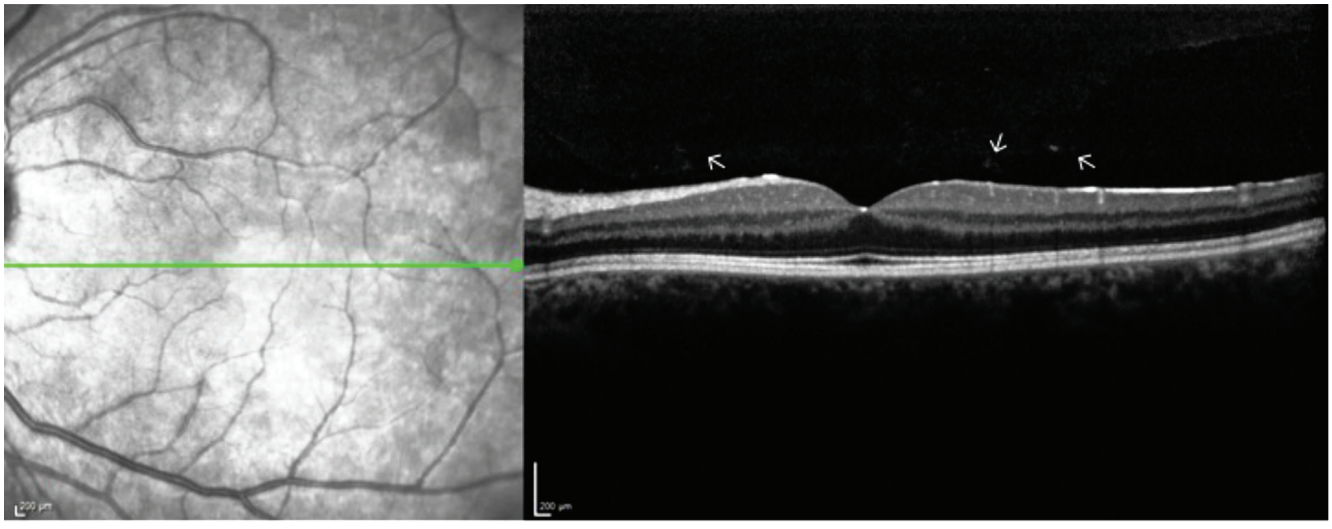

Figure 1. Optical coherence tomography of the posterior pole. Note the clumps of cells in the posterior vitreous showing hyperreflectivity (arrows)

Nuhkan Görkemli, Analysis or Interpretation: Selçuk Sızmaz, Ebru Esen, Nihal Demircan, Literature Search: Selçuk Sızmaz, Nuhkan Görkemli, Writing: Selçuk Sızmaz, Ebru Esen, Nihal Demircan.

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

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

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Letter to the Editor

Corneal, Scleral, Choroidal, and Foveal Thickness in Patients with Rheumatoid Arthritis

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Dear Editor,

We congratulate Gökmen et al.[1] for their paper evaluating corneal, scleral, choroidal, and foveal thickness in patients with rheumatoid arthritis (RA). While the authors found that female patients with RA had a thinner sclera compared to healthy subjects, there was no difference for corneal, choroidal and foveal thickness.

Assessment of the choroid is important because it provides nutrition to the outer retinal structures and hence plays a role in many chorioretinal diseases. While the authors did not find any statistical difference in choroidal thicknesses between the two groups, those with RA were noted to have consistently thicker choroids in all measurements points except at 3 mm nasally. This trend may be interesting.

The authors obtained the choroidal thickness by averaging measurements taken at seven specific points. However, the choroid is a three-dimensional structure with considerable topographic variation.[2,3] Measuring the mean choroidal thickness in different regions of the macula by manual segmentation of the choroid-scleral interface may potentially yield interesting findings.

Similarly, this is a potential consideration when assessing retinal thickness. The authors used the central foveal thickness, which was measured manually from the internal limiting membrane to the retinal pigment epithelium at the fovea. An alternative would be to assess the central subfield retinal thickness using the automated segmentation provided by the proprietary software on Optical Coherence Tomography devices.[4] It has also been shown that the central retinal thickness has less variability than the central point thickness.[5]

In summary, the authors presented interesting findings of a thinner sclera in patients with RA as compared to healthy subjects. The use of choroidal segmentation technique and central retinal thickness may enhance the evaluation of the respective anatomical structures in future studies.

Keywords: Rheumatoid arthritis, scleral thickness, corneal thickness, choroidal-retinal thickness, optical coherence tomography

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Authorship Contributions

Literature Search: Kelvin Z. Li, Colin S. Tan, Writing: Kelvin Z. Li, Colin S. Tan.

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Response from the Authors

Dear Editor,

We are happy to receive a letter concerning our study about corneal, scleral, choroidal, and foveal thickness in patients with rheumatoid arthritis (RA) and we thank Li and Tan for their positive contributions to our study.

In our study we used the single-slice manual segmentation technique around the fovea; however, rheumatoid arthritis is a systemic disease and systemic diseases may affect not only the macula, but all retinal and choroidal vascular structures. Perhaps in the near future, newly developed devices may enable wide-field automated choroidal measurements, thus providing a better understanding of the topographic variations of the three-dimensional vascular structure of the choroid.

For scleral measurements we used time domain optical coherence tomography (OCT) with a 45-degree temporal gaze at one point, but laser penetration of the sclera was significantly lower than retina or choroid, which affects resolution of the uvea-scleral junctional image. However, using swept source anterior segment OCT provides much better image quality and the combination of ultrasound biomicroscopy at multiple points may yield higher quality images and data.[1,2]

We concur with Li and Tan regarding automatic segmentation in retinal thickness measurements. The central macula can now be evaluated using OCT automated segmentation mapping, similar to retinal measurements, and choroidal thickness can also be measured with Early Treatment Diabetic Retinopathy Study subfield segmentations.[3] However, using the line-field or wide-field modalities of swept source OCT may also better evaluate the anatomical structures of the choroid and retina in future studies.[4,5]

Best Regards,

Onur Gökmen, Ahmet Akman, Sirel Gür Güngör

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