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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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To ensure controllability of research findings, the study design, study sample, and methodological approaches and practices should be explained with appropriate sources referenced.
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EDITORIAL

2022 Issue 4 at a Glance:

Esteemed colleagues,

In the 4th issue of 2022, the Turkish Journal of Ophthalmology features eight original studies and three case reports.

In their retrospective clinical study titled "Intraocular Lens Elongation Technique with Haptic Modification for Sulcus Implantation", Baykara et al. evaluated 11 patients in whom a Sensar AR40e lens with modified haptics extending the total diameter from 13 mm to 14.5 mm was placed in the sulcus. The authors reported observing no intraocular lens dislocation or decentration in any eye during the 6-month postoperative follow-up period and concluded that this cost-free and easily performed technique would allow stable sulcus implantation in eyes with insufficient capsular support.

In another retrospective study titled "The Effect of Anterior Segment Depth on the Accuracy of 7 Different Intraocular Lens Calculation Formulas", Kesim et al. analyzed the data of 184 patients with axial length of 22.5-24.5 mm who underwent cataract surgery. Anterior segment depth (ASD) was classified into three groups (Group 1: ASD <7.30 mm, Group 2: ASD 7.30-7.90 mm, Group 3: ASD >7.90 mm) and its effect on the accuracy of 7 different intraocular lens formulas (SRK/T, Holladay I, Hoffer Q, Haigis, Olsen OLCR, Barrett II, Hill-RBF) was examined. Subgroup analysis was also performed based on mean keratometry (K) values (Subgroup 1: K <42.0 D, Subgroup 2: K 42.0-44.5 D, Subgroup 3: K >44.5 D). The mean predictive error, mean absolute error, and median absolute error values of each group and the effect of ASD on the predictive errors of the lens formulas were compared. The authors reported that ASD may have an effect on the accuracy of lens formulas, and that for eyes with axis length of 22.5-24.5 mm, lens formula estimates were significantly hyperopic as ASD increased.

Aslan Katırcıoğlu et al. conducted a retrospective study titled "Clinical Results of the Use of Amniotic Membrane Transplantation Alone or in Combination with Adjuvant Therapies in Conjunctival Fornix Reconstruction" including 27 patients who underwent surgery for fornix obliteration. Symblepharon lysis and amniotic membrane transplantation were performed in all patients, and advanced cases underwent amniotic membrane transplantation in combination with 0.04% mitomycin C application, oral mucosa transplantation, fornix anchoring sutures, eyelid surgery, fibrin glue, and limbal autograft. After a mean follow-up of 45.04±8.4 months, the clinical success rate was 88.8%. The authors reported that although amniotic membrane transplantation alone is a successful method in early-stage conjunctival fornix obliteration, combined surgeries are more effective in advanced-stage fornix obliteration.

In their study titled "Ophthalmological Manifestations in Autism Spectrum Disorder", Gutiérrez et al. evaluated 344 patients with autism spectrum disorder (in 4 groups: autism, Asperger syndrome, pervasive developmental disorder not otherwise specified, and "other") over 8.5 years from an ophthalmological perspective. Refractive error (48.4%) and motility disorder (15.4%) were detected most frequently in the patients. The most common refractive errors were hyperopia and astigmatism, and the rate of myopia was higher in Asperger syndrome. The prevalence of strabismus was higher in the autism and "other" groups, while exotropia was more common in the autism group. Convergence was reported to be normal in approximately half of the patients, and the rate of nystagmus was low (0.9%). The authors emphasized that ophthalmological problems are more common in autism spectrum disorders than in the general pediatric population and that ophthalmologic evaluation is necessary in these children.

In a prospective clinical study titled "Optical Coherence Tomography Angiography Findings in Primary Open-Angle and Pseudoexfoliation Glaucoma", Düzova et al. evaluated vascular density in the optic disc and macular region in glaucomatous and normal eyes using optical coherence tomography angiography and investigated its relationship with structural and functional test results. Eyes with primary open-angle glaucoma (POAG) and pseudoexfoliative glaucoma with similar visual field losses were found to have lower vascular density than normal eyes, and a strong correlation was found between structural and functional tests and vascular density values. The authors also observed that vascular density was lower in eyes with pseudoexfoliative glaucoma compared to the POAG group.

Concerning the medical treatment of glaucoma, Tekeli and Köse conducted a prospective clinical study titled "Evaluation of the Use of Brinzolamide-Brimonidine Fixed Combination in Maximum Medical Therapy" in which they showed a significant decrease in intraocular pressure (IOP) values during 6 months of follow-up in 92 patients with glaucoma and ocular hypertension who were switched to a maximum medical therapy regimen including brinzolamide-brimonidine fixed combination (BBFC). The number of topical antiglaucoma drugs used by the patients decreased significantly, while allergic reaction occurred in 8 patients (8.7%), conjunctival hyperemia developed in 5 patients (5.43%), and irritation and discomfort were reported by

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2 patients (2.5%). As a result, the authors stated that using BBFC in the treatment of glaucoma provided effective IOP reduction with acceptable adverse effects.

In their retrospective study titled "Frequency of *RPE65* Gene Mutation in Patients with Hereditary Retinal Dystrophy", Kahraman et al. investigated the frequency and clinical findings of hereditary retinal dystrophy associated with *RPE65* gene mutation, for which a gene therapy drug received FDA approval in 2017. They evaluated 460 hereditary retinal dystrophy patients who underwent genetic analysis and found that homozygous *RPE65* gene mutation was detected in 11 cases. The authors concluded that *RPE65* gene mutation is a rare autosomal recessive inheritance disorder among the hereditary retinal dystrophies, which are a genotypically and phenotypically heterogeneous group, and they emphasized the importance of genetic screening due to the increase in gene therapy opportunities.

Şekeroğlu et al. conducted a retrospective study titled "Prevalence of Serous Macular Detachment in Recurrent Macular Edema Secondary to Retinal Vein Occlusion" evaluating 71 patients who were treated for retinal vein obstruction-related cystoid macular edema (CME) and serous macular detachment (SMD) and developed recurrent CME during follow-up. The 45 patients whose initial treatment was single-dose dexamethasone implant (Group 1) and the 26 patients who initially received three loading doses of ranibizumab (Group 2) had similar time to CME recurrence (mean 4.7±0.8 months) and prevalence of SMD accompanying recurrent CME (Group 1: n=27, 60.0%, Group 2: n=14, 53.8%). SMD was found to be more common in central retinal vein occlusion than branch retinal vein occlusion cases (71.4% vs. 48.8%), and initial treatment was shown to have no effect on the prevalence of SMD accompanying recurrent CME.

The first case report of the issue, from Cankurtaran and Şekeryapan Gediz, is titled "Sub-Tenon Triamcinolone Acetonide Injection in the Acute Treatment of Handheld Laser-Induced Maculopathy." They reported that early sub-Tenon triamcinolone acetonide injection was effective the treatment of handheld laser-induced retinal injury, which is common in recent years and can result in blindness.

In an article titled "Outer Retina Rupture from Subretinal Blood with Spontaneous Sealing and Visual Recovery in Frosted Branch Angiitis from Familial Mediterranean Fever: A Case Report", Vofo and Amer reported that an 18-year-old female patient with familial Mediterranean fever (an autoinflammatory disease) developed sudden vision loss secondary to retinal pathology that resolved with systemic steroid therapy.

Finally, Sundaram and Gelkopf pointed out in their case report titled "Abducens Nerve Palsy as a Presenting Symptom of Multiple Sclerosis" that isolated sixth nerve paralysis could be seen as an initial symptom in multiple sclerosis (MS), a demyelinating disease of the central nervous system, and emphasized that MS should also be considered in the etiology of young patients without risk factors.

Respectfully on behalf of the Editorial Board,

Nilgün Yıldırım, MD

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Turk J Ophthalmol 2022;52:223-227

Original Article

Intraocular Lens Elongation Technique with Haptic Modification for Sulcus Implantation

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Abstract

Objectives: To define a haptic modification technique to increase the overall length of the intraocular lens (IOL) and evaluate the postoperative outcomes of patients in whom this technique was applied.

Materials and Methods: The preoperative and postoperative characteristics of patients who underwent modified IOL implantation into the sulcus between May 2019 and December 2019 were evaluated. Modified Sensar AR40e lenses with hydrophobic acrylic optic and polymethylmethacrylate haptics were implanted to all eyes. Before implanting the IOL, the haptics were grasped with two toothless forceps and bent to elongate the total diameter of the IOL from 13.0 mm to 14.5 mm.

Results: The study included 11 eyes of 11 patients who underwent modified three-piece IOL implantation into the sulcus due to insufficient capsular support. The mean age of the patients was 53.9±12.2 years. The mean axial length was 24.13±1.93 mm. Sulcus implantation was required due to aphakia in 9 eyes and IOL dislocation in 2 eyes. No haptic breakage occurred during the IOL modification technique or implantation. The mean preoperative best corrected visual acuity (BCVA) was 0.88±1.1 logMAR, while postoperative BCVA was 0.28±0.30 logMAR. No IOL dislocation or decentration was observed during 6-month postoperative follow-up.

Conclusion: The larger diameter lenses obtained with this inexpensive and easily applicable technique may allow a more stable sulcus implantation in eyes with inadequate capsular support.

Keywords: Aphakia, ciliary sulcus, intraocular lens implantation, lens dislocation

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Introduction

Ciliary sulcus implantation is one of the surgical options for the management of aphakia in eyes with a compromised capsular bag. Posterior capsular rupture with adequate anterior capsular support and zonular dehiscence are common indications of ciliary sulcus implantation. However, in the absence of anterior capsular support, sulcus implantation is known to be contraindicated, and in such cases, anterior chamber intraocular lens (IOL) implantation, iris fixation, or scleral fixation may be preferred based on the features of the eye.[1,2]

One-piece acrylic IOLs, which are manufactured for intracapsular placement, are poor choices for sulcus implantation. Their overall length is small for the ciliary sulcus, and their optics have no posterior angulation. These structural properties increase the risk of IOL dislocation and pupillary capture.[3] In addition, continuous iris chafing may cause secondary pigment dispersion, a transient increase in intraocular pressure, secondary pigmentary glaucoma, intraocular hemorrhage, iris transillumination defects, recurrent iridocyclitis, and uveitis-glaucoma-hyphema syndrome.[4,5] Moreover, these complications sometimes require surgical interventions such as IOL exchange and glaucoma surgery.

An IOL to be implanted into the ciliary sulcus should have an overall length of at least 12.5 mm to ensure a stable position and avoid IOL tilt and decentration. In addition, the IOL should have posteriorly angulated, thin looped haptics to prevent the complications associated with uveal tissue chafing. In this context, one-piece polymethylmethacrylate (PMMA) or three-piece acrylic or silicone IOLs are regarded as the best options for ciliary sulcus implantation.[1] However, in a recent study, it was suggested that sulcus-fixated three-piece IOLs with an overall length of 13 mm could also have a larger amount of tilt and decentration.[6]

Herein, we present a technique for haptic modification to achieve an IOL with an overall length of 14.5 mm in order to enable the haptics to rest snugly in the ciliary sulcus with adequate outward tension. This provides a more stable sulcus-implanted IOL without tilt and decentration, even in longer eyes that have minimal anterior capsular support.

Materials and Methods

The medical records of patients who underwent modified and elongated three-piece IOL implantation into the sulcus in the Ophthalmology Department of Uludağ University between May 2019 and December 2019 were identified. Those with follow-up longer than 6 months were included in the study. In all cases, demographic characteristics and preoperative and postoperative ophthalmological findings were noted. The ophthalmological examination included best corrected visual acuity (BCVA) (expressed as logarithm of the minimum angle of resolution [logMAR]), biomicroscopy, intraocular pressure, and fundoscopy preoperatively and 6 months postoperatively.

The study adhered to the tenets of the Declaration of Helsinki and approval to review the patient data was obtained from the Institutional Review Board of Uludağ University (11.11.2020, 2020-20/11).

Surgical Technique

Standard surgical asepsis was achieved, followed by peribulbar anesthesia with a 4 mL combination of 2% lidocaine and 0.5% bupivacaine. A corneal side port was created at the 10 o'clock position with a 20-gauge MVR knife. Through the side port, dispersive viscoelastic material (Viscoat® 40 mg sodium chondroitin sulfate-30 mg sodium hyaluronate) was injected into the anterior chamber (Figure 1A). A clear corneal incision was then made at the 12 o'clock position with a 2.2-mm slit knife (Figure 1B).

A three-piece, foldable, monofocal IOL (Sensar AR40e; Johnson & Johnson Vision, Santa Ana, CA, USA) was used for this novel technique. The IOL has a hydrophobic acrylic optic with posterior angulation of 5° and modified C loop PMMA haptics (Table 1). The technique was applied to each haptic under the surgical microscope. Firstly, two toothless forceps were used to grasp the haptic at two points corresponding to one-third (first junction, nearer to the IOL optic) and two-thirds (second junction, nearer to the end of the haptic) of the length of the haptic. The forceps at the first junction were held tight and fixed, while the other forceps at the second junction were pulled back in the opposite direction from the haptic's normal curve (Figure 1C). From this bending movement, the haptic became longer and curved, resembling a "gull wing" or a lower case "m". The same procedure was repeated for the other haptic (Figure 1D). This increased the overall length of the IOL to 14.5 mm (Figure 1E-F). The modified IOL was then inserted into the cartridge, with care taken to fold the lens in the originally posterior angulated position (Figure 2A-B). The modified IOL was introduced into the anterior chamber through the main corneal incision at 12 o'clock (Figure 2C). After the leading haptic was placed in the sulcus, the trailing haptic was gently pushed under the iris with clockwise rotation using a lens hook (Figure 2D-E). Finally, the IOL was centered with better stabilization due to the modified elongated haptics, which provided sufficient outward tension to rest snugly in the ciliary sulcus. The surgery concluded with corneal hydration after removing the viscoelastic (Figure 2F).

At postoperative sixth months, all patients were evaluated with ultrasound biomicroscopy (UBM) to evaluate IOL position (Figure 3A-B).

To clarify the technique, the twisting points on the haptics are illustrated in Figure 4A, and the difference in length between the original and modified IOLs is shown in Figure 4B.

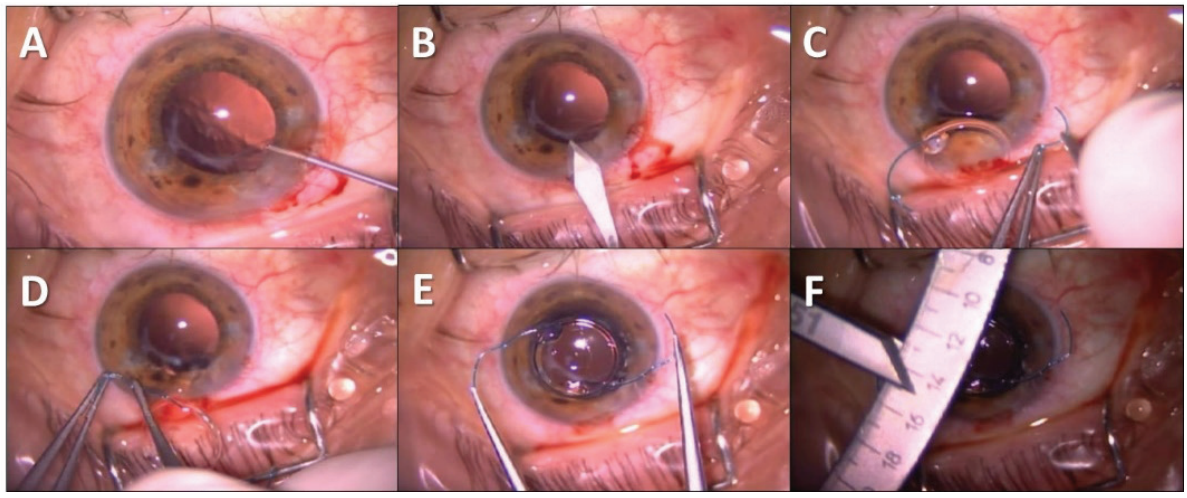

Figure 1. A) Viscoelastic material is injected into the anterior chamber. B) A clear corneal incision is made with a 2.2 mm slit knife. C) One haptic is grasped by two toothless forceps at one-third and two-thirds of the length of the haptic. While the forceps at the first junction are held tight and fixed, the forceps at the second junction are pulled backward in the opposite direction of haptic's normal curve. D) The same procedure is repeated for the other haptic. E) The haptics are thus elongated, resembling a "gull wing." F) The overall length of the lens is increased to 14.5 mm

Table 1. Characteristics of the intraocular lens used in this technique

	Sensar AR40e
Optic characteristics	
Power	+6.0 to +30.0 diopters
Diameter	6 mm
Shape	Biconvex
Material	Hydrophobic acrylic, UV-blocking
A-constant	118.4
Theoretical ACD (mm)	5.2
Refractive index	1.47
Haptic characteristics	
Overall length (mm)	13.0

ACD: Anterior chamber depth, UV: Ultraviolet

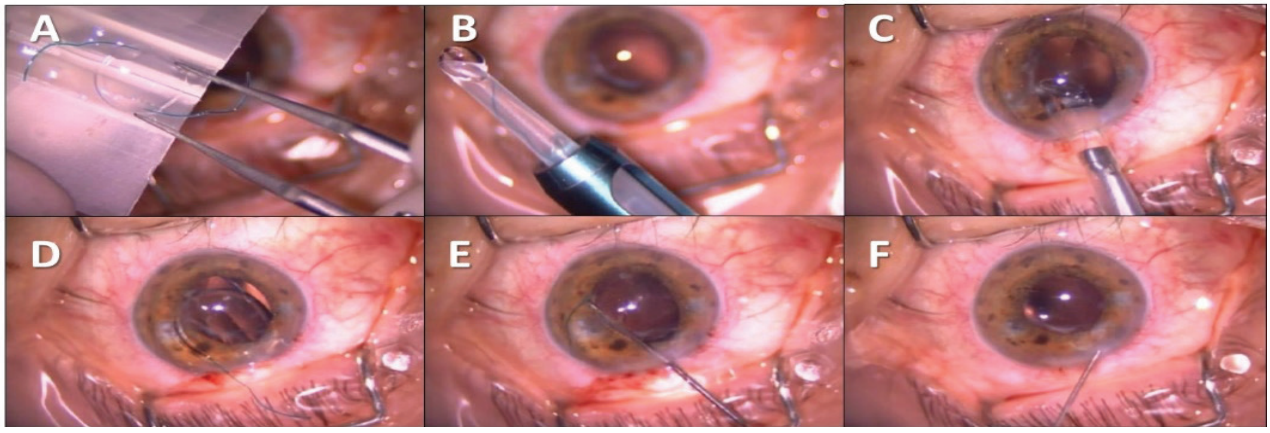

Figure 2. A) The modified intraocular lens (IOL) is inserted into the cartridge. B) The IOL is folded, paying attention to its posterior angulated position. C) The IOL is introduced into the anterior chamber through the main corneal incision at 12 o'clock. D) The leading haptic is placed in the sulcus. E) The trailing haptic is gently pushed under the iris by clockwise rotation using a lens hook. Corneal incisions are closed with hydration after removing the viscoelastic. F) The IOL is seen to be well-stabilized and centered at the end of the surgery

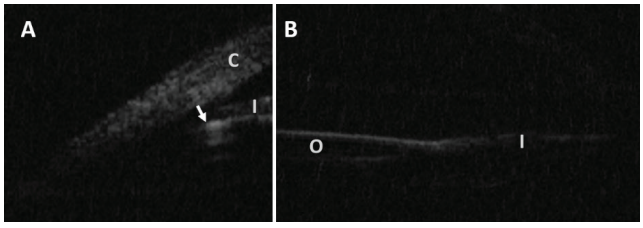

Figure 3. A) Ultrasound biomicroscopic image (UBM) demonstrating a well-positioned haptic of a modified three-piece intraocular lens (IOL). The hyperechoic double line (white arrow) indicates the IOL haptic located in the ciliary sulcus. (C: cornea; I: iris). B) A UBM image showing the optic of the same modified three-piece intraocular lens (O: optic; I: iris)

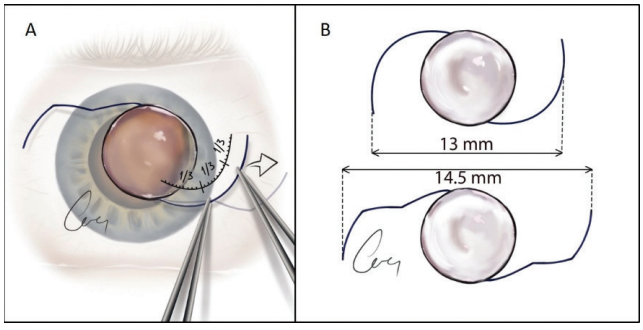

Figure 4. A) The haptic is grasped by two pairs of toothless forceps at the one-third and two-thirds lengths of the haptic. While the forceps at the first junction is held tight and fixed, the other forceps, at the second junction, is pulled backward in the direction opposite the haptic's normal curve (in the direction of the arrow). The final form of the haptic is shown with shaded color. B) After applying the same procedure to both haptics, the overall length of the lens increased from 13 mm to 14.5 mm

Results

Modified and elongated three-piece IOLs were implanted in the ciliary sulcus in 11 eyes of 11 patients with inadequate capsular support. The mean age of the patients was 53.9±12.2 years. Six patients (54.5%) were male. Nine of the 11 eyes were aphakic (due to complicated cataract surgery in 5 eyes and ocular trauma in 4 eyes). In the remaining 2 eyes, ciliary sulcus implantation was required because of previous IOL dislocation.

The mean axial length was 24.13±1.93 mm. The axial length was longer than 24 mm in 4 (36.4%) of 11 eyes. The mean preoperative BCVA was 0.88±1.1 logMAR, while the postoperative BCVA was 0.28±0.30 logMAR. The mean preoperative spherical equivalent (SE) was +9.92±4.43 diopters (D), and at postoperative 6 months, the mean SE was -2.66±1.44 D. The mean intraocular pressure was 16.2±2.6 mmHg at postoperative 6 months.

No haptic breakage occurred during IOL modification and implantation. Postoperatively, no pigmentary dispersion, pupillary capture, IOL dislocation, or decentration were observed upon slit lamp examination in any of the patients during 6-month follow-up. However, IOL tilt angles could not be measured in our study due to technical problems.

Discussion

The safety and efficiency of ciliary sulcus implantation has been well established and accepted in patients with an insufficient lens capsule.[7] However, it is essential to choose the correct IOL, one that is compatible with the sulcus-to-sulcus distance, to decrease the risk of IOL decentration and tilt. The sulcus-to-sulcus distance is estimated to be 11.0 to 12.5 mm based on the measurements taken using endoscopic imaging and UBM. Regarding this, an IOL to be implanted into the sulcus should have an overall length of at least 12.5 mm to generate sufficient outward tension and provide stable haptic fixation.[8,9,10]

A recent study compared the amount of IOL tilt and decentration in lenses implanted in the bag and ciliary sulcus.[6] It was observed that the horizontal and vertical mean tilt were 2.5° and 2.6° for in-the-bag IOLs and 7.68° and 3.01° in sulcus IOLs, respectively. Mean horizontal and vertical decentration were 0.06 mm and 0.02 mm for in-the-bag IOLs and 0.4 mm and 0.31 mm in sulcus IOLs, respectively. Although the IOLs used in that study had an overall length of 13 mm, it was clear that the amount of IOL tilt and decentration was larger in sulcus implantation than in-the-bag implantation.[6]

In a UBM study, the surgeon intended to perform sulcus implantation using IOLs with overall diameters ranging from 12.5 to 14.0 mm in 36 eyes.[11] However, UBM showed that both haptics were in the target position in only 47% of eyes. In the rest of the eyes, one or both haptics were in inadvertent positions, such as in the pars plicata, pars plana, and in-the-bag. In the aforementioned study, the optic of the IOL was found to be tilted in 56% of the patients. However, this was an insignificant tilt ranging from 100 to 200 µm, a degree that could not be detected clinically by slit lamp examination and was only detectable via UBM.[11] In another UBM study, Zhao et al.[7] suggested a greater tendency toward vertical decentration than horizontal decentration in ciliary sulcus fixation in the pediatric age group. They hypothesized that the size disparity between the IOL and ciliary sulcus and gravity may cause IOL decentration. Similarly, Trivedi et al.[12] suggested that longer eyes, associated with wider sulcus-to-sulcus distance, might be prone to IOL decentration.

We describe a novel haptic modification technique intended to decrease the risk of IOL tilt and decentration resulting from the size disparity between the IOL and sulcus. The IOL is modified by elongating its haptics, thereby increasing the overall length from 13 mm to 14.5 mm. We attribute the better IOL centration and stability to the modified, longer haptics, which provide sufficient outward tension to sit tightly in the ciliary sulcus. In addition, the modified IOL could enable sulcus implantation even in eyes with minimal anterior capsular support.

This technique can be used both for primary IOL implantation during cataract surgery complicated by capsular tear and secondary IOL implantation in the management of surgical or traumatic aphakia. Possible complications of the technique include the breakage of the PMMA haptics during the elongation procedure. However, in our small study cohort

(11 eyes), we did not observe any haptic breakage during IOL modification and implantation. In addition, bending the haptic could compromise the structural and mechanical strength of the haptic and lead to breakage in long-term follow-up.

Study Limitations

Limitations of the study are the small number of patients, the retrospective nature of the study, the lack of long-term results, and the inability to measure the amount of IOL decentration and tilt due to technical issues.

Conclusion

In conclusion, this cost-free, easy-to-learn, and easily applicable technique may be a safe and viable alternative method in sulcus implantation, particularly in longer eyes with inadequate capsular support. However, further prospective studies that measure IOL tilt angle via UBM or anterior segment optical coherence tomography in larger numbers of patients with long-term follow-up are required to determine the safety of our technique.

Ethics

Ethics Committee Approval: The study adhered to the tenets of the Declaration of Helsinki and approval to review the patient data was obtained from the Institutional Review Board of Uludağ University (11.11.2020, 2020-20/11).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., Concept: M.B., G.U.G., A.Ç.E., Design: M.B., G.U.G., A.Ç.E., Data Collection or Processing: G.U.G., A.Ç.E., Analysis or Interpretation: M.B., G.U.G., Literature Search: G.U.G., A.Ç.E., Writing: G.U.G.

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

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Original Article

The Effect of Anterior Segment Depth on the Accuracy of 7 Different Intraocular Lens Calculation Formulas

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Abstract

Objectives: To evaluate the effect of anterior segment depth (ASD; sum of anterior chamber depth and lens thickness) on the accuracy of 7 intraocular lens formulas calculated in patients with axial length (AL) between 22.5 and 24.5 mm.

Materials and Methods: In this retrospective study, patients who underwent cataract surgery were divided into three groups based on their ASD measurements (Group I: ASD <7.30 mm, Group II: ASD between 7.30-7.90 mm, Group III: ASD >7.90 mm). The mean predictive error (MPE), mean absolute error (MAE), and median absolute error (MedAE) values of each group were compared. The effect of ASD on the predictive error (PE) of each lens formula was additionally tested in subgroups based on mean keratometry (K) values (Subgroup I: K <42.0 D, Subgroup II: K between 42.0-44.5 D, Subgroup III: K >44.5 D).

Results: The study included 184 eyes of 184 patients. In Group I, all formulas except Olsen OLCR and Barrett II had clinically myopic MPEs. In Group II, the MPEs of all lens formulas except Barrett II were statistically non-different from zero ($p>0.05$). In Group III, the MPEs of all lens formulas were found to be statistically hyperopic. In Group III, all formulas except Olsen OLCR were significantly shifted to more hyperopic results when compared with Groups I and II ($p<0.05$). ASD was positively correlated with the PEs of the SRK/T, Holladay I, Hoffer Q, Barrett II, Hill-RBF, and Haigis formulas. In cases with mean K greater than 42.0 D, ASD was similarly correlated with PE for all formulas except Olsen OLCR.

Conclusion: In eyes with AL between 22.5 and 24.5 mm, the predictions of lens formulas were significantly hyperopic in cases with greater ASD.

Keywords: anterior segment depth, predictive error, lens formula, axial length

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Introduction

With the advent of microincisional techniques, cataract surgery has become the most commonly performed surgery worldwide. Despite groundbreaking advances in intraocular lens (IOL) calculations, 30-40% of cases still miss their predictive refractive targets by ±0.50 diopters (D) or more. This problem is largely due to uncertainty in the prediction of the effective lens position (ELP) preoperatively.[1]

Although axial length (AL) and keratometry (K) measurements are the mainstay parameters of all IOL calculation formulas, they are not directly related to ELP, which is almost synonymous with postoperative anterior chamber depth (ACD). Therefore, newer formulas use preoperative ACD and lens thickness (LT) measurements in isolation to predict ELP.[2,3,4] Unlike AL and K measurements, which are reproducible and remain steady throughout the lifetime, ACD and LT measurements may be significantly affected by conditions such as natural accommodation, pharmacologic cycloplegia, and aging.[5,6,7,8] In these conditions, the increase in LT is accompanied by an approximately equal decrease in ACD, and vice versa.[9] This would result in a relatively stable anterior segment depth (ASD; the sum of ACD and L), which might offer a stable and reliable biometric parameter comparable to AL and K, to predict ELP better than ACD or LT measurement in isolation.

Most commonly used vergence formulas (Holladay 1, SRK/T, Hoffer Q, and Haigis) predict ELP using either AL, K, or ACD measurements (Holladay 1, SRK/T, and Hoffer Q use AL and K; Haigis uses AL and ACD).[10,11,12,13] New-generation formulas seek to improve IOL calculation on different bases. While Barrett II Universal is a 5-variable vergence formula including LT and white-to-white (WTW) measurements, Olsen is based on ray-tracing and a C constant derived from ACD and LT, and Hill-Radial Basis Function (Hill-RBF) is an artificial intelligence-based formula.[3,4,14] The main purpose of this study was to assess the effect of ASD on the predictions of these IOL calculation formulas and to evaluate the postoperative predictive errors (PEs) of these formulas in eyes with different ASD.

Materials and Methods

Study participants

This study was conducted with Koç University Institutional Review Board approval (decision number: 2019.410.IRB2.131), according to the tenets of the Declaration of Helsinki.

Consecutive patients who underwent cataract surgery between July 2018 and May 2019 with AcrySof SN60WF (both Alcon Laboratories, Inc.) by experienced surgeons (A.S., O.M.) were included in this retrospective study. Inclusion criteria were: (1) no history of previous ocular surgery, (2) no ocular condition other than cataract, and (3) AL of 22.5-24.5 mm. Patients who had intraoperative or postoperative complications and with postoperative corrected distance visual acuity worse than 20/40 at 1 month were excluded.

Data Calculation and Analysis

Preoperative AL, mean K, ACD, and LT values were measured with optical low-coherence reflectometry (OLCR) (Lenstar LS900, Haag-Steit AG). Eyes were classified in three groups based on their ASD distribution: Group I included eyes with ASD lower than 7.30 mm, Group II included eyes with ASD in the 7.30-7.90 mm range, and Group III included eyes with ASD greater than 7.90 mm. Manifest refraction was performed by an experienced ophthalmologist (C.K.) at least 1 month postoperatively for each eye.

The accuracy of 4 vergence formulas (SRK/T, Holladay 1, Hoffer Q, Haigis) and 3 new-generation formulas (Olsen, Barrett II, Hill-RBF) were evaluated. User Group for Laser Interference Biometry (ULIB) lens constants were used for each IOL.[15] All formula calculations were obtained from the default software program of the OLCR device (EyeSuite, Haag-Steit AG). The formulas were not optimized to detect systemic PEs in this study population. The PE for each formula was calculated by subtracting the predicted refractive error from the actual postoperative spherical refraction; therefore, a negative PE indicated a refractive result that was more myopic than predicted by the formula. Mean predictive errors (MPE) and median absolute errors (MedAE) were noted. The possible effect of K on the correlation between ASD and PEs was additionally investigated in three subgroups based on mean K values (Subgroup I: Mean K less than 42.0 D, Subgroup II: Mean K between 42.0 and 44.5 D, Subgroup III: Mean K greater than 44.5 D).

Statistical Analysis

SPSS Statistics software (version 20.0, IBM, Armonk, NY, USA) was used for statistical analysis. Data distribution was checked for normality with Kolmogorov-Smirnov analysis. One-sample t-test was performed to evaluate whether the MPE values of lens formulas were different from zero. MPE differences between three groups were analyzed with one-way analysis of variance (ANOVA), which was followed by post-hoc t-tests with Bonferroni correction. Friedman test was performed to compare MedAEs between formulas for each group to evaluate accuracy, which was followed by Wilcoxon signed-rank test with Bonferroni correction for post-hoc analysis. Correlation analysis between biometric parameters and the PEs of the lens formulas was performed with Spearman's rho analysis. A probability less than 5% ($p<.05$) was considered statistically significant.

Results

The study included 184 eyes of 184 patients (age: 69±9 years, 116 women) who underwent cataract surgery. Table 1 shows the demographic and biometric findings in total and in the three study groups. There was no significant difference between the groups in terms of age or mean K values ($p>.05$). Figure 1 shows the mean PEs of different formulas according to

ASD range. There was an apparent relation between ASD and MPE for all formulas, showing a tendency towards hyperopic error with increasing ASD and a tendency towards myopic error with decreasing ASD. There were 29 patients were in Group I, 107 patients in Group II, and 48 patients in Group III. Although AL was statistically higher in Group III than Groups I and II (p<.05 for both), it was clinically negligible (23.23±0.48 in Group I, 23.31±0.55 in Group II, and 23.61±0.51 in Group III).

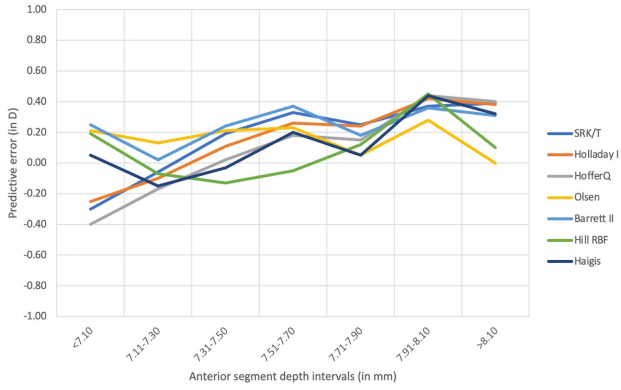

Figure 1. Line graph showing mean predictive error values (in diopters) of 7 lens formulas based on anterior segment depth intervals (in mm)

Predictive Errors of Lens Formulas

Table 2 shows the MPE values of the three groups with their one sample t-test results. MPE values nearest to zero were obtained with Haigis in Group I (-0.03±0.73 D), Hill-RBF in Group II (-0.02±0.49 D), and Olsen OLCR in Group III (0.27±0.44 D). In Group I, the Hoffer Q formula had an MPE value statistically different from zero (p=.008), while the predictions of the other formulas were statistically equivalent to postoperative refraction. In Group II, all formulas but Hill-RBF and Haigis had MPE values statistically different from zero (p<.05 for all except Hill-RBF: -0.02±0.49 D, p=.684 and Haigis: -0.03±0.46 D, p=.197). In Group III, the MPE results of all formulas were found to be statistically hyperopic (p<.05 for all). The MPE of the Olsen formula was mathematically closest to zero (0.27±0.44 D), which was still statistically different from zero. Group-related differences for all lens formulas are shown in Figure 2. One-way ANOVA showed that PE differed significantly between the three groups for all formulas except Olsen OLCR and Barrett II (p<.05 for all except Olsen: p=.896 and Barrett: p=.299). Post-hoc tests showed that all remaining 5 formulas had more hyperopic PE values in Group III eyes than in Group I eyes (p<.05 for all). In addition, the PEs of SRK/T, Holladay 1, and Hoffer Q were also more hyperopic for Group II eyes than for Group I eyes (p<.05 for all), and the PEs of Hill-RBF and Haigis were significantly more hyperopic for Group III eyes than for Group II eyes (p<.05 for all).

Table 1. Demographic and biometric data of the study

Parameter		Total (n=184)	Group I (n=30)	Group II (n=106)	Group III (n=48)	p (ANOVA)
Age	Mean ± SD	69±9	68±9	69±9	71±8	0.275
	(Range)	(48, 87)	(49, 87)	(48, 86)	(56, 85)	
AL (mm)	Mean ± SD	23.38±0.55	23.23±0.48	23.31±0.55	23.63±0.51	0.001
	(Range)	(22.50, 24.48)	(22.55, 24.32)	(22.50, 24.41)	(22.68, 24.48)	
Mean K (D)	Mean ± SD	43.58±1.42	43.57±1.34	43.40±1.42	43.96±1.41	0.072
	(Range)	(40.46, 46.25)	(41.60, 45.75)	40.46, 46.25)	(41.25, 46.12)	
CCT (µm)	Mean ± SD	544±34	548±36	542 ± 32	547±39	0.532
	(Range)	(476, 633)	(479, 633)	(477, 620)	(476, 616)	
ACD (mm)	Mean ± SD	3.09±0.33	2.93±0.28	3.07 0.33	3.22±0.32	0.001
	(Range)	(2.16, 4.04)	(2.41, 3.50)	(2.16, 3.75)	(2.38, 4.04)	
LT (mm)	Mean ± SD	4.57±0.41	4.19±0.29	4.54±0.36	4.87±0.35	<0.001
	(Range)	(3.67, 5.66)	(3.67, 4.76)	(3.71, 5.30)	(4.08, 5.66)	
IOL power (D)	Mean ± SD	22.2±1.89	22.47±1.49	22.65±1.89	21.04±1.59	<0.001
	(Range)	(17.5, 27.0)	(20.0, 25.5)	(18.0, 27.0)	(17.5, 24.5)	
ASD (mm)	Mean ± SD	7.66±0.35	7.12±0.18	7.61±0.17	8.09±0.17	<0.001
	(Range)	(6.68, 8.68)	(6.68, 7.30)	(7.31, 7.90)	(7.92, 8.68)	

AL: Axial length, K: Keratometry, CCT: Central corneal thickness, ACD: Anterior chamber depth, LT: Lens thickness, IOL: Intraocular lens, ASD: Anterior segment depth, ANOVA: Analysis of variance, SD: Standard deviation. Note the statistically significant differences in AL between Groups I and III (p=0.005) and Groups II and III (p=0.002).

The MedAEs of the formulas are shown in Table 3 and Figures 3A-C. There were no differences between the formulas' MedAE values in Groups I and II. In Group III, Hill-RBF had lower MedAE than Haigis (0.38 and 0.46 respectively, p<.007 with Bonferroni adjustment). There was no statistically significant difference between the other formulas.

Correlations Between Ocular Biometrics and Predictive Error

The results of correlation analysis between the PEs of the 7 lens calculation formulas and the ocular biometric parameters of ACD, LT, and ASD are shown in Table 4. PE was positively correlated with ACD for Hoffer Q (r=0.280, p<.01) and with LT

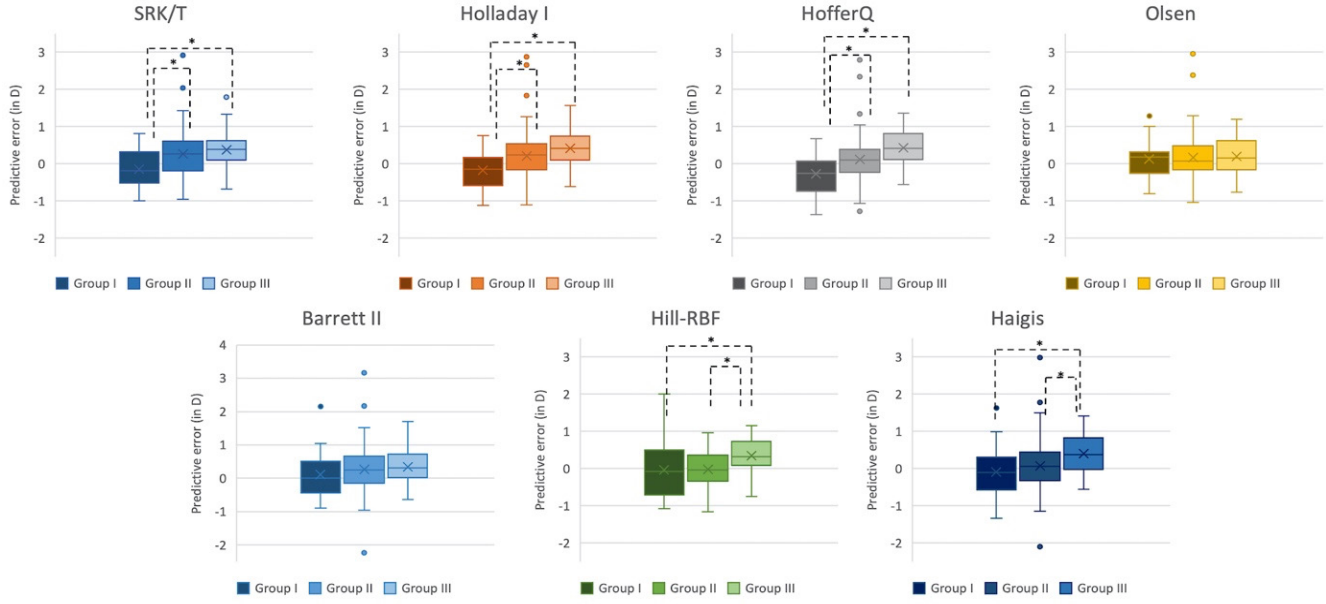

Figure 2. Box plot presentation of predictive errors (PEs) (in diopters) for 7 lens formulas. Results for Group I (anterior segment depth [ASD] <7.30 mm), Group II (ASD 7.30-7.90 mm) and Group III (ASD >7.90 mm) are given in separate box plots for each formula (outliers shown as individual dots). *Statistically significant (p<.05)

Table 2. Mean predictive errors (MPE) of 7 lens calculation formulas in the anterior segment depth (ASD) groups

Formula		Group I ASD <7.30 mm	Group II ASD 7.30-7.90 mm	Group III ASD >7.90 mm
SRK/T	MPE	-0.11±0.58	0.13±0.51	0.36±0.29
	p	0.131	<0.001	<0.001
Holladay	MPE	-0.15±0.55	0.05±0.47	0.42±0.40
	p	0.058	0.001	<0.001
Hoffer Q	MPE	-0.24±0.59	-0.04±0.45	0.45±0.43
	p	0.008	0.049	<0.001
Olsen	MPE	0.14±0.60	0.06±0.42	0.27±0.44
	p	0.197	0.008	0.008
Barrett II	MPE	0.22±0.76	0.14±0.49	0.37±0.37
	p	0.364	<0.001	<0.001
Hill-RBF	MPE	-0.03±0.76	-0.02±0.49	0.35±0.41
	p	0.868	0.684	<0.001
Haigis	MPE	-0.03±0.73	-0.03±0.46	0.45±0.44
	p	0.442	0.197	<0.001

For each formula, the first row gives MPE value (in diopters) and the second row gives the p value from one-sample t-test comparing predictive error with zero. A p value less than 0.05 was considered statistically significant.

for SRK/T (r=0.203, p<.01). ASD showed significant positive correlation with PE for 5 formulas, SRK/T (r=0.273, p<.01), Holladay 1 (r=0.347, p<.01), Hoffer Q (r=0.408, p<.01), Hill-RBF (r=0.292, p<.01), and Haigis (r=0.295, p<.04), but not for Olsen OLCR and Barrett II (r=0.011, p<.881 and r=0.119, p<.110, respectively).

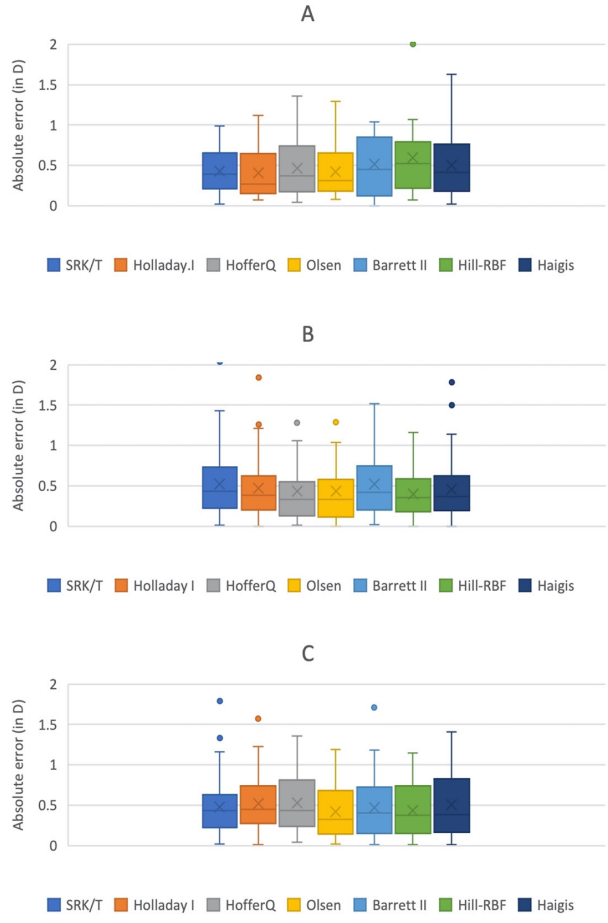

Figure 3. Box plot presentation of absolute errors (AEs) in diopters (D): A) in eyes with anterior segment depth (ASD) less than 7.30 mm, B) in eyes with ASD between 7.30 and 7.90 mm, C) in eyes with ASD greater than 7.90 mm. Outliers shown as individual dots

The effect of K on the correlation between ASD and PE is shown in Table 5. No correlation was found between ASD and the PEs of the formulas in Subgroup I except for a weak correlation for Hoffer Q (r=0.364, p=0.048). In Subgroup II, ASD was positively correlated with the PEs of SRK/T, Holladay 1, Hoffer Q, and Haigis. In Subgroup III, ASD was positively correlated with SRK/T, Holladay 1, Hoffer Q, Hill-RBF, and Haigis.

Discussion

Precise prediction of ELP remains among the unresolved challenges of current cataract surgery. As a biometric parameter that is created following the removal of the crystalline lens, ELP should either be assessed by direct intraoperative measurement of the distance between the posterior corneal surface and posterior lens capsule, or indirect preoperative prediction by lens regression formulas, the latter being the most commonly used method in clinical practice. The advent of high-resolution OLCR and optical coherence tomography (OCT) techniques enabled the incorporation of ACD and LT parameters separately to increase the precision of these formulas. Although ASD might simply be regarded as the combination of ACD and LT, this parameter could present variations that are not strictly dependent on the dimensions of ACD and LT. Therefore, ASD might have a separate effect on ELP which otherwise cannot be predicted by ACD and LT values, resulting in PEs that are detectable by ASD assessment in particular.

The current study revealed a trend towards postoperative hyperopic error in IOL predictions with increasing ASD (particularly more than 7.90 mm) and towards myopic error with decreasing ASD (particularly less than 7.30 mm), regardless of the lens formula used. The lens formulas successfully predicted IOL power when ASD was between 7.60 and 7.90 mm, giving PEs that were non-different from zero. The shift from myopia to hyperopia is shown in Table 3, with the highest rate of hyperopic results found in Group III.

Table 3. Median absolute errors (in diopters) of 7 lens calculation formulas in the anterior segment depth (ASD) groups

Formula	SRK/T	Holladay	Hoffer Q	Olsen	Barrett II	Hill-RBF	Haigis	p (Friedman's test)
Group I, ASD <7.30 mm	0.43	0.48	0.42	0.42	0.51	0.52	0.59	0.720
Group II, ASD 7.30-7.90 mm	0.39	0.37	0.31	0.27	0.34	0.36	0.28	0.155
Group III, ASD >7.90 mm	0.33	0.45	0.51	0.34	0.32	0.38	0.46	0.001

Table 4. Correlation analysis between the predictive error of 7 formulas and biometric parameters

Formulas		Parameters			
		Mean K	**ACD**	**LT**	**ASD**
SRK/T	rho	-0.313	0.028	0.203	0.273
	p	<0.001	0.701	0.006	<0.001
Holladay 1	rho	-0.107	0.165	0.162	0.347
	p	0.151	0.026	0.029	<0.001
Hoffer Q	rho	0.072	0.280	0.120	0.408
	p	0.332	<0.001	0.103	<0.001
Olsen OLCR	rho	0.007	-0.071	0.065	0.011
	p	0.924	0.346	0.388	0.881
Barrett II	rho	-0.267	-0.050	0.129	0.119
	p	<0.001	0.504	0.081	0.110
Hill-RBF	rho	-0.055	0.111	0.150	0.292
	p	0.552	0.226	0.100	0.001
Haigis	rho	0.076	0.089	0.174	0.295
	p	0.302	0.231	0.018	<0.001

K: Keratometry, ACD: Anterior chamber depth, LT: Lens thickness, ASD: Anterior segment depth. For each formula, the first row gives the Spearman's rho value and the second row gives its corresponding p value

Table 5. Correlation analysis between the predictive errors of 7 formulas and anterior segment depth (ASD) in mean keratometry (K) subgroups

Formulas		Mean K values		
		K <42.0 D	**K: 42.0-44.5 D**	**K >44.5 D**
		n=30	**n=100**	**n=54**
SRK/T	Rho:	0.313	0.304	0.378
	P:	0.092	0.002	0.005
Holladay 1	Rho:	0.342	0.321	0.454
	P:	0.065	0.001	0.001
Hoffer Q	Rho:	0.364	0.362	0.500
	P:	0.048	<0.001	<0.001
Olsen OLCR	Rho:	0.005	-0.084	0.218
	P:	0.979	0.410	0.120
Barrett II	Rho:	0.042	0.114	0.251
	P:	0.825	0.257	0.070
Hill-RBF	Rho:	0.179	0.174	0.571
	P:	0.450	0.163	<0.001
Haigis	Rho:	0.251	0.257	0.402
	P:	0.181	0.010	0.003

D: Diopters. For each formula, the first row gives the Spearman's rho value and the second row gives its corresponding p value

In our study, we also analyzed whether ASD or ACD variations were more reliable to predict hyperopic shift in the PEs of lens formulas. As shown in Table 4, ASD was strongly correlated with the PEs of 5 lens formulas, whereas ACD was only correlated with the PE of the Hoffer Q formula. The only two lens formulas that were not biased by ASD variations were Olsen OLCR and Barrett II. Our results were similar in subgroups with normal and high mean K values, showing that the effect of ASD was mostly independent from keratometric parameters.

A study conducted by Gökce et al.[16] investigated the effect of ACD on the accuracy of 8 IOL calculation formulas. They found that the PEs of the Holladay 1 and Hoffer Q formulas were myopic in eyes with ACD lower than 3.00 mm and hyperopic in those with ACD greater than 3.50 mm, whereas the results of Olsen OLCR were inversely hyperopic in shallow ACD and myopic in deeper ACD. In their study, the Holladay 2, Barrett II, and Haigis formulas had lower PEs that were non-different from zero in the same groups. They also showed that while Holladay 1, Hoffer Q, and Hill-RBF were positively correlated with ACD, Olsen OLCR was negatively correlated. In contrast, the Holladay 2, Barrett II, Haigis, and the purchased version of the Olsen formula were not correlated. With these results, they concluded that while the implanted IOLs were more posteriorly located than predicted by the Holladay 1 and Hoffer Q formulas, the inclusion of ACD in the Holladay 2, Barrett II, Haigis, and the purchased Olsen formulas improved the accuracy of ELP prediction. They also acknowledged that in their study, eyes with shallower ACD had greater LT. Thus, they concluded that it would be prudent to use lens formulas that include both ACD and LT together (Holladay 2, Barrett II, and Olsen). In our study, we showed that despite the inclusion of ACD and LT, two of these formulas (Barrett II and Olsen) still yielded significantly hyperopic PEs, which might be explained by an alteration of ASD as a whole, rather than separate ACD or LT variations. In view of these findings, we suggest that eyes with larger ASD might have more posteriorly located ELPs than the preoperative estimations of the lens formulas, which resulted in their hyperopic predictions, and ASD might be a better ocular parameter than ACD or LT alone in predicting ELP.

As mentioned above, ACD and LT measurements could vary with cycloplegic examination. The impact of these variations on IOL calculation results have been investigated in several studies.[6,7,8] By measuring with a swept-source OCT-based biometer (IOLMaster 700®), Arriola-Villalobos et al.[7] showed no effect of cycloplegia-related ACD and LT variations on the Holladay 2 and SRK/T formulas. However, Huang et al.[6] reported a significant difference between IOL calculations of the Haigis formula with and without cycloplegia when measured with Lenstar LS900®. In addition to Haigis, Ozyol et al.[8] showed a significant difference in Holladay 2 formula calculations when measured with the IOLMaster 700®. Based on these results, it should be noted that lens formulas including ACD parameters are likely to be affected by changes in ACD induced by cycloplegia. Presumably, ASD might not be affected by accommodation and cycloplegia, and thus could be a more stable and reliable biometric parameter than ACD.

Melles et al.[17] conducted a large population study evaluating the bias introduced by ocular biometric parameters in lens calculation formulas. Based on their results, they concluded that Barrett II and Olsen OLCR had the best outcomes in terms of the accuracy of postoperative spherical equivalent. They also emphasized that most of the formulas were affected by ocular biometric changes. They demonstrated that SRK/T was particularly affected by changes in mean K, whereas Hoffer Q and Olsen OLCR had significant bias with varying ACD, and Haigis was the formula most affected by LT variations. These results were the driving factors for investigating the effect of ASD on the predictions of lens formulas in our current study.

There are two recent articles in the literature which investigated the effect of ASD on ELP. Plat et al.[18] analyzed correlations between preoperatively acquired biometric parameters and postoperative actual lens position (ALP) with OLCR. They demonstrated that AL, ACD, ASD, and WTW measurements were correlated with ALP. Satou et al.[19] analyzed anterior segment anatomy with anterior segment OCT, in which they identified anterior, equatorial, and posterior surface depth of the crystalline lens preoperatively (hence anterior surface depth and posterior surface depth correspond to ACD and ASD in our study, respectively). They concluded that lens equatorial and posterior surface depth were correlated with IOL position as well as with the refractive PE of the SRK/T formula. Both studies made the assumption that including ASD (or posterior surface depth) in the lens calculation would improve ELP predictions.

The effect of ASD on vergence lens calculation formulas was first analyzed by Olsen and Hoffmann,[4] who showed that the PEs of SRK/T, Holladay I, Haigis, and Hoffer Q had bias in terms of the AL, K, and ASD, which led them to introduce the C constant into the Olsen formula in order to reduce the effect of LT (and therefore ASD) on ELP preoperatively. In the current study, we further developed this approach by including new-generation Barrett II and Hill-RBF formulas and comparing the performances of both old- and new-generation formulas in eyes grouped according to their ASD values. Our results have shown that, although both old- and new-generation formulas were affected by ASD variations, Olsen OLCR and Barrett II seemed to be the least affected formulas. This is likely because both of these formulas include ACD and LT changes in their calculations.[4,20] However, Olsen OLCR still had more hyperopic than myopic results in all groups, which makes it less reliable for eyes with ASD lower than 7.90 mm, as other lens formulas provided better estimations in this range. On the other hand, as described by Cooke and Cooke,[21] the two types of Olsen formula (Olsen OLCR and Olsen Phacooptics) might have different

accuracy outcomes. In our study, the presented results belonged to Olsen OLCR formula. Observing the apparent success of older formulas in eyes with ASD less than 7.90 mm, adjusting these formulas according to ASD changes might be considered as an effective option to improve their results for eyes with ASD greater than 7.90 mm. Norrby et al.[22] argued that using ACD as the sole predictor for postoperative IOL position was sufficient. However, our findings suggest that using ASD, which includes LT measurement as an intrinsic adjusting factor for ACD, might also be beneficial.

Study limitations

Limitations of this study are its small sample size, retrospective design, and the inability to analyze AL and mean K variations in the three ASD groups due to the sample size, which are equally important to explain the PEs of lens formulas. We calculated ocular biometric parameters with the OLCR device only, which is not considered the gold standard for anatomical measurements. Despite these limitations, our study offers a new approach to classifying cataract surgery candidates preoperatively to assess postoperative ELP which indicates more accurate lens formulas for different ASD values. Further studies with larger sample sizes (1) to evaluate the effect of ASD on lens formulas in eyes with short and long ALs, (2) to compare different biometric measurement devices that use OLCR, partial coherence interferometry, and ultrasound in the calculation of ASD, and (3) to detect the ability of ASD to predict ELP with the calculation of postoperative IOL position might show promising results.

Conclusion

Our study showed that ASD seems to be important in assessing postoperative refraction predictions of IOL calculation formulas. Although most IOL calculation formulas do well between ASD 7.30 mm and 7.90 mm, selecting formulas which take ACD and LT into account may achieve better results when ASD is out of this range. Variations in ASD affected the PEs of older vergence formulas and Hill-RBF. Therefore, including ASD in ELP calculations would improve IOL predictions. More and possibly larger studies including extreme biometric measurements are needed to further evaluate the effects of ASD on IOL calculation predictions.

Ethics

Ethics Committee Approval: This study was conducted with Koç University Institutional Review Board approval (decision number: 2019.410.IRB2.131), according to the tenets of the Declaration of Helsinki.

Informed Consent: Patient consent was obtained for the use of their medical records.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ş., O.M., Concept: A.Ş., O.M., M.H., Design: A.Ş., O.M., Data Collection or Processing: C.K., A.Y.T., M.Z.K., Analysis or Interpretation: C.K., A.Ş., O.M., Literature Search: C.K., A.Y.T., M.Z.K., Writing: C.K.

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Original Article

Clinical Results of the Use of Amniotic Membrane Transplantation Alone or in Combination with Adjuvant Therapies in Conjunctival Fornix Reconstruction

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Abstract

Objectives: To evaluate the clinical results of amniotic membrane transplantation alone or in combination with adjuvant therapies in conjunctival fornix reconstruction.

Materials and Methods: The clinical results of patients who presented to our clinic between 2002 and 2016 due to conjunctival fornix obliteration and underwent amniotic membrane transplantation alone or in combination with additional treatments were retrospectively analyzed. The Foster and Mondino classifications were used to grade fornix obliteration. In all cases, the area of conjunctival defect formed after symblepharon lysis was covered with amniotic membrane. In advanced fornix obliteration, amniotic membrane transplantation was combined with 0.04% mitomycin-C (MMC), oral mucosal transplantation, fornix formation (anchoring) sutures, symblepharon ring, eyelid surgery, fibrin glue, and limbal autograft. Deep and scarless restoration of the fornix was considered surgical success.

Results: Twenty-two men and 5 women with a mean age of 45.54±4.17 years were included in the study. The etiology of fornix obliteration was mechanical trauma in 16 cases, chemical burn in 6 cases, recurrent pterygium in 3 cases, thermal burn in 1 case, and recurrent chalazion surgery in 1 case. Indications for amniotic membrane transplantation were socket insufficiency in 12 cases, cosmetic reasons in 4 cases, keratoplasty preparation in 3 cases, ptosis in 3 cases, entropion in 2 cases, strabismus in 2 cases, and diplopia in 1 case. The mean follow-up period was 45.04±8.4 months. Twenty-four of 27 cases (88.8%) were successful, while 3 (12.2%) failed due to recurrence of symblepharon.

Conclusion: Amniotic membrane transplantation is a successful method when used alone in the reconstruction of early-stage conjunctival fornix obliteration and provides safe and effective results in advanced-stage fornix obliteration when performed in combination with topical 0.04% MMC, oral mucosal transplantation, and limbal autograft surgeries.

Keywords: Adjuvant treatments, amniotic membrane transplantation, fornix stenosis, mitomycin-C, symblepharon

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Introduction

The conjunctival fornix is anatomically crucial for providing a tear reservoir and also facilitates the full range of ocular motility when there is natural, smooth contact between the lid and globe during blinking.[1] Obliteration of the fornix may be caused by various ocular surface disorders such as chemical and thermal burns, mechanical trauma, mucous membrane pemphigoid, Stevens-Johnson syndrome, adenoviral membranous conjunctivitis, recurrent pterygium, and evisceration or enucleation surgeries.[1,2,3,4]

Fornix obliteration associated with different etiologies may affect ocular surface health through a number of pathogenic mechanisms: reduction of the tear reservoir, interruption of tear flow and spread, blink-related microtrauma resulting from an irregular tarsal surface, cicatricial entropion and trichiasis, limitation of Bell's phenomenon, inflammation in the conjunctival epithelium, restriction of ocular motility, strabismus and visual loss related to ptosis, and inadequate socket for prosthesis wear.[4,5]

Symblepharon lysis is the first procedure performed in fornix reconstruction surgeries in patients with symblepharon or fornix contracture. Various tissue grafts (autologous conjunctiva, amniotic membrane, buccal or nasal mucosa) are used to cover the palpebral or bulbar conjunctival defects. This is usually followed by an additional procedure to prevent re-adhesion, such as the use of symblepharon rings, silicone implants, anchoring sutures, placement of a custom conformer, or application of beta radiation, topical cyclosporine, or topical 0.04% mitomycin-C (MMC).[6,7,8,9,10]

Limited usability and scarring in the donor area are serious problems in autologous conjunctival grafts.[10] Buccal-nasal mucosa grafts have the disadvantages of poor cosmetic outlook and risk of infection. Successful outcomes have been reported after fornix reconstructions with symblepharon lysis followed by amniotic membrane transplantation (AMT) and intraoperative MMC in cicatricial pemphigoid, Stevens-Johnson syndrome, chemical burns, recurrent pterygium excision, and contracted sockets.[3,4,11,12]

Herein we report the outcomes of AMT alone or in combination with adjuvant therapies such as MMC application, oral mucosa transplantation (OMT), anchoring sutures, and limbal autografting for reconstruction of the fornix in various ocular surface disorders.

Materials and Methods

The study conformed to the tenets of the Declaration of Helsinki (clinical trial number: 3167). The medical records of patients with fornix obliteration and inadequate conjunctival tissue to cover the whole tarsus or symblepharon at the Ankara Training and Education Hospital between 2002 and 2016 were retrospectively screened. Patients with a follow-up duration shorter than 6 months were excluded. Two grading systems, the Foster and Mondino, were used to evaluate fornix obliteration.[13] Grade 1 and 2 were regarded as early stages, and grade 3 and 4 were considered advanced stages.

In patients with chemical or thermal burn, the surgery was delayed 6 months to allow the resolution of inflammation. All operations were performed after ocular surface inflammation signs subsided. All of the surgeries were done by the same surgeon (Y.K.).

Surgical Procedures for Fornix Reconstruction

Symblepharon Lysis: After placing the lid margin and the limbal traction sutures, symblepharon was released by conjunctival dissections. All adhesions of the residual conjunctiva and/or lid margin to the sclera were meticulously dissected to expose the sclera. Subconjunctival scar tissue was removed extensively, leaving the conjunctiva intact. All scar tissues at the insertion of the rectus muscles were removed to achieve a free and mobile globe.

AMT: Amniotic membranes (AM) were prepared as described by Lee and Tseng.[14] The AM was trimmed to fit the entire conjunctival defect, including the bulbar surface of the fornix and the deeper portion of the palpebral aspect of the fornix. The membrane was then secured to the recessed conjunctival edge with a few interrupted stitches or continuous 8/0 Vicryl, with its margin placed under the conjunctival margins to facilitate epithelial growth over the membrane.

Adjuvant Treatments

MMC Application: After cauterizing focal hemorrhages, 0.04% MMC-soaked sponges were applied to the conjunctival fornices for 3 minutes. After this procedure, the fornices were irrigated with 100 ml saline solution. AMT was performed to cover the defect area (Figure 1).

OMT: In advanced cases where there was no residual tarsal conjunctiva or it was not sufficient to cover the whole width of the tarsus, it was decided to use an oral mucosal graft with AMT. In these advanced cases, after minimal cauterization of the bleeding vessels to the defect area, multiple pieces of surgical sponge soaked in 0.04% MMC were applied to the fornix for 5 minutes, then the eye was washed with 100 mL of balanced salt solution. An oral mucosal graft 30% larger than the tarsal conjunctival defect was harvested from the lower lip using manual dissection. The submucosal tissue was shaved off to obtain a thin graft. With the anterior epithelial surface facing the globe, the superior edge of the oral mucosal graft was sutured to the residual conjunctival edge or lid margin using 8-0 Vicryl suture with a continuous lock technique. The inferior edge of the oral mucosal graft was secured deep in the fornix using one transcutaneous double-armed 5-0 polypropylene suture (Ethicon Inc, Somerville, NJ, USA) in each quadrant (anchoring sutures). Then, a single layer of cryopreserved AM, stromal side down, was used to cover the exposed sclera using fibrin glue (Tisseel; Baxter Inc, Vienna, Austria) when necessary. A muscle hook was used to push the AM deep into the fornix to create an anatomically deep fornix (Figure 2). When a socket procedure was needed, the conjunctiva of the contracted socket was incised at the involved fornix. Dissection was carried down to the orbital rim. All fibrotic scar tissue was carefully excised. The AM graft was placed over the exposed area. The graft was sutured to the

conjunctival margin with continuous 8/0 Vicryl sutures and secured to the fornix with anchoring sutures by passing two double-armed mattress sutures through the full thickness of the lid and tied over the skin with bolsters (Figure 3).

A symblepharon ring was secured behind the eyelids with pressure into the fornix to prevent re-obliteration of the anatomical fornix that was formed at the end of the surgery. An anchoring suture was often placed for the same reason in advanced cases. The procedure was concluded with temporary tarsorrhaphy.

Postoperatively, all patients were treated with topical corticosteroids and tapered off in 3 months. Topical antibiotics were applied three or four times a day until epithelialization of the AM was completed. Full epithelialization was determined on the first visit at 2 weeks postoperatively, when no fluorescein staining was demonstrated over the AM. Sutures were removed at postoperative 2 weeks. The anchoring sutures and temporary tarsorrhaphy sutures and symblepharon ring were removed at postoperative 4 weeks.

Demographic characteristics, causes of acquired anophthalmia, the underlying disease, duration of obliteration, and the number of previous socket operations were recorded. Clinical data including follow-up time, results, ocular surface complications, and recurrences were also documented. Success was defined as an anatomically deep fornix without scarring or motility restriction and ability to wear prothesis during the last visit. SPSS version 14 (SPSS Inc, Chicago, IL, USA) was used for descriptive statistics.

Results

Our study included 27 eyes of 27 patients with fornix obliteration. The mean age was 45.54±4.17 years (range: 17-84); 22 patients (81.5%) were men and 5 (18.5%) were women. The demographic data, clinical presentation, and surgical outcomes are summarized in Table 1.

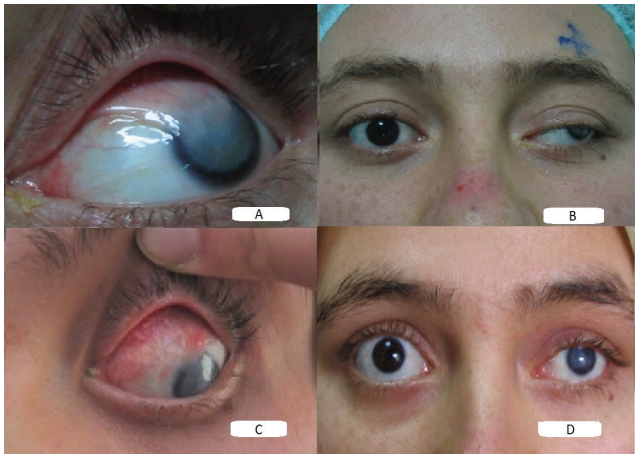

Figure 1. A, B) A 19-year-old woman with thermal burn, stage 3c obliteration of the upper fornix, and ptosis. **C)** Postoperative 1 month after symblepharon lysis, mitomycin-C application, and amniotic membrane transplantation. **D)** After 65 months, the patient has a deep upper fornix with no ptosis or recurrence

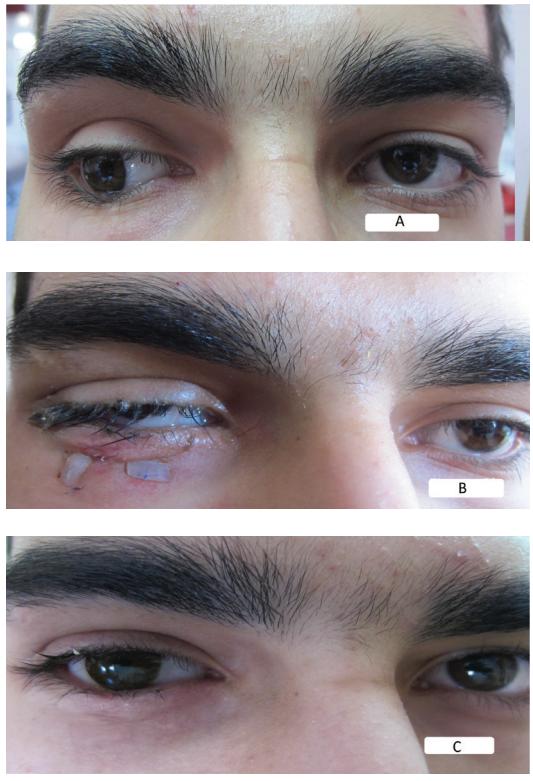

Figure 2. A) A 17-year-old male patient with stage 2c obliteration of the lower fornix, cicatricial entropion, and inability to wear the prosthesis after evisceration surgery. **B)** Postoperative 1 week after symblepharon lysis, amniotic membrane transplantation, and anchoring suture surgery. **C)** After 28 months, the patient has a deep lower fornix, no entropion or recurrence, and can wear the prosthesis

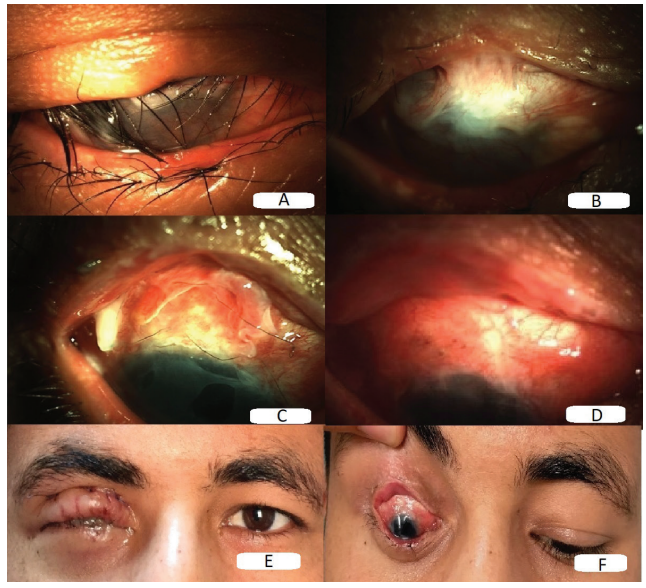

Figure 3. A, B) A 25-year-old man with grade 3a obliteration of the upper fornix after alkali burn and entropion. **C)** Postoperative 6 months after symblepharon lysis, mitomycin C application, and amniotic membrane transplantation. **D)** Deep upper fornix on downgaze. **E)** Postoperative 3 weeks after limbal autograft, amniotic membrane transplantation, oral mucosa graft, and anchoring suture surgery. **F)** After 25 months, the patient has a deep upper fornix with no entropion or recurrences.

Table 1. Patient data and surgical outcomes

	Age/ sex	Etiology	Previous surgeries	Indication	Preoperative FO grade	Recurrence	Outcome	Anchoring sutures	Symblepharon ring	Ocular motility disorder	Treatments	Follow-up time (months)
1	70, M	Mechanical trauma	1	FO	2b	-	S	+	-	++	AMT	62
2	45, M	Alkali burn	2	FO, cosmetic	1c	-	S	-	+	-	AMT, OMT	53
3	36, F	Mechanical trauma	1	FO, ptosis	2b	-	S	+	-	-	AMT, MMC	57
4	83, F	Mechanical trauma	2	FO	2d	-	S	-	+	-	AMT, MMC	34
5	40, F	Mechanical trauma	2	FO	2b	-	S	-	+	-	AMT, MMC	55
6	28, M	Mechanical trauma	2	FO	2a	-	S	+	-	-	AMT, MMC	29
7	19, M	Alkali burn	2	Ptosis	3d	3d	F	-	+	+++	AMT	175
8	54, M	Mechanical trauma	1	FO	2b	-	S	+	-	-	AMT, MMC	150
9	78, M	Mechanical trauma	4	FO	2b	-	S	-	+	-	AMT, MMC	64
10	46, M	Iatrogenic (recurrent chalazion)	3	FO, cosmetic	2a	-	S	+	-	++	AMT	49
11	38, M	Mechanical trauma	2	FO, entropion	2c	-	S	+	-	++	AMT, eyelid surgery	57
12	65, M	Mechanical trauma	2	FO	2c	-	S	-	+	-	AMT	57
13	19, F	Thermal burn	-	FO, ptosis	3c	-	S	+	-	++	AMT, MMC	65
14	17, M	Mechanical trauma	1	FO, entropion	2c	-	S	+	-	-	AMT, eyelid surgery	28
15	25, M	Mechanical trauma	1	FO	2b	-	S	-	+	-	AMT	55
16	44, M	Alkali burn	2	PrePK	3c	-	S	-	+	++	AMT, MMC	12
17	35, M	Alkali burn	5	PrePK, FO, entropion	3c	-	S	+	+	++	AMT, MMC, OMT	12

Table 1. Patient data and surgical outcomes

	Age/ sex	Etiology	Previous surgeries	Indication	Preoperative FO grade	Recurrence	Outcome	Anchoring sutures	Symblepharon ring	Ocular motility disorder	Treatments	Follow-up time (months)
18	60, M	Mechanical trauma	1	FO	2b	2b	F	-	+	-	AMT, MMC	12
19	69, F	Recurrent pterygium	1	FO, strabismus	3b	3a	F	-	+	+++	AMT, MMC	8
20	19, M	Mechanical trauma	2	PrePK, FO, entropion	3c	-	S	+	-	++	AMT, eyelid surgery	6
21	64, M	Recurrent pterygium	3	FO, strabismus	4	-	S	+	-	+++	AMT, medial rectus recession, fibrin glue	6
22	35, M	Mechanical trauma	1	FO	2c	-	S	+	-	-	AMT	118
23	34, M	Mechanical trauma	0	Cosmetic	2c	-	S	-	+	-	AMT	6
24	84, M	Recurrent pterygium	2	Strabismus	3b	-	S	+	+	++	AMT, fibrin glue, OMT	6
25	76, M	Alkali burn	1	Cosmetic	3b	-	S	-	+	+	AMT	6
26	25, M	Alkali burn	1	Entropion	3a	-	S	+	-	+	AMT, MMC, OMT, LOG	25
27	21, M	Mechanical trauma	0	FO	3b	-	S	-	+	+++	AMT	9

+: Mild ocular motility disorder, ++: Moderate ocular motility disorder, +++: Severe ocular motility disorder
S: Success, F: Failure, AMT: Amniotic membrane transplantation, MMC: Mitomycin-C, OMT: Oral mucosa transplantation, LAG: Limbal autografting, PrePK: Before penetrating keratoplasty, FO: Fornix obliteration

We performed only AMT in 6 patients in the early stage and obtained successful results in all cases. Additional treatments were applied in the other 10 early-stage patients because they had previous surgery or eyelid malposition. Failure was observed only in 1 of 16 (6.3%) patients with early-stage disease. We performed only AMT in 3 of 11 advanced cases and failure was observed in 1 case (9.1%). We achieved successful results with additional treatments in the other 8 advanced cases. The mean follow-up period was 45.0±8.4 months (range: 6-175).

The most common underlying etiology associated with symblepharon was mechanical trauma (blunt/penetrating eye injuries) (n=16, 59.2%). Other causes of symblepharon were alkali burns in 6 patients (22.2%), recurrent pterygium in 3 patients (11.1%), thermal trauma in 1 patient (3.7%), and recurrent chalazion surgery in 1 patient (3.7%).

The most common indication for surgery was fornix obliteration (n=12, 44.4%). The surgery was performed in 4 patients (14.8%) for cosmetic reasons, 3 patients (11.1%) for preparation before keratoplasty to maintain ocular surface regularity, 3 patients (11.1%) for blepharoptosis, 3 patients (11.1%) for restrictive strabismus, and 2 patients (7.4%) for entropion. Patients had an average of 1.67±0.22 (range: 0-5) ophthalmologic surgeries before symblepharon surgery.

AMT was performed in all cases after symblepharon lysis and symblepharon ring was used after surgery in 15 cases (55.5%). Adjuvant treatments were performed after AMT in necessary cases. MMC (0.04%) was applied topically for 3 minutes before the defect site was covered with AM in 11 patients (40.7%) with severe symblepharon. No surgical complications were encountered in any of these patients. Other methods and procedures used in combination with AMT for fornix reconstruction included OMT in 3 patients (11.1%), anchoring sutures in 14 patients (51.8%), eyelid surgery in 2 patients (7.4%), fibrin glue in 2 patients (7.4%), limbal autografting in 1 patient (3.7%), and medial rectus recession in 1 patient (3.7%). Fornix obliteration and restrictive strabismus were present in the patient with recurrence of pterygium (3 times). A defect in the medial rectus muscle was detected intraoperatively. The surgical treatment involved symblepharon lysis and AMT, as well as medial rectus repair and recession, fibrin glue, and anchoring sutures. The patient's strabismus improved and no recurrence was observed during follow-up (Figure 4a).

In postoperative examinations, the AM completely covered the conjunctiva, and signs of transient inflammation in the AM graft site resolved within two weeks in all patients.

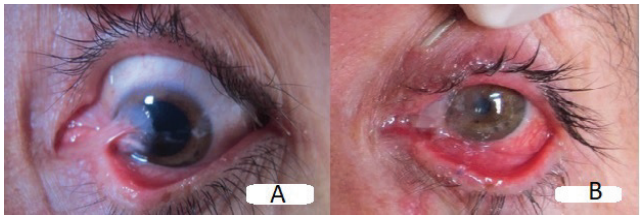

Figure 4. **A)** A 64-year-old man with grade 4 obliteration of the lower fornix and restrictive strabismus after recurrent pterygium. **B)** Postoperative 3 weeks after amniotic membrane transplantation, medial rectus recession, fibrin glue, and anchoring suture surgery

Anatomical success (deep fornix) was achieved in 24 patients (88.8%). In 3 patients, failure occurred due to symblepharon recurrence (11.1%). In one of the failed cases, the etiology was alkali burn and only AMT was performed. The other failed cases were associated with mechanical trauma or recurrent pterygium and we performed AMT with MMC. In three failed cases, symblepharon reoccurred 2-4 months postoperatively. In these 3 patients, in whom we used a symblepharon ring, the tarsorrhaphy sutures were opened in the first week, resulting in the ring becoming dislodged, which we believe allowed fornix obliteration to recur in a short time. In these cases, after 6 months to allow resolution of active inflammation, fornix reconstruction was planned with AMT and additional treatments. An anatomically successful deep fornix was followed up with photographic documentation. In socket patients, success was evaluated with photographic documentation and ability to wear the prosthesis.

Discussion

The current study showed that a high success rate (88.8%) was achieved with or without adjuvant treatments such as intraoperative MMC application, anchoring sutures, OMT, eyelid surgery, limbal autografting, and medial rectus recession in addition to symblepharon lysis and AMT during 45.04±8.4 months of postoperative follow-up in 27 eyes with fornix obliteration.

Obliteration of the fornices can cause many ocular pathologies such as dry eye, irregular tarsal surface and blink-related microtrauma, entropion, trichiasis, limitation of Bell's phenomenon, restriction of eye movements, loss of vision due to strabismus and ptosis, inflammation in the conjunctival epithelium, and inability to retain an ocular prosthesis.

Numerous methods have been developed for reconstructing the fornix with cheek and lip mucosa grafts, conjunctival autograft, and AMT.[12,15] Fornix depth and conjunctival surface area should be augmented by using grafts of optimal type and appropriate size.[16] Advantages of oral mucosal grafts are graft stability and the ability to easily procure sufficiently sized grafts, even for repeated procedures. Disadvantages of oral mucosal grafts include prolonged operative time, discomfort at the donor site, color mismatch of the graft, and risk of failure due to infection. Kurtul et al.[17] pointed out that although AMT and OMT provided similar results in terms of socket reconstruction, AMT was superior in terms of impression cytology and inflammation. Conjunctival autograft also has limited availability, and fibrosis can occur in the recipient region.[18] Conjunctival autograft use after pterygium excision is very successful but may result in postoperative complications such as subconjunctival fibrosis in the harvest area and diplopia due to restrictive strabismus created by scar tissue.[19] AM consists of a single epithelium, thick basal membrane, and avascular stroma. It is used for many ocular and conjunctival disorders.[20] AM promotes the differentiation

of goblet cells and survival of conjunctival epithelium.[20] AM acts directly on ocular surface fibroblasts by suppressing tumor growth factor-beta signals and allowing the formation of the normal keratocyte phenotype not only pathologically, but also physiologically.[21] The advantages of AM over the mucous membrane and conjunctival autografts are its anti-inflammatory and anti-infective properties, lack of immunogenicity, unlimited availability, the absence of donor site trauma to the patient, shorter operative time, faster recovery, and matching the color of the surrounding conjunctiva after complete healing because of its translucency.[3,10,22,23] For this reason, we covered the defect area with AM in all our cases.

Although AMT alone has been successfully used to reconstruct the fornix in eyes with lower grades of symblepharon severity,[16] its usefulness is limited in eyes with severe symblepharon. We performed only AMT in 6 patients in the early stage and successful results were obtained in all cases. Since the other 10 early-stage cases had previous surgery or eyelid malposition, additional treatments were applied and only 1 failure occurred. We performed only AMT in 3 of 11 cases with advanced-stage disease, and although we observed failure in only 1 case, successful results were achieved with additional treatment in 8 cases.

Kheirkhah et al.[15] evaluated symblepharon severity according to photographic documentation and reported that cicatricial lysis and AMT achieved overall success in 92.8% of grade I eyes and in 100% of grade II eyes. Additional anchoring sutures improved success rates to 100% of grade I eyes and 71.4% of grade III/IV eyes. Additional oral mucosa or conjunctival autograft improved the success rate to 100% in grade III/IV eyes. In our study, OMT was required in 3 cases (11.1%), limbal autografting in 1 case (3.7%), and anchoring sutures in 14 cases (51.8%) in combination with AMT for fornix reconstruction. Success was achieved in cases where we used OMT and anchoring sutures with AMT.

Several reports also showed that fornix reconstruction could be accomplished by AMT with or without intraoperative MMC.[18,24] Some authors recommended the use of MMC for active and aggressive recurrent pterygium or in combination with a grafting procedure, as used in this study. This is because it is not theoretically possible to completely remove the subconjunctival fibrous tissue, especially in recurrent pterygium, as inflamed tissue extends deep into the fornix.[25] In our study, AMT with MMC failed in 2 of 10 cases. One of these patients had early-stage fornix obliteration, the other had advanced fornix obliteration, recurrent pterygium, and restrictive strabismus.

Restrictive esotropia is a rare severe complication after pterygium excision surgery. Restrictive esotropia may occur due to scarring of the conjunctiva surrounding complex connective tissue, direct trauma to the rectus muscle, formation of symblepharon, and recurrence of pterygium.[2,26] Increased pterygium recurrence increases the risk of restrictive strabismus.[27] Surgical treatment is challenging because it requires a combination of surgery on the conjunctival-perimuscular connective tissue complex and the medial rectus muscle. Surgery is effective in improving the primary position deviation, but some restricted esotropia may persist.[28] AMT seems to help prevent recurrence of adhesions in patients with restrictive strabismus caused by conjunctival scarring.[29] Management of recurrent pterygium with severe symblepharon using MMC, double AMT, cryopreserved limbal allograft, and a conjunctival flap was reported to be effective.[30] In our study, two of three patients who developed restrictive esotropia due to recurrent pterygium achieved good results with the use of AMT plus adjuvant treatment. Only one of the three recurrent pterygium cases with restrictive strabismus recurred. We applied adjuvant therapies with AMT in all of them. In our unsuccessful case, we applied MMC together with AMT.

Kheirkhah et al.[15] showed that a combined approach of cicatricial lysis, intraoperative MMC application, OMT, and sutureless AMT is an effective surgical strategy for the management of severe symblepharon. They concluded that adjuvant mucosal grafting is needed to improve the clinical outcome and that oral mucosa may be a good option for this. Oral mucosal grafts have long been used to cover conjunctival defects during fornix reconstruction in eyes with symblepharon or surgical correction of anophthalmic contracted sockets.[16,31] We also achieved successful results when OMT was added to adjuvant treatments combined with AMT and intraoperative MMC application in 2 patients with advanced and 1 patient with early-stage fornix obliteration.

Contracted socket and fornix shortening in the anophthalmic orbit can lead to inadequate space for the retention of a prosthesis. Socket contracture may result from various processes such as fibrosis from a severe initial injury, implant extrusion, chronic infection, and inability to wear a prosthesis or conformer.[32] An AM is a useful option for forniceal reconstruction in socket contracture. This technique achieved a success rate of 80% without serious complications.[33] Bajaj et al.[34] evaluated 20 patients who underwent AMT or OMT for socket failure and reported that lower fornix depth and socket volume were similar in both of the groups. An AM has many advantages in socket reconstruction, such as having an anti-fibrotic effect on the mucous membrane, being translucent, and acting as a substrate graft. Hao et al.[35] emphasized that the use of AMT in contracted sockets was associated with a more favorable outcome compared to buccal mucosa and nasal mucosal grafts. In our study, we performed AMT alone in 5 of 12 patients with socket contracture and AMT with MMC in the other 7 patients, and obtained successful results in all cases.

Study Limitations

The main limitations of our study are the lack of a control group and our inability to compare results between the groups due to the small number of patients who developed symblepharon secondary to various diseases that may require different surgical approaches included in this study. With these limitations in mind, our results underlined that cicatricial lysis and AMT with or without adjuvant therapy is an effective surgical method for the management of fornix obliteration. Fornix reconstruction surgeries using the correct and effective approach according to

the severity of symblepharon and underlying reason for fornix obliteration yielded successful results both in functional and cosmetic terms.

Conclusion

Surgical treatment with AMT alone yielded satisfactory outcomes in patients with early-stage fornix obliteration. In patients with early disease who have previous surgical history and eyelid malposition, successful results can be obtained by applying additional treatments together with AMT. In patients with advanced fornix obliteration for which AMT alone is inadequate, adjuvant treatment with OMT, anchoring sutures, eyelid surgery, fibrin glue, limbal autografting, and MMC in addition to AMT provides successful, safe, and effective outcomes.

Ethics

Ethics Committee Approval: Ankara Training and Research Hospital, 2814.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.K., Concept: Y.K., A.K., Design: Y.K., A.K., E.Ş.Ö., Data Collection or Processing: Y.K., A.K., Analysis or Interpretation: Y.K., A.K., E.Ş.Ö., Literature Search: A.K., E.Ş.Ö., Writing: Y.K., A.K., E.Ş.Ö.

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

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Original Article

Ophthalmologic Manifestations in Autism Spectrum Disorder

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Abstract

Objectives: The purpose of this study was to describe the ophthalmologic manifestations found in patients with autism spectrum disorder (ASD) and to assess their prevalence in the different types of ASD.

Materials and Methods: This prospective observational study included 344 patients with ASD seen over a period of 8.5 years. They were classified into four subgroups (autism, Asperger syndrome, pervasive developmental disorders not otherwise specified [PDD-NOS], and other). Data obtained from ophthalmological examinations were compared between the groups. Statistical analysis was performed with chi-square, Kruskal-Wallis, and Mann-Whitney tests.

Results: Refractive defects were detected in 48.4% of the patients, with the most prevalent being hyperopia and astigmatism. There was a higher prevalence of myopia in Asperger syndrome. Evaluation of extraocular motility revealed the presence of strabismus in 15.4% of patients, with a statistically significantly higher prevalence in autism and the "other" disorders group. The most frequent type of strabismus was exotropia. Convergence was found to be normal in 43.6% of the patients. Nystagmus was observed in only 0.9% of patients. In the binocular sensory tests performed, patients with Asperger syndrome had significantly better results compared to the other groups. Optic nerve abnormalities were found in 4% of patients, with significantly higher prevalence in the "other" disorders group.

Conclusion: Ophthalmologic manifestations occur more frequently in patients with ASD than in the general child population. Of these, the most frequent are refractive defects and ocular motility disorder. Therefore, we consider it necessary to perform an ophthalmological evaluation in patients with ASDs.

Keywords: Autism spectrum disorder, refractive errors, strabismus, amblyopia, optic nerve hypoplasia

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Introduction

Autism spectrum disorder (ASD) refers to a range of neurodevelopmental conditions characterized by a certain degree of social, communication, and language impairment and the presence of restricted, stereotyped, and repetitive patterns of behavior, interests, and activities. ASD encompasses autism, Asperger's syndrome, Rett's syndrome, Heller's syndrome, fragile X syndrome, and other less common disorders that are included in the pervasive developmental disorders not otherwise specified (PDD-NOS). ASD manifests during childhood and tends to persist into adolescence and adulthood. In most cases, the condition becomes apparent during the first 5 years of life.

Twenty-five years ago, the incidence of ASD was estimated as 1:2.500, whereas the reported current prevalence ranges from 1:250 to 1:88, which supports the notion that the prevalence of ASD appears to be increasing globally. The current reported prevalence of ASD portrays the high impact that this condition has in a community at the social and clinical level.[1] There are many possible explanations for this apparent increase, including improved awareness, expansion of diagnostic criteria, better diagnostic tools, and improved and rigorous reporting.

Numerous studies have associated the communication and social interaction deficiencies in ASD patients with visual processing capacity.[1,2,3,4,5,6,7,8] The prevalence of ophthalmologic disorders was found to be more frequent among these patients than in the general pediatric population.[9,10,11] The most frequent eye disorders identified in ASD patients are strabismus, nystagmus, and refractive errors or amblyopia. Optic nerve hypoplasia or retinal alterations evidenced in the electroretinogram have also been described.[1,12,13,14,15,16]

The purpose of this study was to describe the ophthalmologic manifestations found in these patients and assess their prevalence in the different types of ASD, since these manifestations may contribute to the communication and social interaction deficiencies in ASD patients. Our aim is to raise awareness of the need to protocolize early ophthalmological evaluation in ASD patients.

Materials and Methods

Patient Cohort

The study included 344 patients who were referred to the ophthalmology department of our hospital by the AMITEA (from Spanish: Integral Medical Attention to Patients with Autism Spectrum Disorder) Program during a period of time spanning from the end of 2009 until March 2018.

Of the 344 patients, 28 (8.1%) were consistent with Asperger's syndrome, 219 (63.7%) with autism, 76 (22.1%) presented PDD-NOS, and 21 (6.1%) had other diagnoses (Rett's syndrome, fragile X syndrome, Angelman syndrome, Lennox-Gastaut syndrome, and Klinefelter syndrome). Patients were diagnosed according to the criteria of the AMITEA Program.

Clinical Parameters

In all cases, the following descriptive parameters were analyzed: age, sex, presence of verbal language, presence of mental retardation, and the degree of collaboration (on a scale of 0 to 3 based on the number of tests answered and extent of cooperation in subjective tests).

Subjective tests requiring the patient's collaboration were adapted to their age and IQ level ("retarded," "non-retarded," or "non-evaluated"), which as provided by the AMITEA Program in the patients' clinical records. These tests included monocular visual acuity tests (LEA test, Pigassou optotypes, Snellen E, letters, numbers); ocular motility assessment with cover test and prism cover test; evaluation of ductions, versions, convergence, and presence or absence of nystagmus; and assessment of binocular sensory function using the Lang, TNO, and Worth tests.

Objective tests were also carried out, including cycloplegic refraction by retinoscopy and a pediatric autorefractor and table-top autorefractor, funduscopic examination, and slit-lamp anterior segment examination. Pathological refractive error was defined as more than +2 diopters of hyperopia, more than -0.50 diopters of myopia, and more than +/-0.75 diopters of astigmatism.

Treatment was administered on a patient-by-patient basis.

Statistical Analysis

Statistical analysis was performed with SPSS software (version 24.0 for Windows; IBM Corp, Armonk, NY, USA), including descriptive parameters, frequency and correlation of qualitative variables using chi-square, Kruskal-Wallis, and Mann-Whitney tests.

Statistical significance was accepted at $p<0.05$.

Results

The patient cohort was predominantly male, with 257 male patients (74.7%) versus 87 female patients (25.3%). The mean age at first ophthalmologic consultation was 10.9±8.1 years (mean ± standard deviation). When analyzed by group, the mean age was 10.8±8.9 years in the autism group, 12.5±7.4 years in the Asperger group, 8.2±5.2 years in the PDD-NOS group, and 12.2±7.2 years in the other disorders group. Age at first ophthalmologic consultation was significantly higher in the Asperger syndrome group compared to the autism group ($p<0.003$).

Of the 344 patients, 202 (58.7%) were able to verbally communicate, while 142 (41.3%) were unable to communicate through speech. However, in 11 patients from the latter group, it was still possible to evaluate visual acuity by means of pictograms.

Intellectual deficit was observed in 231 patients (67.2%), while 74 patients (21.5%) presented a normal IQ. Thirty-nine patients (11.3%) had not been evaluated. In the Asperger syndrome group, the incidence of associated intellectual deficit was statistically significantly lower than in the other three patient groups ($p<0.001$).

The degree of collaboration was assessed as null or poor (0-1) in 155 patients (45.1%), intermediate (2) in 55 patients (16.0%) who responded actively to most of the tests requested,

and very good (3) in 134 patients (39.0%). A statistically significant difference in the degree of collaboration and verbal communication was observed between patients with Asperger syndrome and autism, with the latter group displaying poorer collaboration and more limited verbal communication skills (p<0.001).

Visual acuity could be determined for 385 of the 688 eyes analyzed (56.0%), with a slightly higher proportion of right eyes (as a rule, the first to be examined) than left eyes (56.4% vs. 55.5%). Visual acuity was 0.7 or better in 169 right eyes (49.1%) and 167 left eyes (48.6%) and was 0.3 or worse in 8 right eyes (2.3%) and 7 left eyes (2.0%). We observed significantly better visual acuity in the Asperger syndrome group compared to the autism and other disorders groups (p<0.001) (Figure 1).

Total refractive error observed by retinoscopy and autorefractors was determined in 659 eyes (95.8%), of which 340 (51.6%) were emmetropic. The rest of eyes were classified as having astigmatism (130 eyes, 19.7%), myopia (54 eyes, 8.2%), or hyperopia (135 eyes, 20.5%). Refractive error could not be determined in 29 eyes (4.2%) because of poor collaboration.

Regarding the variation in refractive defects according to age, we observed that in children up to 6.5 years of age, there was a higher percentage of hyperopia (29.9%), followed by astigmatism (15.3%). Between 7 and 8 years, most patients were hyperopic (22.9%) or astigmatic (20%). Between 8 and 12 years, most patients presented astigmatism (21.3%), followed by hyperopia (13.1%). Between 12 and 15 years, astigmatism was most common (27.6%), followed by myopia (17.2%).

Calculating the prevalence of refractive defects in the different ASD groups showed that the rate of emmetropia was 51.0% in the autism group, 57.1% in the Asperger syndrome group, 52.7% in the PDD-NOS group, and 36.8% in the other disorders group. The prevalence of astigmatism was 20.5% in the autism group, 17.9% in the Asperger syndrome group, 20.3% in the PDD-NOS group, and 21.1% in the group of other disorders. Hyperopia tended to be more common in autism (19.5%), PDD-NOS (21.6%), and other disorders (42.1%) than in Asperger syndrome (7.14%), whereas myopia was more common in Asperger syndrome (17.9%) than autism (9.1%) and PDD-NOS (5.4%). However, these trends were not statistically significant.

Assessment of extraocular motility revealed strabismus in 53 patients (15.4%), of which 32 (9.3%) exhibited exotropia, 19 (5.5%) esotropia, 1 (0.3%) exophoria, and 1 (0.3%) vertical strabismus. It was not possible to determine the presence or absence of extraocular muscle dysfunction in 4 patients (1.2%).

Strabismus was present in 16.4% of patients with autism, compared to 3.6% of patients with Asperger syndrome. Exotropia was the most common type of strabismus in autism, PDD-NOS, and other disorders, while esotropia was most common in the Asperger group. The incidence of strabismus was significantly lower in the Asperger and PDD-NOS groups in comparison to the group of other disorders (p<0.007).

Convergence could not be determined in 105 cases (30.5%) due to the difficulty caused by inherent sight fixation, which was more prevalent in patients in the autism and other disorders groups. Among the patients who could be examined, convergence was found to be normal in 150 (43.6% of the total), of which 92 patients belonged to the autism group, 37 to the PDD-NOS group, 15 to the Asperger syndrome group, and 6 to the other disorders group. There were 89 cases of convergence deficit (25.9%), of which 52 patients belonged to the autism group, 21 to the PDD-NOS group, 12 to the Asperger syndrome group, and 4 to other disorders. No statistically significant differences in convergence deficit were observed amongst the ASD groups.

Nystagmus was observed in only 3 patients (0.9%), of whom 2 were autistic and 1 was included in the other disorders group. Nystagmus was not detected in the remaining 341 patients either because the patient did not cooperate or because they did not present it.

Among the binocular sensory tests performed, the Worth test was successfully performed on 135 patients (39.2%), of which only 3 suppressed the vision of one eye and 132 fused the vision of both eyes. The Lang test was successfully performed in

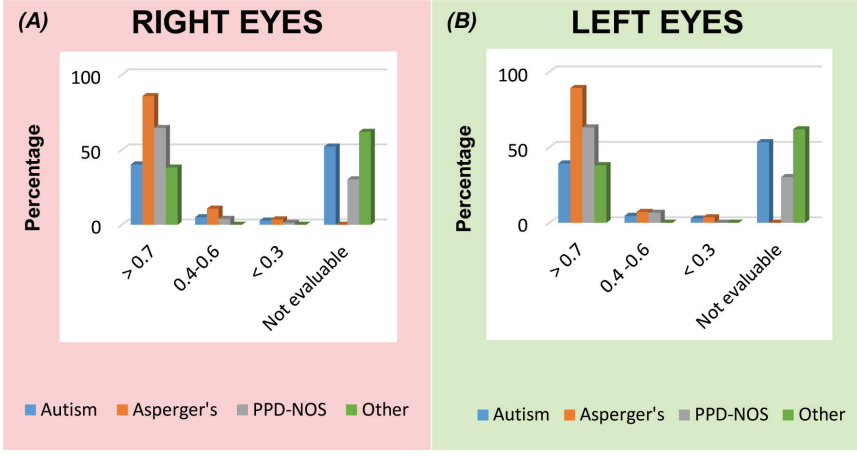

Figure 1. Visual acuity in right eyes (A) and left eyes (B) in different autism spectrum disorder groups. PPD-NOS: Pervasive developmental disorders not otherwise specified

342 patients (99.4%), of whom 126 patients showed stereopsis (36.6%). However, the TNO test revealed only 56 patients (16.3%) with stereopsis. In these three sensory tests, the Asperger syndrome group had significantly better results in comparison to the other ASD groups (p<0.001) (Figure 2).

The fundus could not be examined in 11 patients (3.2%). In those who underwent fundus examination by indirect ophthalmoscopy, a normal fundus was observed in 318 patients (92.4%) and findings of pallor and/or optic nerve atrophy were seen in only 15 patients (4.4%). The incidence of alterations in the optic nerve was higher in the other disorders group compared to the rest of the ASD groups (p<0.006).

No treatment was prescribed to 271 patients (78.8%) either because they had no or negligible ophthalmological defects, or because a full diagnosis and treatment prescription was not possible due to incomplete or inconclusive (lack of collaboration) ophthalmological examination. From the study cohort, only 73 patients (21.2%) required treatment. The most common treatment options were eyeglass prescription for refractive errors, monocular occlusion, and injection of intramuscular botulinum toxin for strabismus control.

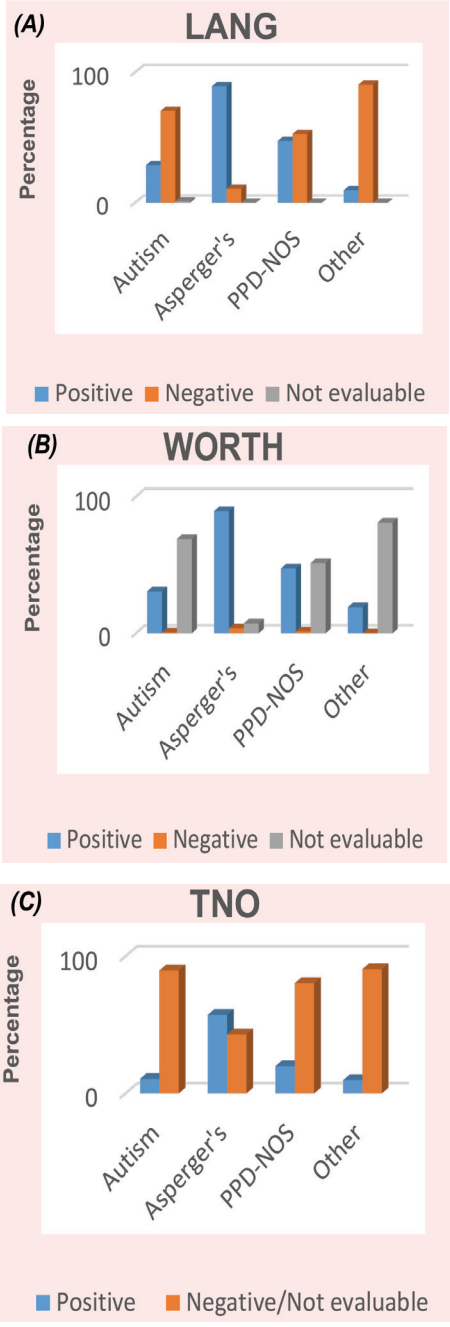

Figure 2. Binocular sensory test results in different autism spectrum disorder groups. (A) Lang test, (B) Worth test, and (C) TNO test. PPD-NOS: Pervasive developmental disorders not otherwise specified

Discussion

The incidence of ASD has increased from an estimated 1:2,500 a quarter century ago to a reported prevalence of 1:250 to 1:88 today. At present, there are approximately 450,000 children with ASD in our region.[17] Some of the possible explanations for this increase in prevalence are greater awareness of these disorders, improvement and expansion of the diagnostic criteria, better diagnostic tools, and more rigorous clinical reporting.[1]

These disorders present diagnostic challenges because of the peculiarities of these patients.[11] In some patients in our cohort, we could not perform certain examinations due to the complete absence of collaboration.

The patient cohort presented in this study is one of the largest and most specific in terms of characterizing ophthalmologic defects in ASD. Importantly, our study focused exclusively on ASD, whereas many of the published studies consider patients with general intellectual disability. This includes not only patients with ASD, but also patients with other conditions characterized by developmental delay (e.g., Moebius syndrome, Charge syndrome, Down syndrome). In all these articles, different ophthalmological manifestations were analyzed and strabismus, nystagmus, and refractive errors or amblyopia were found to be the most common conditions. Optic nerve hypoplasia or retinal alterations evidenced in electroretinogram have also been described.[1,12,13,14,15,16]

The main limitation of our study is that we did not include an age-matched control group in order to compare the prevalence of ophthalmologic defects amongst ASD and the general population, as this program included only children with a diagnosis of PPD.

In our study, the most prevalent alteration of extraocular motility was exotropia, and the most common refractive errors were astigmatism and hyperopia. In a retrospective study published in 2013, Ikeda et al.[16] present results similar to ours. They reported that 21% of patients had strabismus and 29% had refractive errors. However, in their study they determined that accommodative esotropia was most common among those who had strabismus, unlike in our study.

Milne et al.[18] reported in 2009 that of 51 individuals with ASD, most aspects of vision (including visual acuity) were not affected. However, they emphasized that convergence must be assessed, because they observed differences from the general population. Our data confirm their findings, as convergence was altered in 25.9% of the patients examined in our study.

Subjective examinations were more limited than objective tests in this study. Visual acuity could not be determined in 44% of the patients. Convergence could not be determined in 30.5% of the patients, and the presence of nystagmus could be assessed in only a small percentage (0.9%). Of the binocular sensory tests, results could not be obtained in 84% of patients when using the TNO test, in 1% when using the Lang test, and in 61% when using the Worth test. The poor collaboration in this respect precludes valid conclusions regarding the presence of stereopsis and amblyopia in these patients.

The response to binocular tests, especially in the TNO and Worth tests, is once again a true reflection of the varying degree of difficulty in understanding, communicating, and/or cooperating that is characteristic to patients with ASD. In this sense, it is possible that some of the examination methods should be improved to facilitate the collaboration of certain patients.

In approximately half of the children whose vision could be assessed, it was close to normal.[1] This is consistent with the refractive defects found, as we detected astigmatism in 20%, hyperopia in 20%, and myopia in 8% of the patients. Examinations in which the active participation of the patient is not required were much more positive; the fundus could not be examined in only 3% and refractive error could not be analyzed in 4% of the patients.

Regarding the development of new technologies to facilitate ophthalmological examination, it is worth noting the usefulness of tools such as the PlusoptiX photorefractometer for the screening of amblyopia risk factors in patients with ASD, as shown in the recent publications by Singman et al.[19] and McCurry et al.[20]

In recent years, electronic devices have been designed to analyze eye movements such as tracking, fixation, or saccades. These devices seem to enable the very early diagnosis of alterations in ocular motility and thus allow much earlier initiation of a treatment regimen.[2,4,5,6,7,21] Because our study started in 2009, we did not perform such an evaluation, as patients recruited earlier could not be examined in this way.

Study Limitations

The rate of optic nerve pathology observed in our study was markedly lower than that reported in the literature.[12,13] Papillary alteration was found in only 3%. However, we are aware that limitations in examination may lead to slight papillary pallor being overlooked.

The fact that children do not have social interaction, are not able to follow objects, and present limitations in language does not mean in any way that they cannot be examined. Ophthalmologists can learn other forms of communication to adapt to these patients' disability. In fact, from the time recruitment started, we used pictograms that eased patient collaboration.

Conclusion

The present study illustrates the need for ophthalmological evaluation in patients with ASD, as refractive errors as well as ocular motility disorder are common.[3,10] Therefore, we consider it necessary to implement evaluation protocols to manage these patients in a holistic way that will facilitate improvements in their quality of life and social functioning.[1,8,11,15,22] Future studies should investigate whether the follow-up and appropriate treatment of ophthalmological manifestations might improve these patients' social interaction and communication.

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Ethics

Ethics Committee Approval: Since the study was conducted with ophthalmologists, not on patients, the permission of the ethics committee was not required.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.G.L., P.M., C.G., J.L.M., Concept: P.G.L., P.M., Design: P.G.L., P.M., Data Collection or Processing: P.G.L., P.M., C.G., J.L.M., Analysis or Interpretation: P.G.L., P.M., C.G., J.L.M., Literature Search: C.G., J.L.M., Writing: P.G.L., P.M., C.G., J.L.M.

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Original Article

Optical Coherence Tomography Angiography Findings in Primary Open-Angle and Pseudoexfoliation Glaucoma

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Abstract

Objectives: To compare the optical disc and macular vascular density values of patients with glaucoma and healthy individuals by using optical coherence tomography angiography and evaluate the relationship between structural and functional test results and vascular density.

Materials and Methods: The study included 128 eyes in total: 31 with pseudoexfoliation glaucoma (PEG), 55 with primary open-angle glaucoma (POAG) and similar visual field defects, and 42 healthy eyes. Whole image peripapillary vessel density (wpVD), intradisc vessel density (idVD), peripapillary vessel density (pVD), whole image macular vessel density (wmVD), and parafoveal vessel density (pfVD) values were compared between the groups. Correlations between visual field findings, retinal nerve fiber layer (RNFL) and optic nerve head measurements and peripapillary and macular vascular density were analyzed.

Results: In the PEG and POAG groups, wpVD, idVD, wmVD, and pfVD values were significantly lower in than the control group. In the PEG group, wpVD was found to be significantly lower than the POAG group ($p<0.001$). There was no significant difference between the PEG and POAG groups in wmVD and pfVD except for nasal pfVD. There were strong positive correlations between RNFL thickness and pVD in the glaucoma groups ($p<0.001$). Significant correlations were found between visual field mean deviation and pattern standard deviation values and peripapillary and macular vessel density values in the glaucoma groups.

Conclusion: Vascular density values were lower in glaucoma patients compared to normal individuals, and there is a strong correlation between structural and functional tests and vessel density values. The lower vascular density in the PEG group compared to the POAG group indicates that vascular damage may be more common in PEG patients.

Keywords: Optical coherence tomography angiography, vessel density, primary open-angle glaucoma, pseudoexfoliation glaucoma, visual field

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Introduction

Glaucoma is a group of optic neuropathies characterized by progressive degeneration of the retinal ganglion cells. It is the leading cause of irreversible blindness worldwide.[1] Primary open-angle glaucoma (POAG) is the most common type of open-angle glaucoma, and its pathophysiology and factors involved in its progression are not fully understood. However, damage to the retinal ganglion cells and their axons is known to occur in the early stage, and progression of this damage results in vision loss. Risk factors for POAG include high intraocular pressure (IOP), advanced age, and central corneal thinning.[2,3] Vascular dysfunction in the optic nerve head and peripapillary region is thought to play a role in the pathogenesis of POAG.[4] Pseudoexfoliation syndrome is an age-related systemic disorder characterized by the accumulation of white fibrogranular material (pseudoexfoliation material) in the extracellular matrix of different tissues in the body.[5] Pseudoexfoliation syndrome is associated with the accumulation of small white deposits in the anterior segment of the eye, most often at the pupil margin and on the anterior lens capsule. Contact between the lens and iris during pupil movement results in pseudoexfoliation material being scraped from the anterior lens surface and collecting in the trabecular network.[6] Pseudoexfoliation glaucoma (PEG) is one of the most common causes of open-angle glaucoma.[7,8]

The relationship between retinal microvascularity and glaucoma progression has previously been investigated using various methods such as fundus fluorescein angiography, indocyanine green angiography, scanner laser angiography, and laser Doppler flowmeter.[9,10,11,12] Although these methods have demonstrated impaired optic nerve head circulation in the pathogenesis of glaucoma, they have not been adopted as standard examinations in glaucoma diagnosis because of their low reproducibility and potential adverse effects.[13]

Optical coherence tomography angiography (OCTA) is a noninvasive, high-resolution, fluorescence-free angiography technique that has become widespread in recent years.[14] OCTA detects blood flow based on the motion contrast of red blood cells in the vessels. Unlike fundus fluorescein angiography, it does not require the use of any intravenous contrast agent.[15] OCTA allows the examination of vessel density in different layers of the retina, including the macula and optic nerve head.[16,17,18] In addition, the microvascular structure of the retina can be evaluated quantitatively and reproducibly using a special software called split-spectrum amplitude-decorrelation angiography.[19,20,21]

Previous studies have demonstrated low vessel density in the optic nerve head and peripapillary region in eyes with POAG.[17,20,22] Similarly, there are also studies showing that macular vessel density is lower in eyes with glaucoma compared to normal eyes.[23,24] However, of the studies comparing POAG and PEG patients in the literature, most investigated either the peripapillary region or the macular region.[25,26]

The present study aimed to investigate both peripapillary and macular vessel density parameters in POAG and PEG patients with OCTA and compare these data with a normal control group to evaluate the vascular changes that occur in glaucomatous optic neuropathy. In addition, we aimed to examine the relationship of vascular density values with retinal nerve fiber layer thickness (RNFLT), optic nerve head parameters, and visual field, which are widely used in the diagnosis and follow-up of glaucoma.

Materials and Methods

This prospective observational study was conducted in the glaucoma unit of the ophthalmology department of Ankara Training and Research Hospital. Ethical approval was obtained from the Ankara Training and Research Hospital Ethics Committee (no: 102, date: 01 October 2019), and all study procedures were carried out in accordance with the Declaration of Helsinki.

POAG was diagnosed based on the presence of open angle on gonioscopy, typical glaucomatous appearance of the optic disc on fundus examination, glaucomatous RNFL thinning on OCT, and visual field findings. PEG was diagnosed in the presence of similar findings plus pseudoexfoliation material detected on biomicroscopic and gonioscopic examination.

The study included 55 POAG eyes, 31 PEG eyes, and one eye of 42 healthy individuals. Inclusion criteria were age of 40-80 years; absence of systemic diseases with potential vascular manifestations, such as diabetes mellitus and arterial hypertension; no previous surgical history other than uncomplicated cataract surgery; absence of any ocular pathology other than glaucoma; Snellen best corrected visual acuity of 0.5 or better; absence of cataract, vitreous opacity, or corneal haze severe enough to interfere with signal strength during imaging; and less than ±5 diopters spherical and ±3 diopters cylindrical refractive error. The control group included individuals with no ophthalmologic disease or family history of glaucoma. The affected eyes of patients with unilateral disease and the right eyes of patients with bilateral disease and control subjects were included in the study.

All study participants underwent objective refraction measurement with Huvitz MRK-3100 (Huvitz, Korea), best corrected visual acuity measurement using Snellen chart, slit-lamp biomicroscopic examination, IOP measurement with Goldmann applanation tonometry, and central corneal thickness and axial length measurement with optical biometry AL-Scan (Nidek Co., Ltd., Gamagori, Japan).

After pupil dilation with 0.5% tropicamide, detailed fundus examination and RNFLT measurement were performed with spectral domain OCT device (SD-OCT, Heidelberg Engineering, Germany). Macular OCT 6x6 mm retinal angiography and optic nerve head-centered 4.5 x 4.5 mm disc angiography were then performed using the AngioVue device (RTVue-XR, Fremont, California, USA; software version 2017.1.0.151).

The OCTA system performs optic disc measurements using two circles 2 mm and 4 mm in diameter centered on the optic disc. A 4.5x4.5 mm field is used as the total image area. The area within the 2-mm circle is considered the intrapapillary zone and the area between the 2-mm and 4-mm circles is considered

the peripapillary zone. Whole image peripapillary vessel density (wpVD) measurements are evaluated in the entire 4.5x4.5 mm image area. To detect the radial peripapillary capillary plexus, the software automatically segments the region of interest into four layers, and radial peripapillary capillary plexus measurements are obtained as the vessel density in the area between the internal limiting membrane and the lower boundary of the RNFL. The software used in the study allows measurement of both vessel density in only the capillary plexus and total density ratios in the capillary plexus and large vessels. In order to evaluate the microvasculature in this study, we used capillary vessel density as the study parameter instead of the total vessel density in the measured areas. The software also automatically obtains peripapillary, intrapapillary, superior and inferior hemisphere peripapillary, and capillary densities in the inferior, nasal, superior, and temporal quadrants (Figure 1).

A 6x6 mm macular scan can also be obtained with the OCTA software. To evaluate the superficial plexus, which supplies the ganglion cell layer, a layer between the upper boundary of the internal limiting membrane to the lower boundary 10 µm below the inner plexiform layer is automatically segmented. A 9-zone map is automatically centered on the fovea to create quadrants. This map consists of 3 concentric circles, with the innermost 1-mm diameter area representing the fovea. The area between the central zone and the middle 3-mm diameter circle represents the parafovea, and the area between the middle circle and outer 6-mm diameter circle represents the perifovea. Whole image macular vessel density (wmVD) is calculated from the entire 6x6 mm scan area. In our study, we analyzed the vascular densities of the superficial plexus, which provides the blood supply for the ganglion cells, in the parafoveal area, where this layer is densest. The parameters analyzed were wmVD, average parafoveal VD, VD in the superior and inferior halves of the parafoveal ring, and superficial plexus VD in the inferior, nasal, temporal, and superior quadrants of the parafoveal ring (Figure 2).

Glaucoma patients underwent 24-2 visual field measurements (24-2 Swedish interactive thresholding algorithm) performed using a Humphrey Field Analyzer II 750 (Carl Zeiss Meditec). Those with false-negative and false-positive rates below 30% were included in the study. The mean deviation (MD) and pattern standard deviation (PSD) values of the patients were included in the study.

Statistical Analysis

SPSS Statistics version 22.0 software package (IBM Corp, Armonk, NY, USA) was used. When analyzing the data, qualitative data were expressed as frequency and percentage. Quantitative data were expressed using mean and standard deviation values as descriptive statistics. The Kolmogorov-Smirnov test was used to determine whether data were normally distributed. Normally distributed quantitative data were analyzed using Student's t-test for comparisons between 2 groups and one-way analysis of variance (ANOVA) for comparisons among 3 or more groups. One-way ANOVA was followed by the least significant difference method for multiple pairwise comparisons. Non-normally distributed quantitative data were analyzed using Mann-Whitney U test for comparisons between 2 groups and Kruskal-Wallis test for comparisons among 3 or more groups. The Conover-Iman method was used for multiple pairwise comparisons of data analyzed by Kruskal-Wallis test. Pearson or

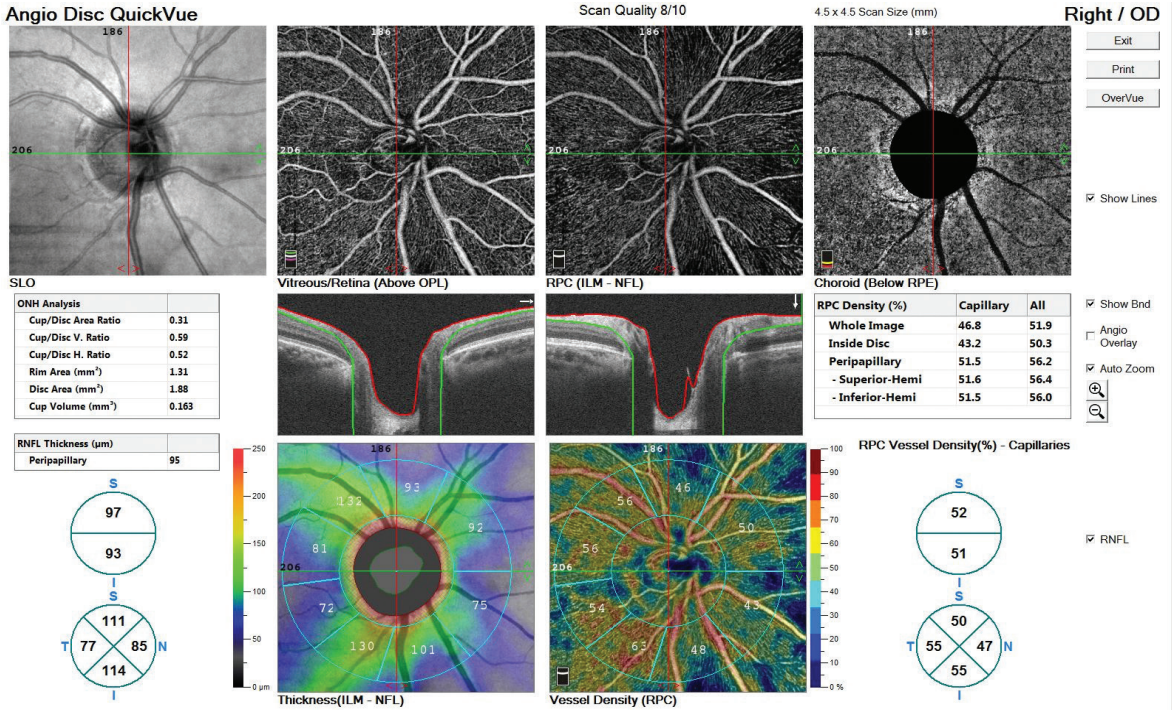

Figure 1. Image of 4.5x4.5 mm disc scan of the right eye of a patient with primary open-angle glaucoma

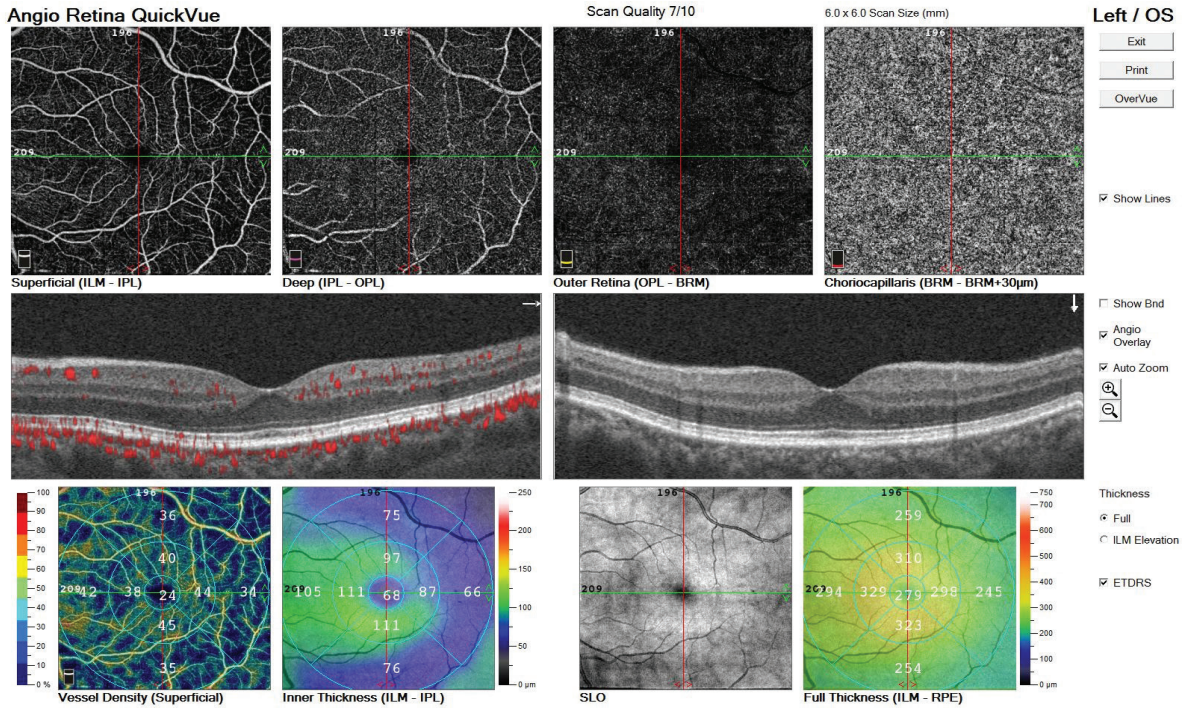

Figure 2. Image of a 6x6 mm macular optical coherence tomography angiography scan of the left eye a patient with pseudoexfoliation glaucoma

Spearman correlation analysis was used to evaluate relationships between quantitative data. Partial correlation analysis was performed to identify relationships between variables while controlling for age. All statistical calculations were evaluated within a 95% confidence interval and at a significance level of $p<0.05$.

Results

Demographic and Ocular Characteristics

The study included single eyes of a total of 128 individuals: 31 (24.2%) PEG patients, 55 (43.0%) POAG patients, and 42 (32.8%) controls. The demographic and ocular characteristics of the study participants are shown in Table 1.

Vascular Characteristics

Radial peripapillary capillary densities are compared in Table 2. WpVD, intradisc vessel density (idVD), and peripapillary vessel density (pVD) (all quadrants) were significantly higher in the control group than the glaucoma groups. There was no significant difference between the glaucoma groups in terms of idVD. However, wpVD and pVD (except in the nasal quadrant) were significantly higher in the POAG group compared to the PEG group.

Macular vessel density values are compared in Table 3. The control group had significantly higher wmVD and parafoveal vessel density (pfVD) (all quadrants) values than the glaucoma groups. There was no statistically significant difference between the glaucoma groups in terms of macular vessel density (except for pfVD in the nasal quadrant).

Peripapillary and macular vascular density values of patients with mild glaucoma of both types are compared in Table 4. WpVD, peripapillary vascular density in the inferior hemisphere (pVD-IH), and pVD values in the inferior and nasal quadrants were found to be significantly lower in the PEG group than the POAG group. The other parameters did not differ significantly between the groups.

Correlations Between Vascular, Structural, and Functional Parameters

Table 5 shows the correlation between RNFLT and pVD values in the glaucoma and control groups. Statistically significant positive correlations were detected in all quadrants in the whole patient group. RNFLT and pVD were significantly correlated in the temporal quadrant in the PEG group and the superior and temporal quadrants in the POAG group. In the control group, there was significant correlation in the average, superior, and inferior quadrant values.

Table 6 shows the correlation between MD and PSD values and pVD, wmVD, and pfVD values in the glaucoma groups. The strongest correlations were between MD and wmVD in the PEG group and between MD and pVD in the POAG group ($p=0.001$ and $p=0.004$, respectively).

Table 1. Demographic and ocular characteristics

	Groups			p value
	PEG (n=31)	POAG (n=55)	Control group (n=42)	
Age (years)[β]	68.06±7.73	62.29±8.80	56.93±6.56	<0.001
Male/female (n)	15/16	20/35	22/20	0.257
BCVA (Snellen decimal)[β]	0.95±0.09	0.94±0.10	0.99±0.05	0.013c
IOP (mmHg)[β]	16.35±5.78	16.04±2.76	12.98±2.23	<0.001[b,c]
AL (mm)*	23.22±0.98	23.37±0.93	23.15±0.89	0.493
CCT (µm)*	525.55±30.50	542.95±31.74	524.12±33.06	0.007[a,c]
RNFLT (µm)[β]	82.10±15.84	91.81±16.62	102.98±8.62	<0.001[a,b,c]
C/D ratio	0.55±0.16	0.52±0.17	0.39±0.14	<0.001[b, c]
Rim area (mm)^2	1.36±0.36	1.54±0.36	1.67±0.33	0.002[a,b]
MD (dB)	-5.30±5.92	-4.18±4.73		0.128
Glaucoma stage				
Mild (MD >6 dB)	22 (78.6%)	42 (84.0%)		0.679
Moderate (MD 6-12 dB)	4 (14.3%)	4 (8.0%)		
Severe (MD <12 dB)	2 (7.1%)	4 (8.0%)		

PEG: Pseudoexfoliative glaucoma, POAG: Primary open-angle glaucoma, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, AL: Axial length, CCT: Central corneal thickness, MD: Mean deviation, C/D: Cup/disc. Data expressed as mean ± SD (standard deviation) or n (%). Pairwise comparisons were performed using *one-way ANOVA for normally distributed data and [β]Kruskal-Wallis test for non-normally distributed data. LSD or Conover-Iman test was used for multiple comparisons between groups. Statistically significant differences in [a]PEG vs. POAG, [b]PEG vs. control, [c]POAG vs. control.

Table 2. Comparison of radial peripapillary capillary densities between the glaucoma and control groups

	Groups			p value
	PEG (n=31)	POAG (n=55)	Control group (n=42)	
wpVD[β]	44.12±5.75	46.93±5.46	50.39±2.63	<0.001[a,b,c]
pfVD*	43.73±4.96	43.35±5.18	46.48±4.67	0.007[b, c]
pVD[β]	46.81±7.17	50.42±6.70	54.22±2.84	<0.001 [a,b,c]
pVD-SH[β]	47.05±7.70	50.91±6.85	54.47±2.88	<0.001[a,b,c]
pVD-IH[β]	46.54±6.97	49.89±7.08	53.95±3.20	<0.00 [a,b,c]
pVD-inferior[β]	48.58±7.20	51.64±7.91	55.36±4.62	<0.001[a,b,c]
pVD-nasal[β]	46.90±10.60	50.73±10.50	54.76±6.66	0.005[b]
pVD-superior[β]	46.68±9.42	49.62±9.27	55.24±3.59	<0.001[a,b,c]
pVD-temporal[β]	45.81±8.15	48.89±8.03	52.60±4.76	0.001[a,b,c]

wpVD: Whole image peripapillary vessel density, idVD: Intradisc vessel density, pVD: Peripapillary vessel density, SH: Superior hemisphere, IH: Inferior hemisphere. Data expressed as mean ± SD (standard deviation). Pairwise comparisons were performed using *one-way ANOVA for normally distributed data and [β]Kruskal-Wallis test for non-normally distributed data. LSD or Conover-Iman test was used for multiple comparisons between groups. Statistically significant differences in [a]PEG vs. POAG, [b]PEG vs. control, [c]POAG vs. control.

Table 3. Comparison of macular vessel density values by group

	Groups			p
	PEG (n=31)	POAG (n=55)	Control Group (n=42)	
wmVD$^{\beta}$	41.35±4.78	43.59±5.22	48.33±2.88	<0.001 ^{b,c}
pfVD*	42.97±5.03	44.90±5.23	49.58±3.56	<0.001 ^{b,c}
pfVD-SH*	43.08±5.12	44.92±5.49	49.58±3.84	<0.001 ^{b,c}
pfVD-IH*	42.89±5.38	44.90±5.58	49.57±3.63	<0.001 ^{b,c}
pfVD-inferior*	43.71±5.99	45.61±6.32	50.71±4.23	<0.001 ^{b,c}
pfVD-nasal*	39.03±5.99	42.97±5.42	45.56±3.96	<0.001 ^{a,b,c}
pfVD-superior*	44.45±4.87	45.77±5.78	50.86±4.61	<0.001 ^{b,c}
pfVD-temporal$^{\beta}$	44.67±6.16	45.19±7.20	51.20±3.79	<0.001 ^{b,c}

wmVD: Whole image macular vessel density, pfVD: Parafoveal vessel density, SH: Superior hemisphere, IH: Inferior hemisphere. Note: Data expressed as mean ± SD (standard deviation). Pairwise comparisons were performed using *one-way ANOVA for normally distributed data and $^{\beta}$Kruskal-Wallis test for non-normally distributed data. LSD or Conover-Iman test was used for multiple comparisons between groups. Statistically significant differences in ^{a}PEG vs. POAG, ^{b}PEG vs. control, ^{c}POAG vs. control.

Table 4. Comparison of peripapillary and macular vessel densities in patients with mild glaucoma

	Glaucoma type		p value
	PEG (n:22)	PAAG (n:42)	
wpVD*	46.28±3.56	48.24±3.63	**0.043**
idVD*	43.10±4.85	43.27±5.28	0.902
pVD*	49.78±4.09	51.96±4.61	0.066
pVD-SH*	50.31±3.88	52.26±5.36	0.136
pVD-IH*	49.20±4.65	51.64±4.48	**0.045**
pVD-inferior*	50.00±4.88	53.36±6.16	**0.030**
pVD-nasal*	49.95±9.39	53.00±7.80	0.172
pVD-superior$^{\beta}$	50.36±6.54	51.43±7.82	0.308
pVD-temporal$^{\beta}$	48.91±5.81	49.98±7.05	0.605
wmVD$^{\beta}$	42.54±4.11	44.48±4.25	0.064
pfVD*	44.15±4.26	45.37±4.76	0.314
pfVD-SH*	44.33±4.40	45.32±5.15	0.447
pfVD-IH*	43.98±4.68	45.46±4.97	0.252
pfVD-inferior*	44.82±4.78	45.91±5.98	0.461
pfVD-nasal*	39.76±6.33	43.04±5.63	**0.038**
pfVD-superior*	45.53±4.41	46.48±5.32	0.479
pfVD-temporal*	46.43±4.67	45.95±5.69	0.735

wpVD: Whole image peripapillary vessel density, idVD: Intradisc vessel density, pVD: Peripapillary vessel density, SH: Superior hemisphere, IH: Inferior hemisphere, wmVD: Whole image macular vessel density, pfVD: Parafoveal vessel density. Data expressed in mean ± SD (standard deviation). Pairwise comparisons performed using *Student's t-test for normally distributed data and $^{\beta}$Mann-Whitney U test for non-normally distributed data

Table 5. Correlation between retinal nerve fiber layer thickness and peripapillary vessel density values in the glaucoma groups, total patient group, and control group

	PEG		POAG		PEG + POAG		Control Group	
	r	p	r	p	r	p	r	p
RNFLT/pVD	0.793	<0.001	0.786	<0.001	0.793	<0.001	0.558	<0.001
RNFLT/pVD-SH	0.790	<0.001	0.784	<0.001	0.787	<0.001	0.548	<0.001
RNFLT/pVD-IH	0.809	<0.001	0.792	<0.001	0.803	<0.001	0.486	0.001
RNFLT/pVD-Inferior	0.388	0.034	0.581	<0.001	0.545	<0.001	0.373	0.016
RNFLT/pVD-nasal	0.369	0.045	0.428	0.001	0.426	<0.001	0.077	0.631
RNFLT/pVD-superior	0.603	<0.001	0.176	0.209	0.305	0.005	0.039	0.806
RNFLT/pVD-temporal	0.272	0.145	0.327	0.017	0.317	0.003	0.039	0.811

PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma, RNFLT: Retinal nerve fiber layer thickness, pVD: Peripapillary vessel density, SH: Superior hemisphere, IH: Inferior hemisphere. Note: Controlled for age. Partial correlation analysis was used

Table 6. Correlation of mean deviation, pattern standard deviation, and vessel density values in the glaucoma groups

		PEG		POAG	
		MD	PSD	MD	PSD
pVD	r	0.393	-0.537	0.401	-0.397
	p	0.039	0.003	0.004	0.004
wmVD	r	0.589	-0.414	0.382	-0.209
	p	0.001	0.029	0.006	0.145
pfVD	r	0.455	-0.216	0.201	-0.050
	p	0.015	0.269	0.162	0.728

PEG: Pseudoexfoliation glaucoma, POAG: Primary open-angle glaucoma, MD: Mean deviation, PSD: Pattern standard deviation, pVD: Peripapillary vessel density, wmVD: Whole image macular vessel density, pfVD: Parafoveal vessel density

Discussion

Detection of RNFL damage is important in the early diagnosis and treatment of glaucomatous optic neuropathy. This damage later leads to functional loss detected by perimetry.[27] In our study, there was a significant difference in mean RNFLT between the glaucoma groups and the control group. This result is consistent with other studies in the literature.[28,29]

Focal RNFL damage is typically observed in early-stage glaucoma. The inferotemporal quadrant is most affected, followed by the superotemporal quadrant.[30] The course of the radial peripapillary capillaries within the RNFL and parallel to the retinal nerve fibers is believed to enable supply of the retinal nerve fibers and be associated with its function.[31] In our study, we conducted separate comparisons of pVD average, superior and inferior hemisphere, and inferior, nasal, superior, and temporal quadrant values between the groups. There was a significant decrease in pVD in all quadrants except the nasal quadrant between the POAG and PEG groups. Lommatzsch et al.[32] examined pVD average and sector values (superonasal, superotemporal, nasal, inferonasal, inferotemporal, temporal) in 97 glaucoma patients (41 with POAG, 26 with PEG, 24 with normal tension glaucoma, and 6 with primary angle-closure glaucoma, and found significant reduction in pVD mean and all sector values. Clinically, typical glaucomatous damage first begins in the inferotemporal and superotemporal quadrants, and nasalization of the central vessels is observed in the advanced stage of the disease.[33] Therefore, pVD in glaucoma patients is expected to decrease most in the temporal quadrant. The literature data on this subject vary. Lommatzsch et al.[32] found that pVD was lowest in the nasal and superonasal quadrants. Jia et al.[34] found that vessel density decreased significantly in the temporal quadrant, while Rao et al.[35] found that there was no significant difference between the temporal quadrant and other quadrants. In our study, we determined the temporal quadrant to have the lowest vessel density in the glaucoma groups. The reason for this difference in the literature data is difficult to explain, and further studies on this subject are needed. Lu et al.[24] conducted a study with 44 preperimetric glaucoma (PPG), 42 early-stage glaucoma, and 41 normal eyes and found that the RNFL was significantly thinner in the inferotemporal

and superotemporal quadrants in the early glaucoma group compared to the PPG group, while pVD was significantly lower only in the inferotemporal quadrant. The authors noted that this supports observations that structural damage occurs earlier than vascular damage in glaucoma.

In our study, we examined wpVD, idVD, and pVD values, parameters related to optic disc vascularity, in all three groups and found that vessel densities in the glaucoma groups were significantly lower than those of the control group in all quadrants except the nasal quadrant. In this respect, our study is consistent with the literature. Liu et al.[20] compared 9 perimetric and 3 preperimetric POAG groups with normal eyes and found a significant decrease in pVD compared to normal eyes. Similarly, in the study of Rao et al.[35], pVD was significantly lower in the POAG group compared to the control group. There are many OCTA studies conducted with different glaucoma types in the literature. In a study by Park et al.[36] comparing PEG and POAG patients with a similar disease stage, pVD values were found to be lower in the PEG group, especially in the nasal and inferonasal quadrants. In a study by Suwan et al.[25] investigating pVD in POAG, pseudoexfoliation syndrome, PEG, and healthy individuals, it was shown that vascular density was lower in POAG and PEG patients compared to the control group. In their study, they found that among patients with similar stage POAG and PEG, vascular density was lower in the PEG group. Similarly, in our study, we compared patients in the POAG and PEG groups at similar stages and determined that peripapillary vessel densities were significantly lower in the PEG group, especially in the inferior quadrant. This is consistent with the literature data and supports that PEG is a more aggressive type of glaucoma and progresses faster and shows a poorer response to treatment than POAG. The lower mean IOP in our control group during measurement may have had an impact on the difference between the study and control groups.[20]

In this study, the average, superior and inferior hemisphere, and quadrant RNFLT and sector pVD values were investigated in all three groups. In the entire patient group (POAG + PEG), there was a significant correlation between these parameters in all quadrants. Mansoori et al.[37] examined the relationship between radial peripapillary capillary vessel density and RNFLT in 8 sectors in 24 patients with early POAG and found no significant correlation except in the superotemporal and inferotemporal sectors. Mase et al.[38] observed a stronger correlation between the superotemporal and inferotemporal quadrants than other quadrants. In their study, Triola et al.[39] found a strong correlation between superior, inferior, and average RNFLT and pVD in eyes with glaucoma. In a study by Chung et al.[40] comparing eyes with early, moderate, and advanced glaucoma and healthy eyes, there was a strong correlation between pVD and RNFLT, but no correlation was found between the temporal and inferotemporal quadrants in eyes with early glaucoma. These findings of the present study and similar studies in the literature demonstrate the significant relationship between structural and vascular parameters.

In this study, we evaluated the patients' visual field findings and their correlation with OCTA parameters. For this purpose, we analyzed whether MD and PSD were correlated with pVD, wmVD, and pfVD and found significant correlations. The strongest correlations were between MD and wmVD in the PEG group and between MD and pVD in the POAG group. Looking at the literature data on this subject, a study by Poli et al.[41] investigating the relationship between peripapillary and macular vascular densities and structural and functional tests in glaucoma patients showed that vascular density more strongly correlated with structural tests than functional tests. They also observed greater correlation with peripapillary vessel density values than macular vessel density values. The correlation of visual field findings with both peripapillary and macular vessel densities in our study and similar studies in the literature may be important in terms of the future use of OCTA in glaucoma diagnosis and follow-up.

Study Limitations

Our study has certain limitations. The rather small number of patients in the study group is an important limitation. Another limitation of our study was that patients in the PEG group were relatively older than the POAG group and those in the POAG group relatively older than the control group. This affects vascular density values but is actually an expected result due to the fact that PEG presents at a later age and has a worse prognosis. Although the average RNFLT values were lower in the eyes with PEG than those with POAG, we noted that the patients included in the study had similar glaucoma duration and glaucoma stage assessed according to visual field. Another limitation of our study is the effect of topical antiglaucoma therapy on vessel density. All of the patients in our study were receiving topical antiglaucoma treatment. Prospective studies investigating the effect of antiglaucoma agents on vascular density are needed.

Conclusion

Although there are various theories, the etiopathogenesis of glaucoma remains unclear. This study focused on changes in the vasculature of glaucomatous eyes. We found that vessel density was reduced in eyes with glaucoma compared to healthy eyes, and vessel densities significantly correlated with both visual field and RNFL analysis. It was also determined that in POAG and PEG patients at a similar stage according to visual field findings, eyes with PEG had statistically significantly lower RNFLT and vessel densities. This result shows that PEG is a more aggressive type of glaucoma and that structural and vascular damage occur earlier than functional damage. This information is consistent with the current literature data and leads to the conclusion that OCTA can be used as a reproducible and reliable examination in addition to visual field and structural tests in the diagnosis and follow-up of glaucoma. It may also be preferrable in patients who do not cooperate with visual field testing or advanced glaucoma patients who cannot be monitored for progression due to the

floor effect in structural analyses. Correlation studies between central visual field values and OCTA parameters in eyes with advanced glaucoma in particular will provide more information on this subject.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ankara Training and Research Hospital Ethics Committee (no: 102, date: 01 October 2019), and all study procedures were carried out in accordance with the Declaration of Helsinki.

Informed Consent: Prospective.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., G.Ü., M.Y., S.Ö-U., Ü.E., Concept: E.D., G.D., Design: E.D., G.D., Data Collection or Processing: E.D., Analysis or Interpretation: A.K., G.D., Literature Search: E.D., A.K., Writing: E.D., A.K.

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Original Article

Evaluation of the Use of Brinzolamide-Brimonidine Fixed Combination in Maximum Medical Therapy

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Abstract

Objectives: To investigate the intraocular pressure (IOP)-lowering efficacy, safety, and treatment tolerability of brinzolamide/brimonidine fixed combination (BBFC) in maximum medical therapy.

Materials and Methods: The medical records of 92 patients with glaucoma or ocular hypertension who had previously been treated with a different antiglaucomatous regimen and were switched to a treatment regimen that included BBFC were retrospectively analyzed. Patients were divided into 4 groups including 22, 20, 27, and 23 patients based on previous glaucoma treatment. All patients received maximum medical treatment regimen by adding a combination of beta blocker-prostaglandin analogue therapy along with BBFC. IOP values at baseline and month 1, month 3 and month 6 after starting BBFC and ocular adverse effects at follow-up visits were evaluated.

Results: The mean age of all patients was 62.7±16.6 years (range: 18-90). Fifty-two patients (56.5%) were women and 40 (43.5%) were men. Forty-eight (52.2%) patients had primary open-angle glaucoma, 35 (38.0%) had pseudoexfoliation glaucoma, and 9 (9.8%) had ocular hypertension. The IOP of the all eyes was 21.1±4.8 mmHg (range: 17-25) before and 17.6±3.7 mmHg, 17.3±3.4, and 17.0±3.5 mmHg at month 1, 3, and 6 after the introduction of BBFC, respectively ($p<0.001$ for all time points compared to baseline). In all 4 groups, a significant decrease in IOP was observed at month 1, 3, and 6 follow-ups compared to baseline after the introduction of BBFC. The mean number of antiglaucoma drops was significantly reduced from 2.5±0.6 at baseline to 2 after BBFC ($p<0.001$). The most frequent ocular adverse event was ocular allergic reactions reported in 8 patients (8.7%), conjunctival hyperemia in 5 patients (5.4%), and ocular discomfort in 2 patients (2.5%).

Conclusion: Maximum medical therapy with BBFC provides significant IOP reduction and antiglaucoma therapy simplification with a favorable safety profile in patients with glaucoma.

Keywords: Brimonidine, brinzolamide, fixed combination, glaucoma, intraocular pressure

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Introduction

Glaucoma is a chronic optic neuropathy characterized by progressive optic nerve head atrophy, retinal ganglion cell degeneration, and typical visual field losses.[1] As many glaucoma patients have severe vision loss at diagnosis and the damage caused is irreversible, early diagnosis and monitoring progression accurately and objectively are important. Intraocular pressure (IOP) is the main parameter used in the diagnosis, treatment, follow-up, and classification of glaucoma. IOP is the best known risk factor for glaucomatous damage and is considered the most important modifiable factor for the prevention of progressive glaucomatous injury.[2,3] Multicenter, large-scale clinical studies have shown that reducing IOP can prevent or delay the progression of visual field defects caused by glaucoma and preserve visual function.[4,5] Determining the target IOP is important in the treatment of glaucoma. Initial glaucoma treatment aims to lower elevated IOP by using one or more topical antiglaucoma drugs to reduce the production of aqueous humor and/or increase aqueous outflow.[6]

Antiglaucoma agents with different mechanisms of action are available. Beta-blockers and carbonic anhydrase inhibitors reduce IOP by reducing aqueous humor production; prostaglandin (PG) analogs increase uveoscleral and trabecular outflow; and alpha-2 agonists lower IOP by both reducing aqueous secretion and increasing uveoscleral flow.[4,6] In a large proportion of glaucoma patients, IOP cannot be lowered to within the target range with a single drug, and a second or third drug must be added to treatment to control glaucoma. In maximum medical therapy, the use of three or more different classes of antiglaucoma agents is required to achieve a sufficient reduction in IOP.[7] In the treatment of glaucoma, two, three, or four-component glaucoma therapies can be applied separately, or they can be used as fixed combinations of two drugs in a single bottle to improve ease of use and reduce the adverse effects associated with preservatives. The use of fixed combinations is known to be more comfortable and more advantageous than the use of multiple drugs in terms of patient compliance, posology, ease of use, and adverse effects.[8,9] Frequently used combinations include the topical beta-blocker timolol 0.5% combined with a PG analog, an alpha-adrenergic receptor agonist, or a topical carbonic anhydrase inhibitor. Although fixed combinations containing beta-blockers generally provide effective IOP reduction, they should not be selected for patients with conditions such as asthma, chronic obstructive pulmonary disease, sinus bradycardia, impotence, and depression.[10]

Brinzolamide 1% and brimonidine 0.2% fixed combination (BBFC) was the first fixed combination produced that did not include a beta-blocker. It can be used alone or together with timolol, PG analogs, and combinations thereof. To the best of our knowledge based on the literature, no studies have been conducted in Turkey to evaluate the efficacy and safety of this fixed combination in IOP control. The aim of this study was to investigate the IOP-lowering effect, adverse effect profile, and treatment adherence in glaucoma patients who receive BBFC therapy.

Materials and Methods

The data of patients who were treated and followed up in the glaucoma unit of the Ankara University Faculty of Medicine Department of Ophthalmology between September 2019 and November 2020 were retrospectively reviewed. The study was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (date: 23.10.2019, decision no: İ8-549-20). Written informed consent was obtained from the patients in the study. The study sample included patients who received different antiglaucoma treatments for glaucoma and ocular hypertension (OHT) and were switched to a maximum medical therapy regimen to achieve target IOP by adding BBFC for reasons such as failure to adhere to the use of 3-4 different glaucoma drugs. All patients received brinzolamide 10 mg/mL (1%) and brimonidine 2 mg/mL (0.2%) fixed combination (Simbrinza®, Novartis Pharma AG, Basel, Switzerland) twice daily. The patients were divided into four groups according to the antiglaucoma treatment used before switching to BBFC therapy:

Group 1: Brinzolamide/beta-blocker fixed combination + PG analog therapy

Group 2: Brinzolamide + beta-blocker/PG fixed combination therapy

Group 3: Brimonidine + brinzolamide/beta-blocker fixed combination + PG analog therapy

Group 4: Brimonidine + brinzolamide + beta-blocker/PG fixed combination therapy

All patients were administered a maximum medical therapy regimen of BBFC with a beta-blocker/PG fixed combination once daily. Each patient received the beta-blocker/PG fixed combination containing the same PG analog used before initiating BBFC.

Inclusion criteria for the study were:

1. Age 18 years or older
2. IOP ≤25 mmHg in both eyes (mean of the last 3 measurements before adding BBFC)
3. For patients with glaucoma, presence of glaucomatous visual field losses and presence of glaucomatous optic nerve head damage on fundus examination (vertical enlargement of the optic pit and thinning of the neural rim; vertical cup/disc ratio >0.6, cup/disc asymmetry >0.2 between the two eyes)
4. For patients with OHT, IOP >21 mmHg in at least two measurements and no glaucomatous visual field defect or optic nerve head damage
5. Angle open in all quadrants on gonioscopic examination
6. No optic media opacity (e.g., corneal opacity, substantial cataract, substantial vitreous opacity) or marked retinal pathology
7. No history of ocular trauma or intraocular surgery other than cataract

In the initial examination of all patients, a detailed history was obtained, followed by best corrected visual acuity measurement, slit-lamp anterior segment examination, dilated fundus examination, IOP measurement with Goldmann applanation tonometer (the average of three consecutive measurements made between 9 and 11 AM by another ophthalmologist not involved in the study), angle examination with an Ocular Instruments 4-mirror goniolens, central corneal thickness measurement by ultrasonic pachymeter, visual field analysis (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA, USA) and retinal nerve fiber layer and ganglion cell complex measurements by spectral domain optical coherence tomography (Carl Zeiss Meditec, Dublin, CA, USA). The patients' records were reviewed to collect the following data: IOP measurements at the last follow-up before and at 1, 3, and 6 months after initiating BBFC, routine ophthalmological examinations, time since treatment modification, topical antiglaucoma treatment regimen used before and after switching to BBFC, total number of drops used, and local and systemic adverse effects associated with BBFC use.

Statistical Analysis

The data were analyzed using SPSS for Windows version 11.5 (SPSS Inc, Chicago, IL, USA) software package. Descriptive statistics were expressed as mean ± standard deviation for normally distributed variables and as number (n) and percentage (%) for nominal variables. After importing the IOP values to the SPSS program, paired samples t-test was used to determine the statistical significance of the differences between baseline and values measured at 1, 3, and 6 months to determine the effect of drug use in the three different periods. Results with $p<0.05$ were considered statistically significant in statistical analyses.

Results

A total of 92 patients were included in the study. Four patients discontinued BBFC at 1-month follow-up because of adverse effects and were not included in the analysis. The mean follow-up period after initiation of BBFC for all patients was 8.7±4.5 months (range: 5-11). The demographic and clinical characteristics of the patients in the four groups are shown in Table 1. There were 22 patients (23.9%) in group 1, 20 (21.7%) in group 2, 27 (29.3%) in group 3, and 23 (25.0%) in group 4. Of all the patients in the study, 52 were women (56.5%) and 40 were men (43.5%). There was no statistically significant difference between the groups in terms of gender distribution ($p>0.05$) (Table 1). The mean age of all patients was 62.7±16.6 years (range: 18-90). Mean age did not differ significantly between the groups ($p>0.05$) (Table 1). In the whole patient group, 48 patients (52.2%) were diagnosed with primary open-angle glaucoma (POAG), 35 (38%) with pseudoexfoliation glaucoma (PEG), and 9 (9.8%) with OHT. There was no statistically significant difference between the groups in terms of glaucoma types ($p>0.05$) (Table 1).

The mean IOP of all patients in the study was 21.1±4.8 mmHg (range: 17-25) before treatment and decreased to 17.6±3.7 mmHg at 1 month, 17.3±3.4 mmHg at 3 months, and 17.0±3.5 mmHg at 6 months ($p<0.001$). The IOP values of patients in all groups before BBFC and at 1, 3, and 6 months after BBFC are shown in Table 2 and Figure 1. In group 1, the mean IOP was 22.1±3.1 mmHg before BBFC and 16.8±3.0 mmHg at 6-month follow-up ($p<0.01$). In group 2, the mean IOP was 21.7±3.2 mmHg before BBFC and 16.9±2.8 mmHg at 6-month follow-up ($p<0.01$). In group 3, the mean IOP was 20.6±5.7 mmHg before BBFC and 17.1±3.6 mmHg at 6-month follow-up ($p<0.01$). In group 4, the mean IOP was 20.3±4.8 mmHg before BBFC and 17.3±3.9 mmHg at 6-month follow-up ($p<0.01$). IOP values measured at 6 months were below 18 mmHg in 82% (18/22) of group 1 patients, 85% (17/20) of group 2 patients, 85% (23/27) of group 3 patients, and 86% (20/23) of group 4 patients. At the end of treatment, IOP was 18 mmHg or lower in 45 (93.7%) of the POAG

Table 1. Evaluation of demographic and clinical characteristics by group

	Group 1 (n=22)	Group 2 (n=20)	Group 3 (n=27)	Group 4 (n=23)	p
Age (years), mean ± SD	64.5±11.9	64.2±12.2	61.8±13.6	64.1±18.2	0.360
Gender, n (%)					0.170
Female	13 (%59.0)	12 (%60.0)	14 (%52.0)	13 (%57.0)	
Male	9 (%41.0)	8 (%40.0)	13 (%48.0)	10 (%43.0)	
Lens status, n (%)					0.240
Pseudophakic	4 (%18.2)	4 (%20.0)	5 (%19.0)	5 (%22.0)	
Phakic	18 (%81.8)	16 (%80.0)	22 (%81.0)	18 (%78.0)	
Glaucoma type, n (%)					0.270
POAG	11 (%50)	8 (%40.0)	15 (%55.5)	14 (%60.9)	
PEG	9 (%40.9)	9 (%45.0)	10 (%37.0)	7 (%30.4)	
OHT	2 (%9.1)	3 (%15.0)	2 (%7.4)	2 (%8.7)	
CCT (µm), mean ± SD	529±38.2	531.3±30.3	538±44.3	536±40.5	0.720

SD: Standard deviation, POAG: Primary open-angle glaucoma, PEG: Pseudoexfoliation glaucoma, OHT: Ocular hypertension, CCT: Central corneal thickness

patients, 32 (91.4%) of the PEG patients, and all (100%) of the OHT patients. At last follow-up, IOP was in the 12-18 mmHg range in 31 (64.6%) of the POAG patients, 22 (62.8%) of the PEG patients, and 7 (77.7%) of the OHT patients, and was 12 mmHg or lower in 14 (29.2%) POAG patients, 10 (28.6%) PEG patients, and 2 (22.2%) OHT patients.

The mean IOP changes of the patients in the four groups after starting BBFC are shown in Table 2. Among all patients in the study, the mean IOP change from baseline was -3.5±3.4 mmHg at 1 month, -3.8±3.5 mmHg at 3 months, and -4.1±3.8 mmHg at 6 months after starting BBFC. The mean percent changes in IOP from baseline to 1 month after BBFC in all patients and in the four groups are shown in Figure 2. In all patients, the mean IOP values decreased by 16.6% at 1 month, 18% at 3 months, and 19.3% at 6 months compared to baseline after BBFC (Figure 2). The mean IOP changes and percent decrease at 6 months by glaucoma diagnosis can be seen in Figure 3. After 6 months, the mean change in IOP from baseline was -4.1±3.4 mmHg (19.5%) in POAG patients, -4.0±3.2 mmHg (18.9%) in PEG patients, and -4.1±3.3 mmHg (19.3%) in OHT patients. There was no statistical difference between glaucoma types in terms of IOP changes or percent decrease compared to baseline.

Before BBFC, patients in groups 1 and 2 used a total of two topical antiglaucoma drugs, and those in groups 3 and 4 used three topical antiglaucoma drugs. The mean number of topical antiglaucoma drugs used in all patients was 2.5±0.6 before BBFC and decreased to 2 after BBFC was initiated ($p<0.001$).

Drug-induced ocular adverse effects were observed in 15 (16.3%) of the patients who received BBFC treatment continuously during the 6-month follow-up period, and 13 (14.1%) of these patients discontinued treatment due to the adverse effects. BBFC therapy was not discontinued in 2 patients with mild ocular irritation. The most common adverse event was allergic reaction to the drug within the first 2 weeks of BBFC (n=8, 8.7%), followed by conjunctival hyperemia in (n=5, 5.4%) and ocular irritation/discomfort (n=2, 2.5%) (Table 3). There was no statistical difference between the groups in terms of the frequency of adverse effects ($p>0.05$). Two patients who had not previously used brimonidine reported systemic hypotension after starting BBFC.

Table 2. Mean IOP and change in IOP values after treatment with brinzolamide/brimonidine fixed combination, by group

	Group 1 (n=22)		Group 2 (n=20)		Group 3 (n=27)		Group 4 (n=23)	
	Mean IOP ± SD (mmHg)	Mean IOP change (mmHg)	Mean IOP ± SD (mmHg)	Mean IOP change (mmHg)	Mean IOP ± SD (mmHg)	Mean IOP change (mmHg)	Mean IOP ± SD (mmHg)	Mean IOP change (mmHg)
Initial	22.1±3.1		21.7±3.2		20.6±5.7		20.3±4.8	
1 month	17.8±3.0	-4.4±2.9	17.7±4.0	-4.0±2.9	18.1±4.1	-2.5±2.8	16.8±3.6	-3.5±3.1
3 months	17.3±2.6	-4.8±2.7	17.2±3.6	-4.5±3.9	17.4±3.9	-3.2±3.0	17.2±3.6	-3.1±2.9
6 months	16.8±3.0	-5.3±3.2	16.9±2.8	-4.8±3.7	17.1±3.6	-3.5±3.2	17.3±3.9	-3.0±2.9

IOP: Intraocular pressure, SD: Standard deviation

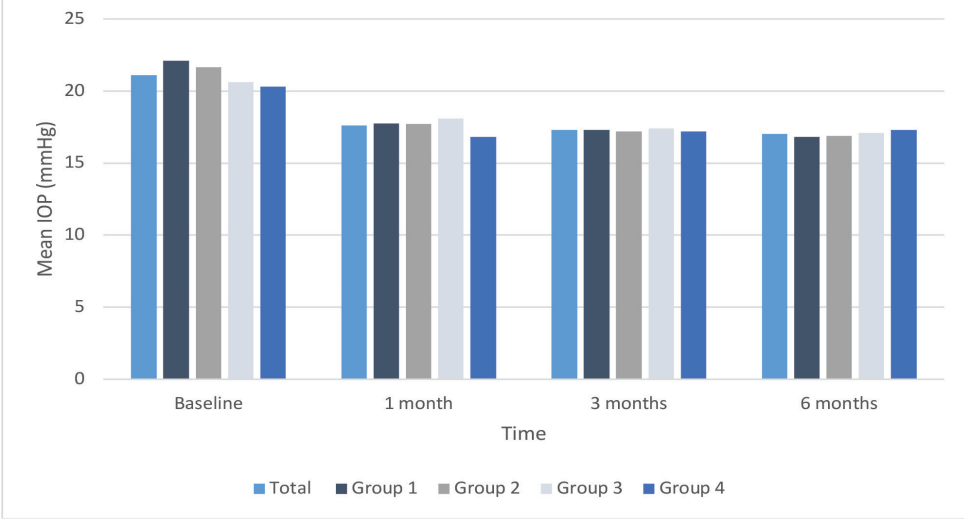

Figure 1. Mean intraocular pressure (IOP) values during follow-up after treatment with brinzolamide/brimonidine fixed combination, all patients and by group

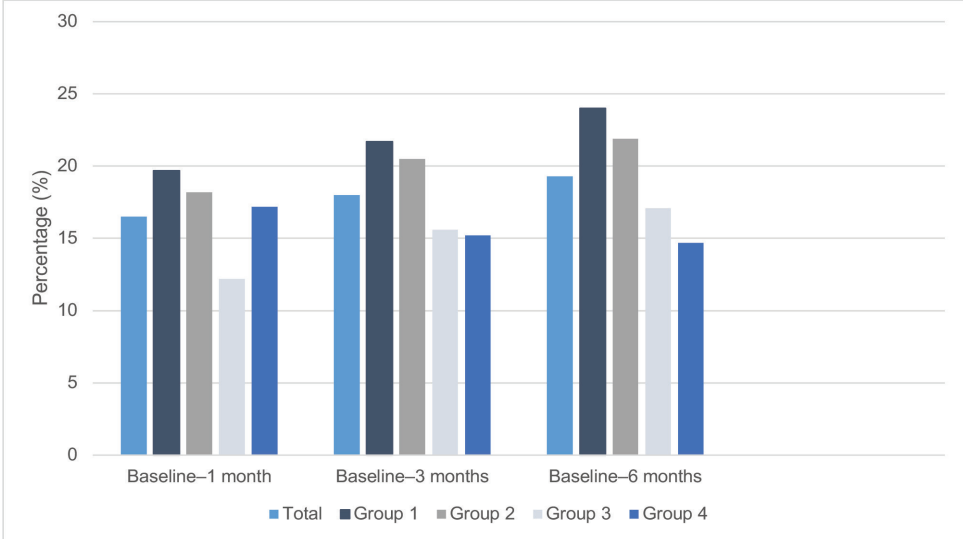

Figure 2. Mean percent change in intraocular pressure (IOP) during follow-up after treatment with brinzolamide/brimonidine fixed combination, all patients and by group

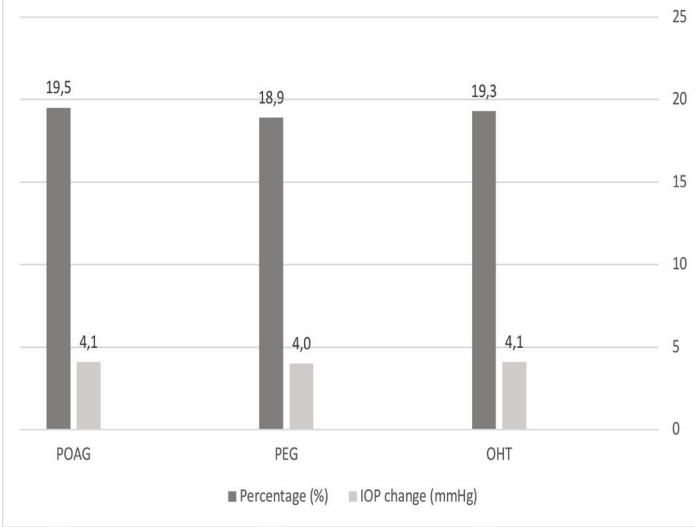

Figure 3. Mean intraocular pressure (IOP) change and percent change at 6 months according to glaucoma diagnosis. POAG: Primary open-angle glaucoma, PEG: Pseudoexfoliative glaucoma, OHT: Ocular hypertension

Table 3. Adverse effects observed after treatment with brinzolamide/brimonidine fixed combination, by group				
	Group 1 (n=22)	**Group 2 (n=20)**	**Group 3 (n=27)**	**Group 4 (n=23)**
Systemic AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ocular AE				
Allergy	2 (9.1%)	2 (10.0%)	3 (11.1%)	2 (8.7%)
Hyperemia	2 (9.1%)	1 (4.0%)	2 (7.4%)	0 (0%)
Irritation, pain	1 (4.5%)	0 (0%)	0 (0%)	1 (4.3%)
AE: Adverse effect				

Discussion

Currently, the first-line treatment of glaucoma is mainly based on the topical application of one or more antiglaucoma drugs to lower IOP. Before resorting to surgical treatment, multidrug regimens must be initiated to achieve target IOP. Studies have shown that using more than two drops a day negatively affects patient compliance and the resulting treatment success.[11,12] Therefore, drugs that act with fewer drops or fixed combinations that contain two drugs in a single bottle are preferred. The fixed-dose combination of 1% brinzolamide (a carbonic anhydrase inhibitor) and 0.2% brimonidine tartrate (an alpha-2 adrenergic receptor agonist) was approved by the U.S. Food and Drug Administration in April 2013 as a new treatment option for patients with POAG or OHT.[13] The drug entered the market for patients in Turkey in September 2019. There is no study conducted in Turkey examining the efficacy and reliability of BBFC in the literature to date.

Our study examined the efficacy of BBFC in 92 patients with POAG, PEG, or OHT who required maximum medical therapy. In this study, BBFC with beta-blocker/PG combination therapy was administered to patients in groups 1 and 2 when a triple therapy with a beta-blocker, PG analog, and carbonic anhydrase inhibitor was insufficient, and a statistically significant decrease in IOP was observed in both groups at 1, 3, and 6 months after switching treatment. In addition, there was a statistically significant decrease in IOP at 1, 3, and 6 months after initiating BBFC and beta-blocker/PG combination therapy in group 3 patients, who previously received brimonidine, combined brinzolamide/beta-blocker, and PG analog therapy in 3 different bottles, and in group 4 patients, who previously received brimonidine, brinzolamide, and beta-blocker/PG combination therapy in 3 different bottles. We believe the significant IOP lowering observed after switching to BBFC in groups 3 and 4, which received four-component antiglaucoma therapy prior to initiating BBFC, can be attributed to improved treatment adherence due to fewer drug bottles and less preservative exposure, as well as reduced potential for the drugs to wash each other out.

Kóthy and Holló[14] studied the effects of BBFC in 52 POAG and OHT cases and reported significant IOP reduction in the majority of eyes included in the study. However, 19 patients (36.5%) in that study had to discontinue treatment due to BBFC-related adverse effects. BBFC therapy was discontinued due to systemic adverse effects in 6 patients (11.5%) and ocular adverse effects in 13 patients (25%).

Gandolfi et al.[15] compared treatment regimens using brinzolamide 1% and brimonidine 0.2% administered as a fixed combination and in separate bottles in patients with POAG and OHT and found that BBFC was as effective in lowering IOP as separate treatment. Based on the results of their study, the authors suggested that BBFC is an effective alternative for patients in whom IOP is not adequately controlled with brinzolamide or brimonidine alone, or in patients with contraindications to PG analog and beta-blockers. Similarly, Wang et al.[16] compared treatment regimens including BBFC and separate brinzolamide and brimonidine drops together in patients with POAG and OHT and found both treatment regimens to have similar efficacy and safety. Kozobolis et al.[17] compared the efficacy of BBFC and a dorzolamide/timolol fixed combination in 44 patients and reported a comparable IOP-lowering effect and safety profile. In this study, they proposed that BBFC is a safe and effective option in patients in whom beta-blocker therapy is contraindicated.

Previous studies in the literature have mostly evaluated the efficacy of BBFC alone in glaucoma patients. In a few recent studies, patients received a maximum medical therapy regimen of BBFC together with a beta-blocker/PG combination. Lerner et al.[7] evaluated maximum medical therapy by investigating the additive efficacy of BBFC with travoprost/timolol fixed combination in 67 open-angle glaucoma and OHT patients and observed a statistically significant reduction in IOP in the group to which BBFC was added. Joh and Jin[18] divided patients who received maximum medical therapy into two groups, triple (dorzolamide-timolol combination + brimonidine + latanoprost) and double (tafluprost/timolol combination + BBFC) maximum therapy. No statistically significant difference was found between the double and triple maximum medical therapy groups in terms of IOP reduction rate, but the rate of ocular adverse effects such as conjunctival hyperemia and dry eye was significantly lower in the double maximum therapy group. Similarly, Wy et al.[19] examined POAG patients who switched from triple maximum medical therapy (dorzolamide/timolol combination + brimonidine + latanoprost) to double maximum medical therapy (tafluprost/timolol combination + BBFC). Although IOP reduction rates were similar between the double and triple maximal medical therapy groups, the dry eye rate was significantly lower in the double maximal therapy group.

Lowering IOP is the only glaucoma treatment option proven to be effective in maintaining visual function. The results of the Early-Onset Glaucoma Study showed that each 1 mmHg decrease in IOP reduced glaucoma progression by 10%.[5] In our study, there was a mean IOP reduction of 4.1 mmHg in the entire patient group according to data obtained at 6 months after the initiation of BBFC. The greatest reduction was 5.3 mmHg in group 1, followed by 4.8 mmHg in group 2, 3.5 mmHg in group 3, and 3.0 mmHg in group 4. Studies have demonstrated that IOP values below 18 mmHg reduce visual impairment.[3] In our study, IOP values measured at 6 months were below 18 mmHg in 82% of patients in group 1, 85% of patients in group 2 and group 3, and 86% of patients in group 4.

The number of topical antiglaucoma drugs used in all patients decreased from an average of 2.5±0.6 before BBFC to 2 after BBFC was initiated. The lower drop number makes use easier and decreases the number of bottles the patient needs to buy, thus decreasing the cost of treatment. We think the increased treatment adherence and lower likelihood of the drugs washing

each other out when using fewer drops played a role in the significant IOP reduction after BBFC. After fixed combination treatment, adverse effects such as ocular surface damage and dry eye associated with the toxic effects of preservatives such as benzalkonium chloride decrease and drug tolerance increases.[15,16]

In our study, the rate of ocular side effects after BBFC was reported to be 16.3%. These included allergic reaction, irritation, and conjunctival hyperemia, which are known side effects of brinzolamide and brimonidine. No serious adverse effects or systemic adverse effects were observed. Previous studies in the literature reported adverse drug reactions similar to those in our study after BBFC.[7,15,16,17,18,19,20] Similar to our study, Lerner et al.[7], reported that the rate of ocular adverse effects was 11.9% in patients who received maximum medical therapy in the form of BBFC and a beta-blocker/PG analog. In the same study, ocular adverse effects were observed in 7.5% of the control group given the beta-blocker/PG analog combination alone.

In previous studies in the literature, it is seen that the majority of patients treated with BBFC are diagnosed with POAG.[15,16,17,18,19] In contrast, our study included 48 patients with POAG (52.2%) and 35 patients with PEG (38.0%). BBFC provided effective IOP reduction in both POAG and PEG patients. At 6 months, IOP decreased from baseline by 4.12±3.37 mmHg (19.5%) in patients with POAG and 4.02±3.17 mmHg (18.9%) in patients with PEG, with no statistical difference in mean IOP change or percent change from baseline between the groups.

Study Limitations

Limitations of our study include the relatively short follow-up period due to the recent introduction of BBFC in Turkey, the lack of a treatment compliance and satisfaction questionnaire for patients after initiating treatment, and the retrospective study design.

Conclusion

The fixed combination of brinzolamide 1% and brimonidine 0.2% provides effective IOP reduction in patients with POAG, PEG, and OHT who need to use multiple antiglaucoma agents. In most patients in our study, BBFC was well tolerated as a part of maximum medical therapy, increased treatment adherence by decreasing the number of drug containers used, and caused no adverse events other than the known ocular side effects of the component drugs.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Clinical Research Ethics Committee, date: 23.10.2020, decision no: İ8-549-20.

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.T., Concept: O.T., H.C.K., Design: O.T., H.C.K., Data Collection or Processing: H.C.K., Analysis or Interpretation: H.C.K., Literature Search: H.C.K., Writing: H.C.K.,

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Original Article

Frequency of *RPE65* Gene Mutation in Patients with Hereditary Retinal Dystrophy

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Abstract

Objectives: Hereditary retinal dystrophies are a rare group of diseases which are heterogeneous in genotype and phenotype and result in total blindness. One of the genetic defects that cause hereditary retinal dystrophy is mutation of the *RPE65* gene. Genetic therapy studies in hereditary retinal dystrophies have increased in number recently, and important developments have been reported in these studies. Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), a gene therapy drug for retinal dystrophy associated with *RPE65* mutation, received Food and Drug Administration approval in 2017. This study aimed to investigate the frequency and clinical findings of patients with *RPE65* gene defects, which may be amenable to genetic treatment.

Materials and Methods: The data of patients diagnosed with hereditary retinal dystrophy who were followed up between 2017 and 2021 were retrospectively reviewed. Of these, 460 patients with genetic analysis results were included in the study. The clinical findings of patients with homozygous (biallelic) *RPE65* mutation were screened.

Results: *RPE65* homozygous gene mutation was detected in only 11 of 460 cases (2.39%). Genetic results of the cases were presented in detail. The inheritance patterns of the cases were autosomal recessive. The demographic data and clinical findings were defined.

Conclusion: *RPE65* gene mutation is a very rare disorder. Genetic screening has gained importance with the emergence of gene therapy alternatives. New treatment methods are promising in cases for which there was no chance of a cure to date.

Keywords: *RPE65* gene, hereditary retinal dystrophy, gene therapy

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Introduction

Hereditary retinal dystrophies are a rare and phenotypically heterogeneous group of diseases that can result in blindness. To date, nearly 250 genetic mutations have been identified, and studies continue to add new mutations to the literature. The disease exhibits a broad clinical spectrum. Clinical entities often cannot be clearly delineated and have overlapping findings.[1,2,3]

Mutations in the *RPE65* gene are among the genetic defects that cause hereditary retinal dystrophy. Clinically, this mutation can be seen in cases of Leber congenital amaurosis (LCA2), severe early childhood-onset retinal dystrophy (SECORD), and non-syndromic retinitis pigmentosa (RP20).[2,4,5] SECORD and LCA caused by genetic defects have similar features. Basically, LCA can be diagnosed if clinical findings occur within the first few months of life.[1,2,3] The features of infancy-onset LCA include progressive visual impairment, nyctalopia, nystagmus, poor pupillary reaction, photophobia, and attenuated electroretinography (ERG) responses. The disease is progressive and can result in blindness in the third and fourth decades. SECORD is clinically milder, with onset between 4 and 6 years of age.[6,7,8]

The *RPE65* gene is involved in vitamin A metabolism in the retinal pigment epithelium cells. Mutations in this gene are fairly rare, with an estimated prevalence of 1/50,000-100,000, and vary between populations.[9,10,11]

Genetic therapy studies in hereditary retinal dystrophies have increased in number recently, and important developments have been reported in these studies. Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) is a gene therapy drug for retinal dystrophy associated with *RPE65* mutation that received Food and Drug Administration (FDA) approval in 2017. Luxturna, the first product approved for hereditary retinal disease in the United States, was also approved for clinical use and introduced in 28 European Union member countries in November 2018.[12,13]

The introduction of gene therapy has further increased the importance of conducting genetic analysis. The genetic and clinical heterogeneity of the disease leads to challenges in the diagnosis. Therefore, gene analysis is also important in terms of identifying the underlying genetic disorder, understanding the genotype-phenotype relationship, and confirming the diagnosis. Thus, patients can be provided counseling regarding future genetic therapy alternatives.

Another benefit of genetic analysis is that it enables genetic counseling of the family. Identifying the causative gene and knowing the inheritance pattern is also important in terms of prevention in our country, which has a high rate of consanguineous marriage. Genetic analysis enables carrier identification, pre-pregnancy counseling, prenatal diagnosis, definitive diagnosis of disease, and clinical prognosis.[14]

This study examined the results of patients who were diagnosed with hereditary retinal dystrophy and underwent genetic analysis in our clinic. The genetic and clinical characteristics of patients with *RPE65* gene mutation were investigated to identify patients eligible for genetic therapy.

Materials and Methods

Patient Identification and Evaluation

In this study, we retrospectively reviewed the records of patients with hereditary retinal dystrophy followed up in our clinic between 2017 and 2021. Ethics committee approval was obtained for the study (2021-09/14). A total of 460 patients with genetic analysis results were included in the study. Clinical examination findings of the patients were examined and best corrected visual acuity (BCVA) was measured with Snellen chart at a distance of 3 meters and recorded by converting to decimal and logMAR. Detailed fundus examination, visual field with Humphrey 30-2 program (Carl Zeiss Meditec AG, Germany), central macular thickness with optic coherence tomography (OCT), and full-field flash ERG (Metrovision, France) results were evaluated.

Genetic Tests

The patients' genetic analyses were performed in universities, training and research hospitals, and private genetic diagnosis centers. We contacted the geneticists in the relevant centers to obtain permission to use the data. Sixty patients were screened by whole exome sequencing (WES), 17 by clinical exome sequencing (CES), and 333 by retinitis pigmentosa (RP) panel for hereditary retinal disease, which includes the *RPE65* gene. Other than these, isolated *RPE65* gene screening was performed in 50 patients. Genetic analyses were performed with new-generation sequencing (NGS) technology using DNA isolated from peripheral blood samples.

Results

The study included 460 patients who were followed up in our clinic and had genetic analysis records. We examined the clinical findings of patients with homozygous (biallelic) RPE65 mutations detected by genetic screening. Patients with mutations in other genes in addition to *RPE65* and patients with heterozygous RPE65 mutations were excluded from the study.

Of the 460 cases screened, only 11 had homozygous *RPE65* gene mutations (2.39%). Of these, 5 patients were female and 6 were male. The patients underwent detailed ophthalmological examinations and their BCVA, fundus examination, visual field, OCT, and ERG findings were evaluated.

The inheritance pattern in these patients was autosomal recessive. In the results of genetic analysis, *RPE65* gene mutation variants were reported as pathogenic, likely pathogenic, or variants of unknown clinical significance; benign conditions were not included in the report. The report details of each patient are shown in Table 1. In the conclusion section of patients 2, 3, 4, and 11, it was reported that pathogenic and likely pathogenic mutations related to the *RPE65* gene could also lead to autosomal recessive LCA2 and RP20, as well as autosomal dominant RP with choroidal involvement. The report of patient 7 indicated that the relevant mutation causes RP20. In the patients' fundus examinations, early-stage patients showed pigment changes in the peripheral retina and areas of geographic atrophy, while

advanced patients showed optic disc pallor, narrowed vessels, and extensive peripheral bone spicules. Figure 1 shows the fundus photographs, OCT macular images, and visual field results of patient 5. All patients exhibited diffuse atrophy in the peripheral retina, although the outer segment/inner segment junction in the subfoveal area was somewhat preserved in patients 1, 4, 5, 6, 7, 8, and 9. In the other patients, widespread disruption and atrophy of the outer segment was detected (Figure 2,3).

Table 1. Genetic analysis results of the patients

Patient No.	Test	Gene	Exon	Variant	Amino acid substitution	Zygosity	Pathogenicity	Inheritance
1	CES	*RPE65* NM_000329	?	c.858+1G>T	Unspecified	Homozygote	P	AR
2	RP Panel	*RPE65* NM_000329	5	c.433G>C	p.Ala145Pro	Homozygote	KÖB	AR
3	RP Panel	*RPE65* NM_000329	3	c.138del	p.Pro47Glnfs*47	Homozygote	P	AR
4	RP Panel	*RPE65* NM_000329	3	c.138del	p.Pro47Glnfs*47	Homozygote	P	AR
5	RP Panel	*RPE65* NM_000329	6	c.499G>T	P.Asp167Tyr	Homozygote	MP	AR
6	RP Panel	*RPE65* NM_000329	2	c.34delT	p.Tyr12Thrfs*19	Homozygote	MP	AR
7	RP Panel	*RPE65* NM_000329.2	9	c.908-999_169del	Unspecified	Homozygote	MP	AR
8	RP Panel	*RPE65* NM_000329.2	10	c.1039C>T	p.Arg347Cys	Homozygote	P	AR
9	RP Panel	*RPE65* NM_000329.2	10	c.1039C>T	p.Arg347Cys	Homozygote	P	AR
10	RP Panel	*RPE65* NM_000329.2	10	c.1039C>T	p.Arg347Cys	Homozygote	P	AR
11	RP Panel	*RPE65* NM_000329	14	c.1460T>C	p.Leu487Pro	Homozygote	MP	AR

KES: Klinik ekzom sekanslama, RP: Retinitis pigmentosa, P: Patojenik, MP: Muhtemel patojenik, KÖB: Klinik önemi bilinmeyen, OR: Otozomal resesif

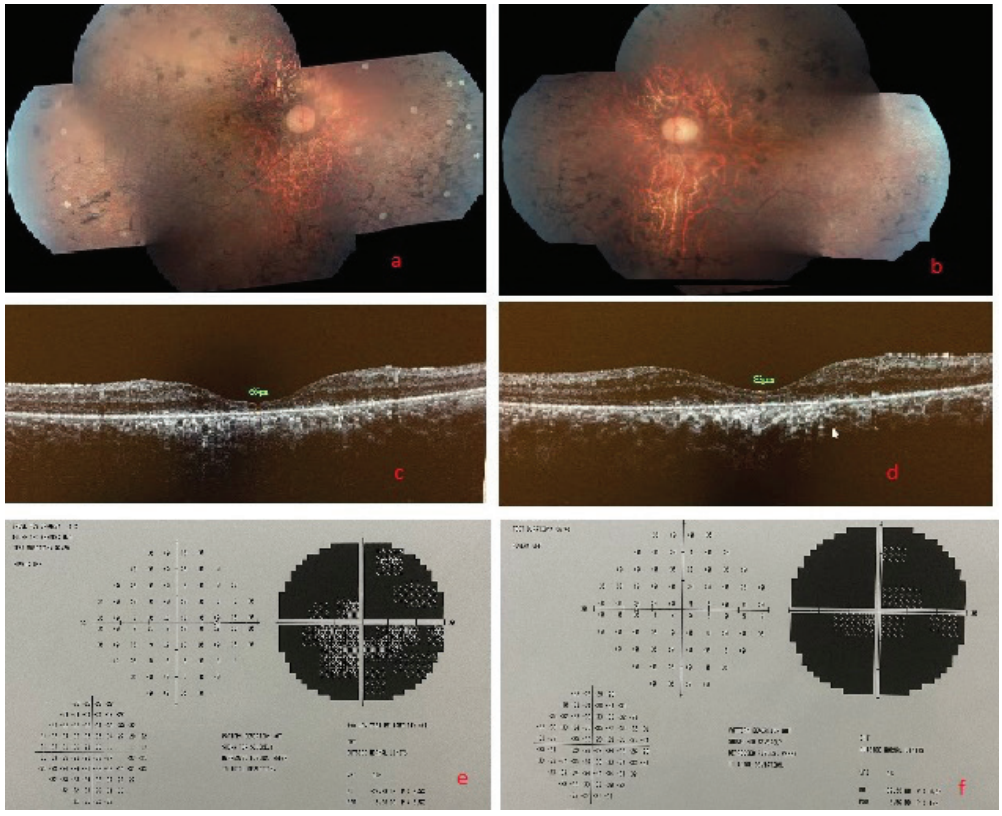

Figure 1. In patient 5, peripheral bone spicules, optic disc pallor, widespread retinal atrophy, and vessel narrowing were observed in right and left fundus photographs (a and b). Macular thinning on optical coherence tomography (c and d) and visual field narrowing (e and f) were also apparent

The age, age at diagnosis, BCVA, visual field mean deviation, and OCT central macular thickness of patients with homozygous *RPE65* mutation are shown in Table 2. These findings were accompanied by nystagmus in patients 1, 8, 9, 10, and 11. In addition, greater than 2 diopters of hyperopia and astigmatism were present in 4 patients and myopic astigmatism in 3 patients. In the other 4 patients, refractive errors were less than 2 diopters.

The patients' full-field flash ERG findings showed diminished responses in most patients. Patients 8, 9, and 10 were siblings. The other patients were unrelated cases.

Discussion

The *RPE65* (retinal pigment epithelium-specific 65 kDa protein) gene is expressed in the retinal pigment epithelium and is involved in vitamin A metabolism. It encodes the enzyme responsible for the isomerization of all-trans-retinyl esters to 11-cis retinol. Mutation in this gene leads to retinyl ester accumulation in the retinal pigment epithelial cells. The visual cycle is disrupted and electrical signals cannot be generated. Degeneration of the retinal pigment epithelium and neural retina results in vision loss.[5,15]

The frequency of RPE65 gene mutation varies between populations. RP20, one of the clinical manifestations of *RPE65* gene mutation, accounts for 1-2% of autosomal recessive RP cases.[5] Studies screening patients with LCA associated with *RPE65* mutation reported prevalence rates between 1% and 16% depending on the geographic region.[11,16,17,18,19] In our study, we screened the genetic results of all patients with hereditary retinal dystrophy, not only LCA, and found homozygous RPE65 gene mutation in 11 (2.39%) of 460 patients.

From previous studies and the new mutations added to the literature, 138 different mutations in the *RPE65* gene have been identified to date.[20] The phenotypic reflection of *RPE65* gene mutations may vary between patients.[21] Six of our patients (including 3 siblings) were found to be consistent with a diagnosis of LCA because of clinical onset in infancy, the presence of nystagmus and weak pupillary reaction, and diminished ERG responses. The other 5 patients were diagnosed after the age of

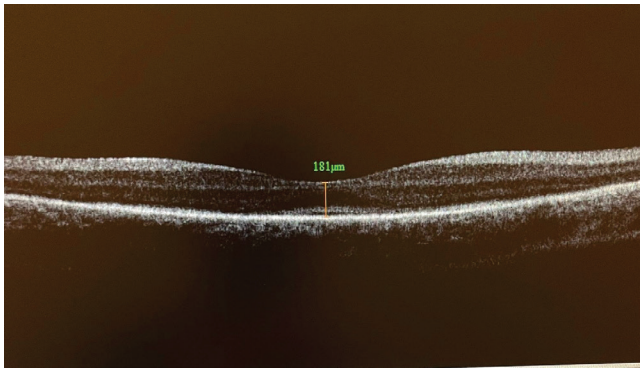

Figure 2. In patient 1, optical coherence tomography demonstrated some preservation of central macular thickness and the retinal outer segment/inner segment junction

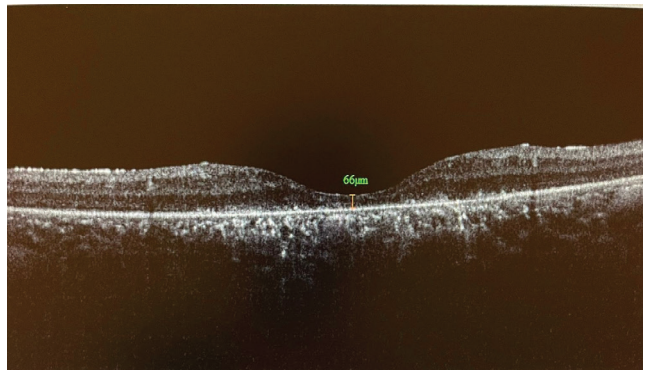

Figure 3. In patient 5, optical coherence tomography showed an extensive retinal degeneration with severe central macular thinning and complete disruption of the retinal outer segment/inner segment junction

Table 2. Clinical findings of our patients

Patient no.	Sex	Age	Age at diagnosis	VA (decimal) right/left	VA (logMAR) right/left	VF MD Value right/left	OCT CMT (µm) right/left
1	F	25 y	5 y	0.05/0.05	1.3/1.3	32.95/32.75	181/170
2	F	33 y	11 y	1 m HM/1 m HM	2.3/2 .3	33.52/33.56	160/185
3	M	26 y	4 mo	P/P	2.5/2.5	33.83/33.81	165/155
4	F	15 y	5 mo	0.05/0.05	1.3 /1.3	27.89/28.21	194/214
5	M	29 y	7 y	0.3/0.05	0.5/1.3	29.99/32.50	66/83
6	F	12 y	6 y	2 m CF/2 m CF	2.3/2 .3	31.13/29.79	160/148
7	M	11 y	6 mo	0.3/0 .15	0.5/0.8	26.53/27.41	190/210
8	F	13 y	4 mo	0.05/0.05	1.3/1.3	30.41/30.98	111/120
9	M	11 y	3 mo	2 m CF/2 m CF	2.3/2 .3	34.68/34.42	84/80
10	M	3 y	3 mo	0.1/0.1	1/1	-	95/90
11	M	46 y	7 y	LP/LP	2.5/2.5	32.82/32.82	74/79

M: Male, F: Female, y: Years, mo: Months, VA: Visual acuity, m: Meter, CF: Counting fingers, HM: Hand movements, LP: Light perception, VF: Visual field, MD: Mean deviation, OCT: Optical coherence tomography, CMT: Central macular thickness, -: The patient could not cooperate with the test.

5 years. These patients' diagnosis could be SECORD or RP20. A study on SECORD and LCA indicated that the RPE65 gene was more associated with SECORD.[8] A diagnosis of SECORD is more likely in our other 5 patients.

It is known that the underlying genetic defect provides insight into the clinical manifestation and disease course that will occur. However, clinical variation between patients and even between family members with the same defect has been reported.[8] Although all of the patients in this study had *RPE65* gene mutations, their age at onset and clinical courses differed. Patients 3 and 4, who were consistent with LCA, had the same mutation (c.138del) and similar clinical features. In addition, sibling patients 8, 9, and 10 (c.1039C>T) had the same clinical findings, with onset in infancy and rapid progression.

Natural history studies have indicated that the disease course is heterogeneous, and the age at onset, clinical findings, and disease severity vary between patients. It was reported that vision level significantly decreases in the first decade, and deterioration of visual acuity and visual field progresses in the second and third decades. Although visual impairment and visual field loss with age are certain, it was emphasized that there may be individual differences. The same patient may exhibit slow progression over the years, as well as exhibit rapid clinical deterioration after a period of stability.[22,23]

All of our patients exhibited significant loss of vision in the first decade. When the clinical findings are examined, 19 of 22 eyes had BCVA below 20/400 (0.05 decimal, 1.3 logMAR). These patients, who also have loss in the central 10 degrees of the visual field, are legally blind according to the World Health Organization ICD-10 coding.[24] In a similar study in the literature, vision loss was reported to progress gradually starting in the first decade and reaching the level of legal blindness (logMAR 1.0, Snellen 20/200) in the second decade.[25]

Studies on gene therapy have accelerated in recent years, and Luxturna completed randomized controlled phase 3 trials and received FDA approval. The phase 3 trial demonstrated the efficacy and safety of the drug, with patients exhibiting increased light sensitivity and improved visual field and performance on mobility tests performed in different lighting.[26]

Patients eligible for gene therapy were identified as those aged 3 years and older with a biallelic (homozygous) *RPE65* gene mutation, visual acuity of 20/60 (0.33 decimal) or less, and more than 20 degrees of visual field narrowing. In order for gene therapy to exert its effect and correct retinal pigment epithelium function, it is essential that there are viable cells in the retina. In advanced cases, extensive degeneration of the outer retinal layers reduces the effectiveness of treatment. To address this, it was reported that the patient must have greater than 100 µm retinal thickness and a level of vision sufficient to perform mobility tests conducted under different lighting conditions. It is recommended that retinal degeneration should not be advanced and treatment should be administered in the early stage. Although the drug prospectus states it can be used in patients over 1 year of age, the consensus is that accepting patients over 3 of age would be more appropriate in terms of vitrectomy-related complications.[12,13,26,27,28]

While all the patients in our study were over the age of 3 years, patients 2, 3, and 11 did not have sufficient visual acuity for the mobility test, and macular thickness was less than 100 µm in patients 5, 9, 10, and 11. Therefore, these patients are not eligible for gene therapy according to the criteria defined. The remaining 5 patients meet the treatment criteria.

Study Limitations

As the disease process is chronic and progressive, longer follow-up would provide more detailed information about disease progression. However, clinical course may not be predictable due to the heterogeneity of the disease and the individual differences in clinical course. In addition, because of the small case number, we could not establish a correlation between the mutations detected and clinical presentation. These data may be obtained in larger-scale studies with longer follow-up.

Conclusion

RPE65 gene mutation is a very rare disorder that can lead to the clinical manifestations of LCA2 and RP20. With the introduction of gene therapy alternatives, genetic screening has gained importance. New treatment methods are promising for patients for whom a cure was not previously possible. Genetic analysis provides guidance in patients' clinical diagnosis, prognosis, and genotype association and is also important in terms of emerging gene therapies.

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Ethics

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Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.Ö., Design: A.Ö., Data Collection or Processing: A.Ö., N.S.K., Y.Ö., M.D., Analysis or Interpretation: A.Ö., N.S.K., Y.Ö., M.D., Literature Search: A.Ö., N.S.K., Writing: A.Ö., N.S.K.

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Original Article

Prevalence of Serous Macular Detachment in Recurrent Macular Edema Secondary to Retinal Vein Occlusion

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Abstract

Objectives: To evaluate the prevalence of serous macular detachment (SMD) accompanying recurrent cystoid macular edema (CME) in patients initially treated for CME secondary to retinal vein occlusion (RVO) with accompanying SMD, and discuss the factors that affect the prevalence.

Materials and Methods: We retrospectively evaluated the medical records of 71 patients with RVO-associated CME and SMD who achieved complete anatomical resolution after treatment with either a single dexamethasone implant or three loading doses of ranibizumab and developed recurrent CME during follow-up.

Results: Initial treatment was a single intravitreal dexamethasone implant in 45 patients (63.4%) (Group 1) and three loading doses of intravitreal ranibizumab in 26 patients (36.6%) (Group 2). The mean time to CME recurrence was 4.7±0.8 months (range, 4-7 months) and was similar in both groups (p=0.984). At the time of CME recurrence, SMD was present in 41 patients (57.7%) and absent in 30 patients (42.3%). SMD was present in 27 (60.0%) of the 45 Group 1 patients and 14 (53.8%) of the 26 Group 2 patients (p=0.613). SMD was present in 48.8% of branch RVO and 71.4% of central RVO patients at the time of recurrence (p<0.001).

Conclusion: SMD accompanied recurrent CME in only 57.7% of patients previously treated for CME and SMD and seems to be more frequent in patients with central RVO. Initial intravitreal treatment choice of either ranibizumab or dexamethasone implant did not affect the prevalence of concurrent SMD in patients with recurrent CME.

Keywords: Cystoid macular edema, optical coherence tomography, serous macular detachment, Branch retinal vein occlusion, central retinal vein occlusion

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Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder, and cystoid macular edema (CME) is the main cause of vision loss in these patients.[1] Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents (ranibizumab, bevacizumab, and aflibercept) and steroids (triamcinolone acetonide and sustained-release dexamethasone implant) has been found to be effective in the treatment of macular edema secondary to RVO.[2,3,4,5,6]

Serous macular detachment (SMD) has been defined as a triangular hyporeflective cavity between the outer retinal layers and retinal pigment epithelium detected with optical coherence tomography (OCT) and is thought to be strongly associated with inflammation.[7,8] It may accompany certain retinal disorders such as RVO, diabetic macular edema, Behçet's disease, postoperative cystoid macular edema, and Coats' disease.[7,8,9,10,11] After the clinical use of OCT in daily practice, it is recognized that SMD is more common than previously thought, and has been reported up to 80% of patients with RVO.[7,12,13] However, no study has investigated the incidence of SMD in recurrent CME secondary to RVO and the factors associated with the incidence of SMD during recurrence.

The aim of the present study was to evaluate the incidence of SMD in patients with recurrent CME secondary to RVO who were initially treated for CME with accompanying SMD and achieved complete anatomical resolution either with a single dose of dexamethasone implant or three loading doses of ranibizumab, and to discuss the factors that affect the prevalance of SMD in these patients.

Materials and Methods

We retrospectively reviewed the medical records of treatment-naive patients who were admitted to the retina department of a single tertiary hospital between June 2013 and June 2017 with an initial diagnosis of CME and accompanying SMD secondary to RVO. The study adhered to the tenets of the Declaration of Helsinki and was carried out upon approval of the Ethics Committee of Numune Training and Research Hospital. Treatment-naive patients who were followed-up for at least 12 months and met the following criteria were included in the study: had CME and SMD secondary to branch RVO (BRVO) or central RVO (CRVO), showed complete anatomical resolution at 3 months after intravitreal injection of either a single dose of sustained-release dexamethasone implant (Ozurdex®) or three monthly loading doses of ranibizumab, and developed CME recurrence detected with spectral domain OCT.

The data collected from the patients' files included past medical and ophthalmic history; demographic data including age and sex; clinical data including the type of RVO (BRVO or CRVO), initial treatment for CME (single intravitreal dexamethasone implant [Group 1] or three monthly ranibizumab injections [Group 2]), logMAR visual acuity, anterior and posterior segment findings on slit-lamp examination, intraocular pressure (IOP) measured by noncontact tonometry, and spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) findings (presence or absence of CME and/or SMD and central macular thickness [CMT]) at each follow-up visit. Patients with a history of previous intraocular surgery and those with evidence of ocular disorders such as diabetic retinopathy, age-related macular degeneration, retinal dystrophies, retinal arterial occlusion, uveitis, vitreoretinal interface disorders, and glaucoma were excluded from the study. Patients whose IOP exceeded 21 mmHg at any point during follow-up and those who were treated with macular or panretinal photocoagulation during follow-up were also excluded.

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM Corp, Armonk, NY, USA). Normal distribution of the variables was tested using visual (histogram and probability graphs) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). Descriptive statistics were expressed as frequency and percentage for categorical variables, whereas quantitative data were expressed as mean ± standard error of mean for normally distributed variables and median (minimum-maximum) for non-normally distributed data. Categorical variables were analyzed by Pearson chi-square test and Fisher's exact test. For the variables that were not normally distributed, Mann-Whitney U test was used to compare two independent groups, Wilcoxon signed rank tests for two dependent groups and Friedman test for three dependent groups. If a significant difference was detected among three dependent groups, post hoc analysis was performed using Wilcoxon signed-rank test with Bonferroni correction. A probability level of $p<0.05$ was considered statistically significant.

Results

A total of 71 eligible patients (37 men, 34 women) with a mean age of 61.4±11.6 years (34-81 years) and a diagnosis of BRVO in 43 (60.6%) and CRVO in 28 (39.4%) were included in the study. The right eye was involved in 36 patients (50.7%) and the left eye in 35 patients (49.3%). Initial treatment was a single intravitreal dexamethasone implant in 45 patients (63.4%) (Group 1) and three loading doses of intravitreal ranibizumab in 26 patients (36.6%) (Group 2). There was no statistically significant difference between the groups with regard to gender distribution ($p=0.209$) or type of RVO ($p=0.898$). However, the mean age was higher in Group 1 than Group 2 ($p<0.001$) (Table 1). Pre-treatment best corrected visual acuity (BCVA) was significantly worse among Group 1 patients when compared to Group 2 (1.29±0.44 and 0.85±0.40 logMAR, respectively; $p<0.001$). Pre-treatment CMT was thicker in Group 1 than Group 2, but the difference was not statistically significant (689.6±166.7 µm and 613.2±163.8 µm, respectively; $p=0.059$).

Following complete anatomical resolution of CME and SMD at 3 months after intravitreal therapy, CME recurred at 4 months in 36 patients (50.7%), at 5 months in 23 patients (32.4%), at 6 months in patients 9 (12.7%), and at 7 months in 3 patients (4.2%), with a mean time of 4.7±0.8 months (range: 4-7 months). The mean time to recurrence was 5.0±0.9 months

(range: 4-7 months) in BRVO patients and 4.3±0.5 months (range: 4-5 months) in CRVO patients (p=0.001). Recurrence times in Group 1 and 2 patients are shown in detail in Table 2 and the mean duration of recurrence was similar for both groups (p=0.984). The patients' mean BCVA and CMT prior to treatment, at 3 months, and at the time of CME recurrence differed significantly (p<0.001 for all) (Table 3).

At the time of CME recurrence, SMD was present in 41 patients (57.7%). SMD was present in 21 (48.8%) of the 43 BRVO patients and 20 (71.4%) of the 28 CRVO patients (p<0.001) and in 27 (60.0%) of the 45 Group 1 patients and 14 (53.8%) of the 26 Group 2 patients (p=0.613) at the time of recurrence.

Discussion

The most common reason for decreased vision in patients with RVO is CME, which is frequently associated with SMD in these patients.[13] However, the pathogenesis of SMD in RVO is still not clearly understood.[13,14,15,16] The occlusion of retinal venous outflow in RVO leads to increased intravascular pressure, particularly in postcapillary venules and capillaries. Venous obstruction also leads to capillary nonperfusion and tissue ischemia, resulting in the production of certain cytokines that enhance vascular permeability. Park et al.[17] reported that aqueous VEGF levels are higher in patients with SMD associated with BRVO compared with patiets without SMD. Thus, it is well known that increased intravascular pressure and vascular

Table 1. Clinical and demographic characteristics of the study population.

	Group 1 (n=45)	Group 2 (n=26)	p
Age (years) Mean ± SD (range)	65.8 ± 9.2 (41-81)	53.8 ± 11.7 (34-73)	<0.001[a]
Gender			
Male, n (%)	26 (57.8%)	11 (42.3%)	0.209b
Female, n (%)	19 (42.2%)	15 (57.7%)	
Type of RVO			
BRVO, n (%)	27 (60.0%)	16 (61.5%)	0.898[b]
CRVO, n (%)	18 (40.0%)	10 (38.5%)	

SD: Standard deviation, RVO: Retinal vein occlusion, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, [a]Mann-Whitney U test, [b]Chi-square test

Table 2. The recurrence time of the study groups

	Group 1 (n=45)	Group 2 (n=26)	p
Timing of recurrence, n (%)			
Month 4	23 (51.2)	13 (50.1)	0.989[a]
Month 5	14 (31.1)	9 (34.6)	
Month 6	6 (13.3)	3 (11.5)	
Month 7	2 (4.4)	1 (3.8)	
Mean time to recurrence (months), mean ± SD (range)	4.7±0.9 (4-7)	4.7±0.8 (4-7)	0.984[b]

SD: Standard deviation, [a]Chi-square test, [b]Mann-Whitney U test

Table 3. Best corrected visual acuity and central macular thickness of patients before treatment, at 3 months, and at time of recurrence

	Pretreatment	Month 3	During recurrence	p*
BCVA (logMAR), mean ± SD (range)	1.13±0.47 (0.30-1.80)	0.33±0.31 (0-1.50)	0.72±0.44 (0.05-1.80)	<0.001
CMT (µm), mean ± SD (range)	661.6±168.6 (331-1,048)	244.6±32.2 (207-270)	531.6±171.8 (285-1,084)	<0.001

BCVA: Best corrected visual acuity, CMT: Central macular thickness, *Friedman Test
Post-hoc comparisons: BCVA: Pretreatment-Month 3 p<0.001, Pretreatment-During recurrence p<0.001, Month 3-During recurrence p<0.001, CMT: Pretreatment-Month 3 p<0.001, Pretreatment-During recurrence p=0.011, Month 3-During recurrence p<0.001

permeability in RVO have important roles in the development of CME and SMD. However, many studies have demonstrated that the pathogenesis of SMD secondary to RVO is not only related to increased intravascular pressure and vascular permeability, but it is presumably multifactorial and also related to inflammation.[16,18,19] Noma et al.[16] reported that vitreous levels of inflammatory factors such as soluble vascular endothelial growth factor receptor-2 and soluble intercellular adhesion molecule-1 were higher and the anti-inflammatory pigment epithelium-derived factor were lower in CRVO patients with SMD, suggesting a role of inflammation in SMD. Dacheva et al.[20] measured the vitreous levels of interleukin 6, monocyte chemoattractant protein-1, and VEGF-A and concluded that inflammatory cytokines were more often correlated with morphological changes (CMT, thickness of the neurosensory retina, extent of SMD, and disintegrity of ellipsoid zone) assessed by OCT, whereas VEGF-A did not correlate with CRVO-associated changes in OCT. Therefore, anti-VEGF therapy alone may not be sufficient to decrease the inflammatory response in CRVO patients with SMD.

Intravitreal anti-VEGF agents and corticosteroids are the main treatment options for the treatment of CME secondary to BRVO and CRVO.[3,4,5,6] Gallego-Pinazo et al.[21] compared the efficacy of intravitreal ranibizumab in the treatment of CME due to BRVO with and without SMD and found that CME improved significantly after a mean of 5 intravitreal ranibizumab injections over a median follow-up of 12.5 months in the patients with SMD and after a mean of 4.3 injections over a median follow-up of 10.4 months in patients without SMD. Although triamcinolone acetonide is the first intravitreal corticosteroid reported to be effective in the treatment of CME and SMD secondary to RVO, sustained-release dexamethasone implant (Ozurdex®) is the preferred intravitreal steroid recently because it has fewer adverse effects compared to triamcinolone acetonide.[4] Maggio et al.[22] determined in their study that Ozurdex® was a safe and effective option for the treatment of RVO-related CME, but the presence of SMD and macular ischemia were negatively associated with visual outcomes. In a study by Elbay et al.[23], CME and SMD regressed after a single intravitreal injection of dexamethasone implant in 23 of 24 patients with SMD secondary to nonischemic CRVO. However, 20 patients relapsed within 5.45±1.45 months and 17 of them had SMD. Karacorlu et al.[6] reported that CME and SMD secondary to CRVO recurred in 50% of patients at 6 months and SMD was again present in all eyes during recurrence. Contrary to these studies, SMD was present in only 57.7% of patients with recurrent CME in our study. The prevalence of SMD during recurrence appeared to be similar for both the dexamethasone and ranibizumab groups in our study. As SMD is a well-known inflammatory biomarker and corticosteroids may have a more prominent anti-inflammatory effect compared to anti-VEGF agents, we would have expected to find a lower SMD prevalence in patients treated with dexamethasone implant. However, we must note that the patients in the dexamethasone group were older and had a lower pretreatment BCVA, probably having more severe disease, which in turn might cause bias in the interpretation of the results.

We evaluated the medical records of patients at 3 months after a single injection of sustained-release dexamethasone implant or a loading dose (three monthly injections) of ranibizumab as first-line therapy in treatment-naive patients with CME and SMD secondary to RVO. If patients exhibited complete anatomical resolution of CME and SMD at 3 months, we continued to examine OCT findings from monthly follow-up visits in order to detect the signs of CME recurrence, such as increased CMT and the appearance of intraretinal cysts. At the time of recurrence, we noted whether SMD was present. In our study, SMD was present during recurrence in only 57.7% of patients who had CME and SMD before treatment. However, the SMD incidence would be lower if the follow-up interval was shorter than one month and higher if it was longer than one month, probably due to the increased amount of CME and further decreased anti-inflammatory effects of intravitreal agents. Thus, it can be speculated that it is important to prevent the occurrence of SMD with timely retreatment in order to achieve better anatomical and functional outcomes. The study data are limited up to the time of first CME recurrence, and the treatment choice at recurrence and the functional and anatomical results of treatment were beyond the scope of the current study.

Study Limitations

This was a preliminary study to evaluate the prevalence of SMD in patients with recurrent CME secondary to RVO who were initially treated for CME with an accompanying SMD and determine the factors affecting the occurrence of SMD in these patients. However, the study has some limitations, including the small sample size and its retrospective nature. In addition, the treatment groups differed in age and some baseline clinical characteristics such as BCVA, which makes interpreting the results difficult and potentially introduces bias. Furthermore, we did not differentiate ischemic and nonischemic RVO, which may affect the results.

Conclusion

In conclusion, this study suggests that SMD seems to be more frequent in patients with recurrent CME secondary to CRVO when compared to BRVO. The choice of initial intravitreal treatment with either ranibizumab or dexamethasone implant did not affect the prevalence of SMD in recurrent CME. However, longer-term prospective studies including a larger number of patients with similar pretreatment baseline characteristics are needed to reach a more accurate and definitive conclusion.

Ethics

Ethics Committee Approval: It was approved by the Ankara Numune Hospital Ethics Committee.

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.Ş., S.D., P.Y., Concept: M.A.Ş., Design: M.A.Ş., Data Collection or Processing: M.A.Ş., F.B.T., S.D., Analysis or Interpretation: M.A.Ş., F.B.T., S.D., Literature Search: M.A.Ş., F.B.T.,S.D., Writing: M.A.Ş.

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Case Report

Sub-Tenon Triamcinolone Acetonide Injection in the Acute Treatment of Handheld Laser-Induced Maculopathy

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Abstract

Handheld laser (HHL)-induced maculopathy has increased in frequency in recent years and can lead to severe retinal damage and vision loss. Although there is no consensus on the treatment of HHL-induced maculopathy, the use of systemic steroids to limit damage to the retina has been discussed. In this article, we present a patient who underwent early sub-Tenon triamcinolone acetonide injection for HHL-induced maculopathy. To our knowledge, sub-Tenon steroid administration has not been previously reported in the treatment of HHL-induced retinopathy.

Keywords: Handheld laser, laser pointer, optical coherence tomography, posterior sub-Tenon triamcinolone acetonide, retinal laser injury

Introduction

The recent introduction of stronger and thus more dangerous laser pointers and the ability to easily obtain these lasers online at relatively low prices has led to an increase in cases of handheld laser (HHL)-induced maculopathy, which can cause severe retinal damage and result in visual impairment.[1,2,3,4,5,6,7,8] They are especially appealing to children and young adults, as they are considered high-tech, are colorful, can ignite paper or matches, and can make holes in objects such as balloons. However, there is a widespread lack of knowledge about the risks and long-term consequences of exposure to high-power laser beams. Because of general unawareness and low vision or scotomas going unnoticed in the pediatric age group, the number of people affected by HHLs is probably higher than reported.

As opposed to clinical manifestations, the finding of a curvilinear hyperreflective band on optical coherence tomography (OCT) is characteristic of HHL-induced maculopathy.[5,9,10] Other reported findings include photoreceptor and retinal pigment epithelium (RPE) damage, full-thickness macular hole, macular hemorrhage, and macular edema.[11,12] Although there is no established consensus regarding treatment necessity and efficacy, it is presumed that early treatment may prevent destruction caused by the photothermal, photomechanical, and

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photochemical interactions of the laser beam. For this purpose, authors have reported administering steroids, usually systemically in HHL-induced maculopathy, systemically and locally in solar retinopathy, or topically in unilateral cases.[5,6,7,8,13,14] Here we present a patient who received early sub-Tenon triamcinolone acetonide injection for HHL-induced maculopathy.

Case Report

A 22-year-old man presented with complaints of low vision in the right eye starting 6 hours earlier and described a paracentral scotoma in his right visual field. Best corrected visual acuity (BCVA) (with Snellen chart) was 20/32 in the right eye and 20/20 in the left eye. Intraocular pressure (IOP) was measured as 16 mmHg in both eyes by tonometry. Eye movements were normal, pupil size was within normal range, direct and indirect light reflexes were intact, and relative afferent pupillary defect was not observed. No pathology was detected in anterior segment slit-lamp examination. On dilated fundus examination, there were no pathological findings other than an area of pallor in the fovea of the right eye; the left eye was normal. When asked what precipitated his vision loss, the patient said that he had taken apart and attempted to repair a handheld green laser he had bought to play with his cat and believed was not functioning. OCT scan revealed a curvilinear hyperreflective band extending from the outer plexiform layer to the ellipsoid zone (Figure 1). According to the information obtained from the website where the patient bought the laser pointer, the laser power was 5,000 mW and it was a green laser. The patient was diagnosed as having HHL-induced maculopathy in the right eye and a sub-Tenon injection of triamcinolone acetonide (40 mg) was administered in the upper temporal quadrant. OCT images obtained on day 4 and at 2 weeks showed progressive resolution of the curvilinear hyperreflective band (Figure 2). At 3-month follow-up, the patient's BCVA was 20/20 in both eyes, IOP was 17 mmHg in the right and 16 mmHg in the left eye, and appearance on OCT was normal (Figure 2). Fundus examination and fundus autofluorescence imaging performed at the same follow-up visit were also normal (Figure 3).

Discussion

HHL-induced maculopathy, first described in 1999, has increased in prevalence in recent years.[1] Although laser-induced macular damage depends on laser characteristics (power, wavelength) and exposure time, the features of the lasers are reported in only one-third of the cases in the literature.[2] According to the United States Food and Drug Administration classification of HHLs, those with power greater than 5 mW are classified as high-power lasers.[2] In addition, lasers with lower

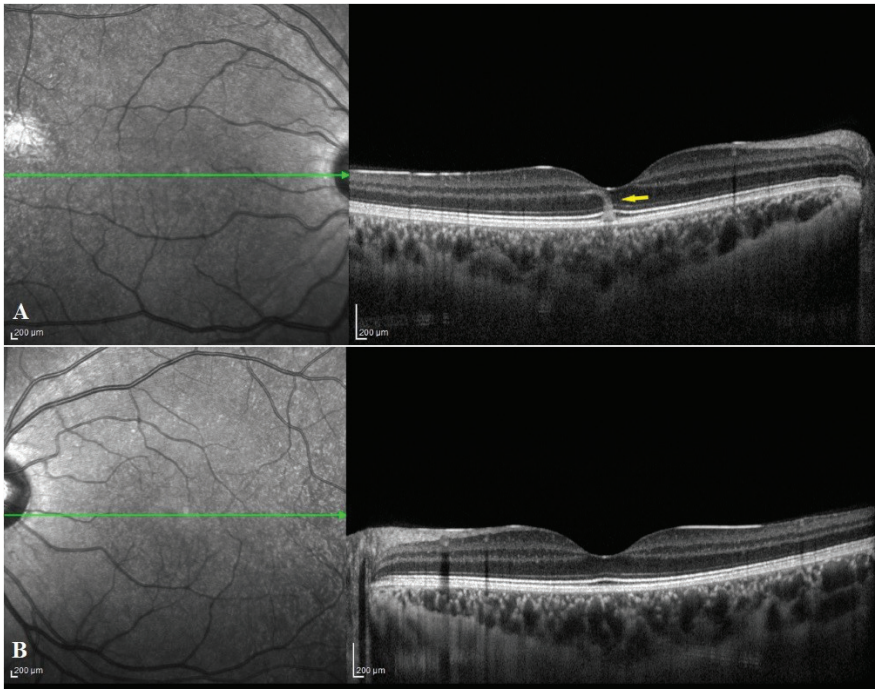

Figure 1. Optical coherence tomography (OCT) image of the patient taken on the same day as the handheld laser injury. A) In the right eye, a curvilinear hyperreflective band extending from the outer plexiform layer to the ellipsoid zone is indicated by a yellow arrow. The hyperreflective band appears to follow the Henle fibers. B) The OCT image in the left eye is normal.

wavelength cause more damage. In our case, the power of the laser that caused the injury was 5,000 mW, which is very high.

Although treatment remains controversial, the use of systemic steroids has been adopted in HHL-induced maculopathy to limit retinal damage. There are a few cases and case series in the literature in which different doses and regimens of systemic corticosteroid were used in patients with different forms and amounts of ocular exposure to different types of lasers. In all reported cases, systemic steroid therapy was reported to have a favorable impact on anatomic and functional recovery.[5,6,7,8] In a study by Chen et al.,[8] patients with HHL exposure were divided into two groups: those who presented within the first week were treated with 1 mg/kg oral prednisolone for 3 days then tapered by 10 mg weekly, while those who presented after the first week received no treatment. Both anatomic and functional outcomes were reported to be better in the treated group at the end of at least 3 months of follow-up. In addition, an animal study demonstrated that treatment with systemic methylprednisolone or indomethacin increased photoreceptor survival in argon laser-induced retinal lesions in rhesus monkeys.[15]

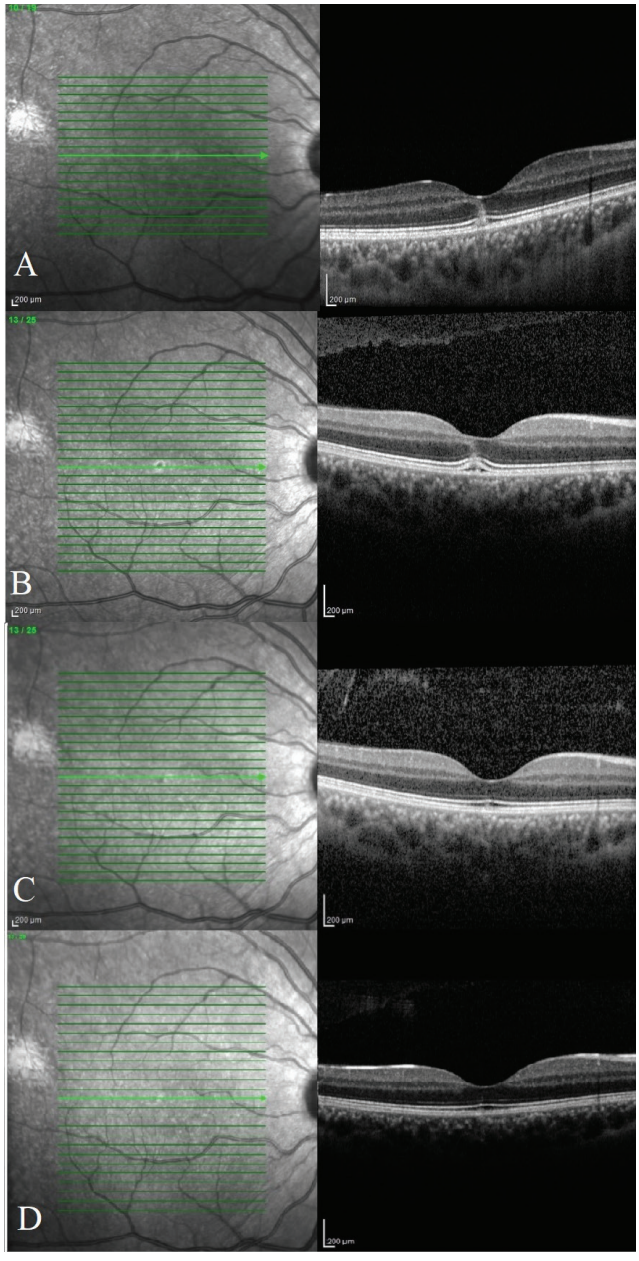

Figure 2. Changes optical coherence tomography images of the right eye obtained over 3 months. The scans were taken on day 1 (A) of visual symptoms and at 4 days (B), 2 weeks (C), and 3 months (D). The vertical curvilinear hyperreflective band was observed to resolve rapidly and disappear, and the subfoveal hyporeflective space that increased on day 4 had completely disappeared at 2 weeks.

In contrast, Dhrami-Gavazi et al.[16] reported resolution of the hyperreflective band within 2 weeks in a patient with HHL-induced maculopathy who received no treatment. However, the authors emphasized that although the patient's visual acuity was improved at 3-month follow-up, the central scotoma persisted. The persistence and degree of damage in HHL-induced maculopathy may vary depending on the laser power and the circumstances and duration of exposure. Systematic controlled studies that would allow evaluation of functional recovery are difficult to design and have not been performed to date, and it is difficult to decide whether treatment is superior to the natural course. However, the presence of persistent OCT findings in long-term follow-up of HHL-induced maculopathy suggests that treatment initiation may be necessary at presentation depending on the laser power, wavelength, and exposure duration.

The pathophysiology of retinal laser damage is known to involve mechanical and thermal destruction of the retinal architecture, as well as retinal and choroidal occlusion.[17] In mild injuries, there may be focal defects in the outer retina and RPE; with more severe injury, external retinal atrophy and choriocapillaris ischemia may occur.[5] Vascular occlusion causes lipid peroxidation and increases retinal damage. Although ellipsoid zone disruption, intraretinal cyst, subretinal fluid, and changes in the inner retinal layers are among the reported OCT signs of retinal damage, the curvilinear hyperreflective band extending from the outer plexiform layer to the ellipsoid zone and characterized by acute opacification of the Henle fibers is typical of HHL-related maculopathy.[5,9,10,11,12]

The strong antioxidant and anti-inflammatory properties of steroids are important in preserving the integrity of the blood-retinal barrier and minimizing laser-induced retinal damage. In our case, treatment was planned because the laser source was very powerful and the patient presented soon after exposure. As the maculopathy was unilateral, we opted for posterior sub-Tenon steroid injection to avoid the undesirable effects of systemic steroid therapy. Posterior sub-Tenon steroid injection is a known treatment option for the treatment of adverse effects such as

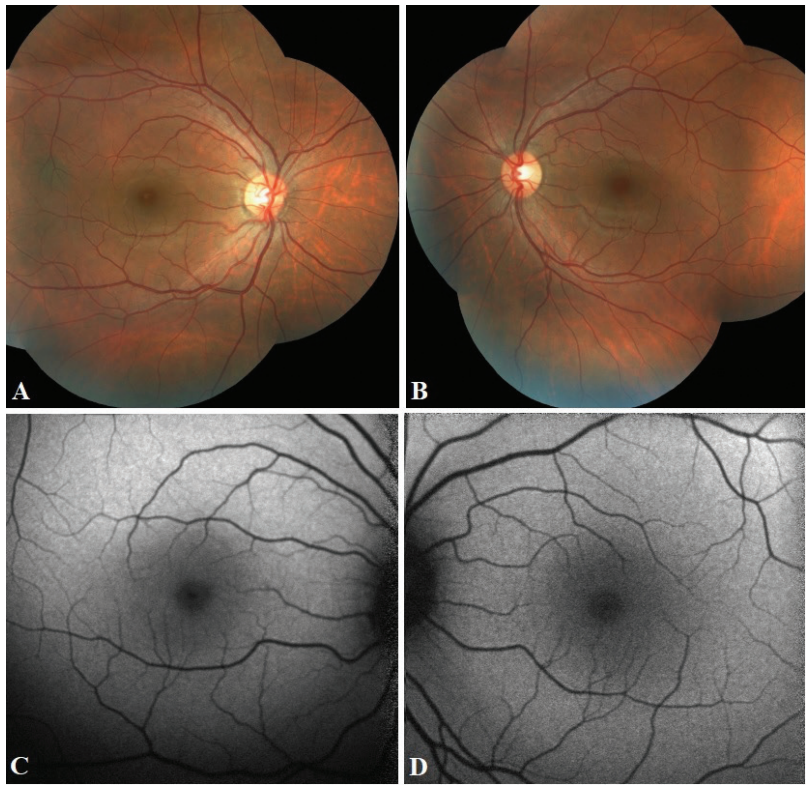

Figure 3. The patient's 3-month follow-up images. A and B) Fundus photographs appear normal in both eyes. C and D) Fundus autofluorescence examination showed no significant loss of autofluorescence in either eye.

macular edema or serous retinal detachment associated with the destructive effect of photocoagulation. To our knowledge, however, sub-Tenon steroid administration for the treatment of HHL-induced maculopathy has not been previously reported in the literature. Posterior sub-Tenon triamcinolone acetonide injection was shown to be effective in the treatment of both macular edema and serous macular detachment by stabilizing the temporary disruption of the blood-retinal barrier caused by the laser.[18,19] In our case, sub-Tenon steroid injection may have allowed faster treatment of thermal and mechanical retinal damage and thus earlier anatomic and visual and functional recovery after HHL exposure.

In conclusion, sub-Tenon steroid injection may be beneficial in obtaining good visual outcome and rapid structural improvement in HHL-induced maculopathy, especially in patients who are affected unilaterally and present soon after laser exposure.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Case Report

Outer Retina Rupture from Subretinal Blood with Spontaneous Sealing and Visual Recovery in Frosted Branch Angiitis from Familial Mediterranean Fever: A Case Report

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Abstract

Familial Mediterranean fever (FMF) is a rare autoinflammatory disorder. Ocular involvement is rare. The full spectrum and response to treatment is poorly understood. An 18-year-old girl previously diagnosed with FMF presented with sudden loss of vision in the left eye (LE). Best-corrected visual acuity (BCVA) in the LE was finger counting at 1.5 meters. Angiitis with mild "frosting," hemi-central retinal vein occlusion (HCRVO), and acute outer retina rupture (ORR) were observed in the LE. Systemic steroids were initiated immediately. The ORR was sealed 2 weeks later while vision improved to 6/15 (near vision: J2) 5 months later. No recurrences were observed over 5 years of follow-up. We report a rare manifestation of frosted branch angiitis with concomitant HCRVO and ORR in a young patient with FMF. Closure of ORR was attained and vision recovered after treatment with high-dose steroids.

Keywords: Frosted branch angiitis, outer retina rupture, hemicentral retinal vein occlusion, Familial Mediterranean Fever, posterior uveitis, retinal vascular sheathing, sudden loss of vision

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Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by mutations in the Mediterranean Fever (MEFV) gene on chromosome 16 and predominantly affects populations of Jewish, Arab, Armenian, and Turkish descent who originated from around the Mediterranean Sea.[1,2,3] Inheritance is autosomal recessive and it manifests with episodes of fever, arthritis, abdominal pain, and erythema that occur sporadically and are self-limiting.[1] Ocular involvement with uveitis is a rare manifestation of the disease. There are a few case reports of anterior, posterior, and intermediate uveitis, frosted branch angiitis (FBA), acute posterior multifocal placoid epitheliopathy, episcleritis, scleritis, and panuveitis.[4,5,6,7,8,9,10,11,12,13,14,15] Due to the plethora of clinical manifestations, some of these cases can be misdiagnosed and pose therapeutic challenges.[16] In this case report, we present the long-term follow-up of a young patient with FMF who presented with acute rupture of the outer retinal layers secondary to FBA-associated hemicentral retinal vein occlusion (HCRVO).

Case Report

An 18-year-old Jewish girl with known FMF confirmed by genetic testing (carrier of M694V and M694I mutations of the *MEFV* gene) and previously treated with colchicine (discontinued 5 years prior to presentation) presented with a sudden loss of vision in the left eye (LE) on awakening from sleep, without any other constitutional symptoms. Best-corrected visual acuity in the LE was finger counting at 1.5 meters and 6/6 in the right eye. Fundoscopy of the LE revealed angiitis with mild frosting in the nasal retina and HCRVO with retinal hemorrhages in the superior retina (Figure 1). Examination of the right eye was normal. Fluorescein angiography of the LE revealed areas of blocked fluorescence, vascular leakage in the superior retina, optic disc leakage and macular hypofluorescence (Figure 2A,B). Spectral-domain optical coherence tomography of the LE demonstrated rupture of the outer retinal layers in the macular area as a result of exudative retinal detachment, with sparing of the inner retina with its internal limiting membrane (ILM) and nerve fiber layer. The outer retinal rupture (ORR) measured more than 400 µm, and the edges had the typical "anvil-shaped" deformity. Vitreous cells and hyperreflective dots were observed along the outer plexiform layer (Figure 2C).

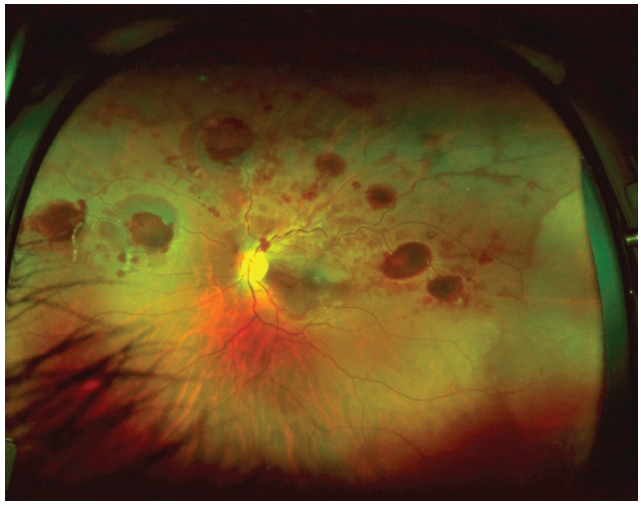

Figure 1. Wide-field pseudo-color fundus image of the left eye shows vasculitis with "mild frosting" in the nasal retina and hemi-central retinal vein occlusion with retinal hemorrhages in the superior retina.

Systemic evaluation ruled out the presence of orogenital ulcers, skin rash, joint pain, and respiratory or gastrointestinal symptoms. Systemic work-up revealed normal liver and kidney function tests. There was mild leukocytosis ($12.6x10^9$/L; normal range: $4.05\text{-}11.84x10^9$/L), ESR was 32 mm/hour (normal range: 0-20 mm/hour), and CRP was 8 mg/L (normal range: 0-5 mg/L). Rheumatic markers were negative (antinuclear antibodies, rheumatoid factor, complement C3, complement C4, anti-cyclic citrullinated peptide antibodies, anti-tissue transglutaminase immunoglobulin (Ig) A [anti-tTG-IgA], cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies). Serological tests for infectious etiologies (Epstein-Barr virus, Venereal Disease Research Laboratory test, *Treponema pallidum* hemagglutination test, *Brucella, Toxoplasma* IgG and IgM, cytomegalovirus IgM) were negative. Mantoux test was negative and chest X-ray was normal. Hematological work-up revealed a slightly elevated lupus anti-coagulant IgM of 72 IgM phospholipid (MPL) units (U)/mL (normal range: 20-39 MPL U/mL), antithrombin activity was 122% (normal range: 80-120%), and anti-cardiolipin IgG was 16.55 U/mL (upper limit 10 U/mL). Factor V Leiden, anti-cardiolipin IgM, anti-B2-glycoprotein (IgG and IgM), coronary artery calcium, dilute Russell viper venom time, and levels of protein C, S, and homocysteine were within normal range or negative.

Intravenous methylprednisolone (250 mg daily for 3 days) was initiated promptly and prednisone was introduced subsequently with a tapering regimen over a period of 13 months. The ORR was sealed 2 weeks later while vision improved to 6/15 (near vision of J2) 5 months later (Figure 3). The angiitis with mild frosting and retinal hemorrhages also resolved by 5 months post-treatment (Figure 4). Treatment with oral colchicine was reintroduced. No recurrence was observed over a follow-up period of 5 years.

Discussion

We report a rare manifestation of acute ORR developing in a young female with FMF who presented with FBA-associated HCRVO. Complete closure of ORR was attained and vision was recovered after the use of high-dose steroids.

Retinal involvement in FMF is rare, with a few reported cases of exudative retinal detachment, epiretinal membrane (ERM),[4] retinal tears requiring barrier laser,[7] neovascularization elsewhere requiring panretinal photocoagulation,[4] and vasculitis manifesting as FBA and retinal artery and vein occlusion.[4,8,13,14,15] Two previously reported cases of retinal vein occlusion (RVO) showed visual improvement, similar to the index case, following steroid treatment. The first case was of a 39-year-old man

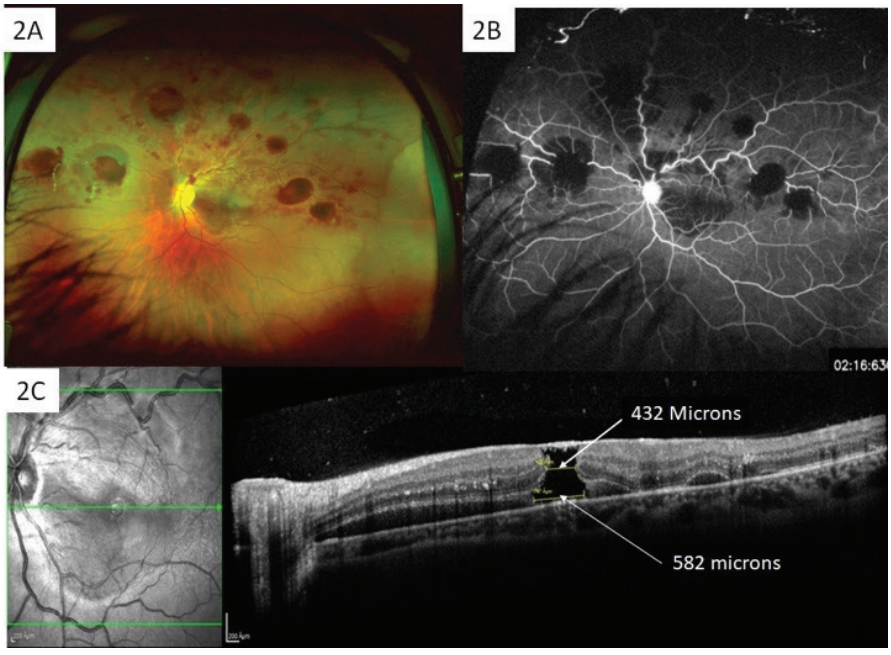

Figure 2. Multimodal imaging of the left eye fundus at presentation. A) Wide-field pseudo-color picture shows multiple foci of retinal hemorrhages mostly in the superior retina. B) Late-phase wide-field fluorescein angiography shows hyperfluorescence of the optic disc and areas of blocked fluorescence in the superior half of the retina and macular hypofluorescence. C) Optical coherence tomography cross-sectional scan across the fovea shows rupture of outer retina layer (measures 432 µm wide at its narrowest point) with the typical "anvil-shaped" deformity of the edges, overlying the internal limiting membrane, nerve fiber layer, and subretinal fluid.

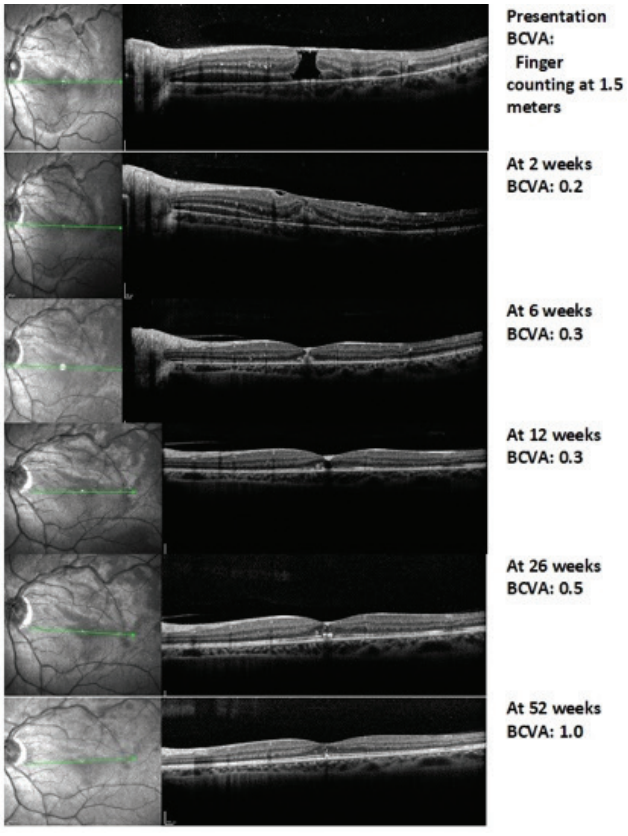

Figure 3. Optical coherence tomography cross-sectional macula scans through the fovea show the progressive closure of outer retina rupture over time, with concomitant visual improvement.

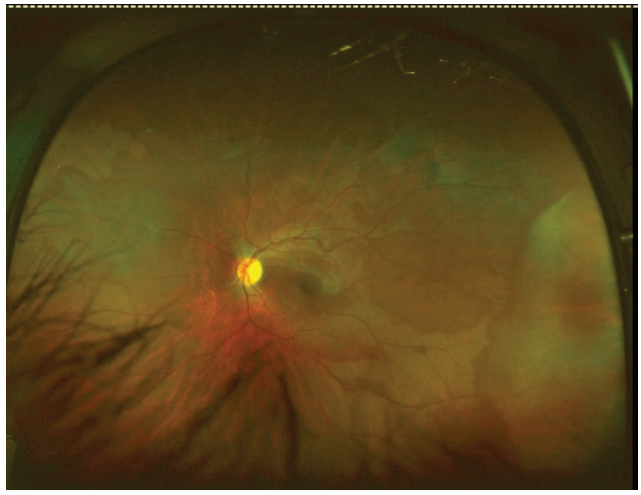

Figure 4. Wide-field pseudo-color fundus image of the left eye 5 months after starting treatment shows resolution of vasculitis and retinal hemorrhages in the superior retina.

who presented with unilateral FBA-associated central RVO. This was the first reported case of FBA associated with FMF in the literature, and vision improved to 6/6 within 7 months after starting immunosuppressants. He was treated with oral methylprednisolone (64 mg/day) with gradual tapering and concomitant azathioprine (150 mg/day) as he developed "moon face" due to corticosteroid use.[8] The second case was of a 53-year-old man who had bilateral vitritis and recurrent retinal vasculitis with resultant cystoid macular edema, ERM, and

branch RVO. Final VA improved to 6/6 after treatment with 3 days of intravenous pulse methylprednisolone (1 g/day) followed by oral prednisolone starting at 1 mg/kg with gradual tapering.[4] A recent article describing vasculitis in 16 patients with FMF also reported good visual recovery after long-term use of corticosteroids and other immunosuppressants.[13] Patients with chronic ocular inflammation often benefit from long-term management with steroid-sparing therapy. Immunomodulators should be considered in patients intolerant to steroid therapy, and they are particularly important because they carry far less risk of causing long-term complications and offer great potential in altering the immune system to induce durable remission.[17] The immediate and progressive favorable response without recurrence or complications observed in our patient under corticosteroid therapy tapered over 13 months made the need to add steroid sparing agents to her therapy less compelling. Moreover, she was restarted on colchicine, which is known to exert an anti-inflammatory effect in FMF.[18]

As a systemic proinflammatory condition, FMF would be expected to trigger hypercoagulability.[19] However, thrombotic events have rarely been reported in FMF. In the few case reports of thrombotic events, extensive work-up usually revealed concomitant multiple inherited and acquired risk factors for thrombosis.[20,21] Possible explanations for this advanced by Tayer-Shifman and Ben-Chetrit[22] include disruption of the balance between coagulation and fibrinolysis, the possibility that proinflammatory factors produced during attacks that would promote hypercoagulability are being consumed in the inflammatory process, and the possible impact of continuous colchicine use by FMF patients on the coagulation pathway. Our patient was not on colchicine treatment, and she had elevated lupus anti-coagulant and anti-cardiolipin levels. These factors may have predisposed to a thrombotic event.[23] On the other hand, anti-thrombin activity, which is supposed to limit clot formation, was borderline high.

To our knowledge, this is the first case of an acute rupture in the outer retina layers developing in the context of retinal vasculitis in a patient with FMF. Our patient had exudative retinal detachment, thus leading to tension and rupture of the outer retina. This mechanism of rupture is extremely rare, with most cases leading to full-thickness macular hole.[24] A similar pattern of healing without surgical intervention was observed in patients with macular holes, especially among young people, trauma patients, and those with deviations of less than 200 µm, as shown in a large series by Uwaydat et al.[24] Though our patient was young, the ORR spanned over 400 µm. However, it closed quickly, within 2 weeks of initiating corticosteroid therapy, with subsequent near-complete restoration of foveal anatomy and contour (Figure 3). No recurrence was observed over a follow-up period of 5 years.

Uveitis recurrence in FMF patients being tapered off steroids has been reported frequently in the literature,[4,7,11] though it is still unclear which factors influence this recurrence. It is possible that certain *MEFV* polymorphisms may be involved; for example, patients who are homozygous for the M694V polymorphism are more likely to manifest severe disease.[25,26]

Behçet's disease is an important differential diagnosis in this case and has even been shown to coexist in patients with FMF.[4] However, the patient's clinical findings did not meet the criteria of the International Uveitis Study Group of Behçet's disease.[27] Extensive laboratory and radiological work-up did not reveal any other pathology or coexistent disorder.

The peculiarity of this case was the presence of a large outer retina layer disruption which eventually self-sealed within 2 weeks of starting steroid therapy. The sudden nature of FBA with concomitant RVO associated with sudden drastic visual loss was also remarkable. This underscores the fact that ophthalmologists working amongst these populations at risk should maintain a high index of suspicion to avoid delays in the diagnosis and treatment of such patients with fulminant presentation.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Peer-review: Externally peer reviewed.

Yazarlık Katkıları

Concept: B.N.V., R.A., Design: B.N.V., R.A., Data Collection or Processing: B.N.V., R.A., Analysis or Interpretation: B.N.V., R.A., Literature Search: B.N.V., R.A., Writing: B.N.V., R.A.

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

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Case Report

Abducens Nerve Palsy as a Presenting Symptom of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic disorder characterized by demyelination of the central nervous system. It often presents in women aged 18-35 with neurological symptoms such as visual loss, paresthesia, focal weakness, and ataxia. Demyelination in the brainstem can result in internuclear ophthalmoplegia causing binocular horizontal diplopia. Our report details a patient with horizontal diplopia from an isolated abducens (sixth) nerve palsy as the initial symptom of MS. While rare, this demonstrates the importance of including MS in the differential diagnosis for an isolated abducens nerve palsy, especially in younger patients with no known vascular risk factors.
Keywords: Abducens nerve palsy, multiple sclerosis, demyelination, diplopia

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disorder caused by destruction and sclerosis of myelin sheath, a protective structure that surrounds nerve fibers in the central nervous system (CNS).[1] Historically, MS was diagnosed when patients had multiple lesions disseminated in time and place and has been treated with corticosteroids during a relapse.[2] Symptoms can be pronounced or subtle, potentially evading medical attention and varying from person to person and throughout the disease course.

Symptoms may include visual loss, limb numbness and/or weakness, loss of coordination, tingling, sexual dysfunction, fatigue, speech difficulties, bowel and bladder dysfunction, or muscle tightness.[1] The disease usually presents between ages 18 and 35, and more commonly in women.[1] The diagnosis of MS has become more specific, utilizing magnetic resonance imaging (MRI) to detect damage around nerve fibers, which is an early sign (T2 lesions).[1] Treatment can be initiated at the first sign of inflammation.[1] However, MS is typically diagnosed in the presence of two or more clinical attacks with two or more CNS lesions at the same or different times.[2] The mainstay of therapy during an acute relapse is an immunosuppressant such as corticosteroids to suppress inflammation of myelin sheath.[1]

MS can result in multiple neuro-ophthalmic manifestations. Optic neuritis is a common initial presentation of MS and typically presents with episodic blurred vision or loss of vision preceded by retrobulbar pain that is worsened by eye movements.[3] Lesions in the brainstem can result in diplopia from internuclear ophthalmoplegia, "one-and-a-half syndrome," or from involvement of fascicles or nuclei of the oculomotor, trochlear, and/or abducens nerves. These symptoms commonly

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appear in association with other symptoms, but can also occur in isolation as a relapse in patients with known MS.[3] Isolated abducens palsy as the initial neuro-ophthalmic manifestation of MS is rare, occurring in approximately 0.4-0.6% of patients.[4,5]

We report a case of abducens palsy as the presenting symptom of MS, which highlights the importance of considering MS in the differential diagnosis of isolated or multiple cranial nerve palsies.

Case Report

A 28-year-old man with no significant past medical history except keratoconus in the right eye was assessed in the neuro-ophthalmology clinic for horizontal diplopia of 2 weeks' duration. He was not on any medications. Family history and social history were non-contributory. Onset of the diplopia was insidious, and there were no other associated neurological symptoms. Three days after the onset of diplopia he had paresthesia in the right upper extremity. This sensory symptom was mild and self-resolved in 2 days. On examination, best corrected visual acuity was 20/50 in the right and 20/30 in the left eye. Abduction was 70% of normal in the left eye, while the remaining extraocular movements were normal (Figure 1). Optic discs were normal. The rest of the neurological exam was unremarkable. Screening for vascular risk factors and autoimmune disorders as well as thyroid function tests were normal. MRI brain revealed several T2/FLAIR hyperintense lesions in the subcortical white matter, predominantly involving the periventricular regions with perpendicular orientation to the ventricular margins. There were scattered lesions in the juxtacortical left frontal region, midbrain, and left cerebellar hemisphere. Spinal MRI revealed multiple T2 hyperintense lesions involving the cervical and thoracic spine. The imaging appearance was highly suggestive of demyelination. The patient was started on glatiramer acetate injections (Copaxone; Teva Pharmaceuticals, Toronto, Canada). In follow-up assessment at 4 months, the left abducens palsy had resolved (Figure 2).

Discussion

The differential diagnosis of abduction palsy includes vasculopathy (including diabetic), inflammatory causes, thyroid eye disease, trauma, and congenital and acquired myasthenia

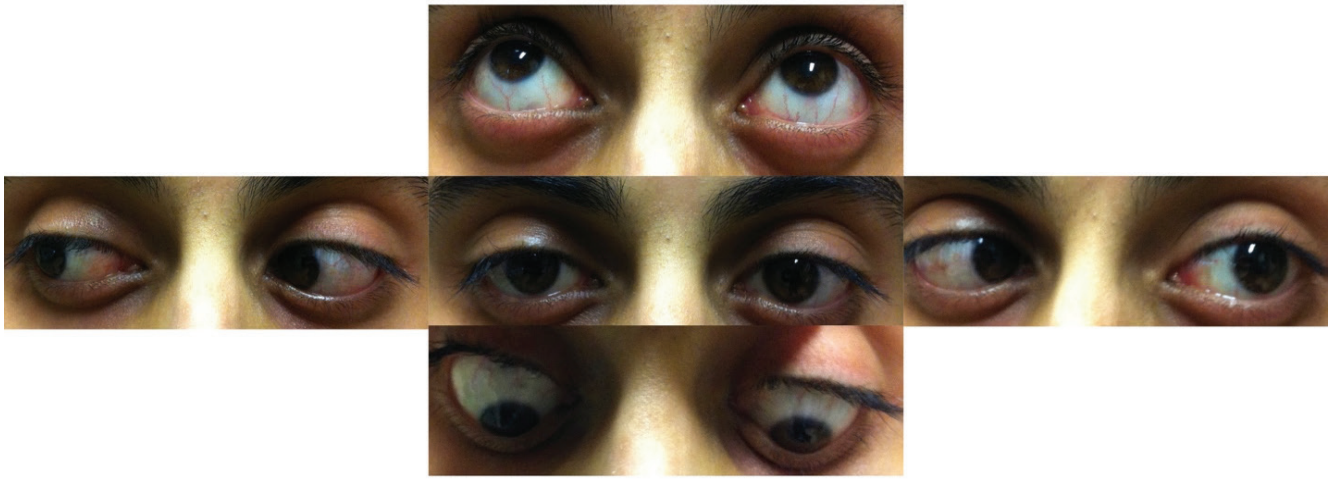


Figure 1. Abduction restriction in the left eye. Pictures taken two weeks after onset of diplopia

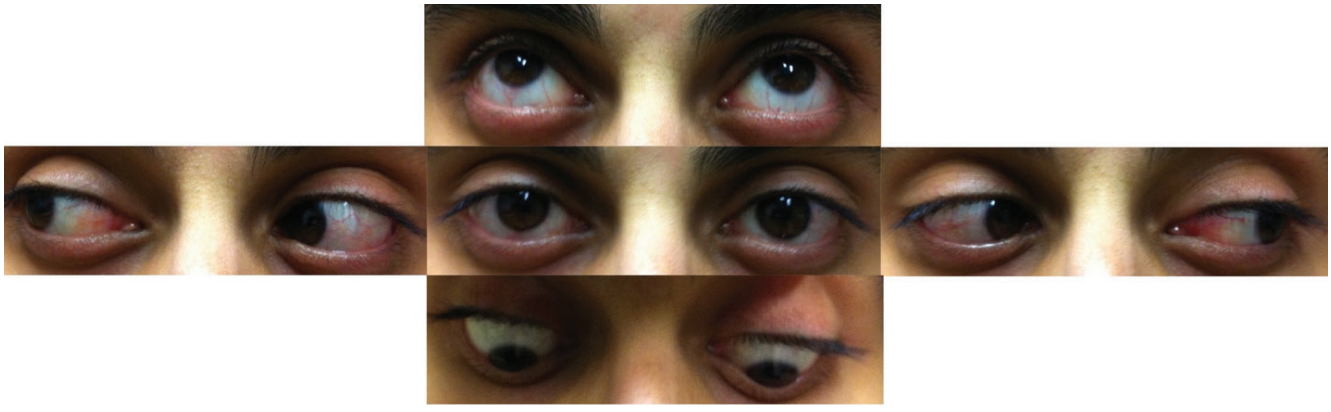
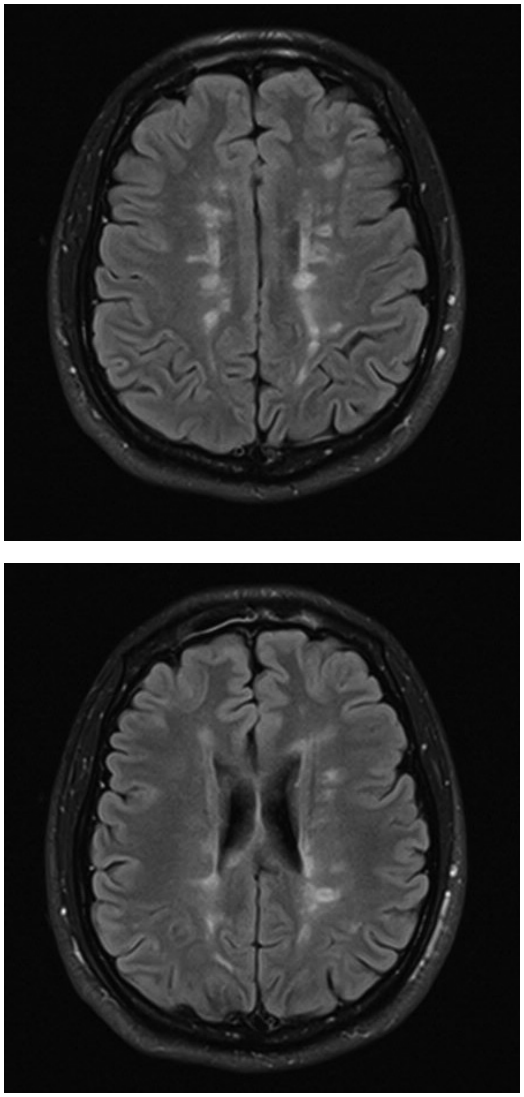


Figure 2. Pictures taken at 4-month follow-up visit showing resolution of the left abducens palsy

gravis. This case presented with MRI findings of demyelination in the brain and spinal cord, supporting the diagnosis of MS, and the abducens palsy resolved before the 4-month follow-up.

MS has been known to cause abnormal eye movements and diplopia due to lesion effects on the cranial nerves. Previous case reports and series discuss isolated nerve palsies in the context of both the presentation and relapse of MS.[5,6,7,8] In 1997, a report detailed 24 patients with MS that had isolated cranial nerve palsies, of which 14 patients had isolated nerve palsies as the presenting symptom (1 third, 1 fourth, 6 sixth, 3 seventh, and 3 eighth cranial nerve), while the remaining 10 patients presented in the context of a relapse.[6] MRI revealed demyelination in more than one location in 11 of the 14 patients.[6] The authors found that the patients most commonly experienced sixth cranial nerve palsy (50%; 12/24) while the remaining patients had third, fourth, eighth, and seventh nerve palsies.[6] Four patients who initially presented with sixth nerve palsy had ipsilateral pontine lesions.[6] A 2002 review determined that 10.4% of 483 MS patients had an isolated cranial nerve palsy, most commonly fifth cranial nerve (4.8%) and seventh cranial nerve (3.7%) followed by sixth (1.0%), third (0.4%), and eighth cranial nerves (0.4%).[4] These palsies were uncommonly the presenting symptom-specifically involving the third (0.4%), fifth (3.5%), sixth (0.6%), and seventh (2.7%) cranial nerves.[4] In non-traumatic sixth nerve palsies, MS was found to be the cause of 24% of cases in patients aged 20-50.[9]



Figures 3 and 4. MRI brain axial FLAIR sequences showing multiple periventricular white matter hyperintense lesions with perpendicular orientation to the ventricular margins, consistent with demyelination
MRI: Magnetic resonance imaging

Bet-Shlimon and Etienne[10] reported isolated abducens nerve palsy in MS. MRI revealed an enhancing lesion in the medial pons on MRI that correlated with an abducens palsy and an additional non-active lesion. Barr et al.[5] detailed three cases of isolated sixth nerve palsy as the only clinical symptom of MS in patients later diagnosed with MS. They discovered that 0.5% of MS patients presented with isolated sixth nerve palsy in their neuro-ophthalmology clinic over 16 years, supporting it as a rare presentation.[5] Two of the cases had discrete hyperintense lesions in the fasciculus of the pontine segment of the left side.[5] Our patient had a lesion in the midbrain, but there were no lesions in the pons. We propose that there was demyelination of the fascicular portion of the left abducens nerve without radiological evidence. Also, the abducens nucleus on that side was spared. For this reason, the patient presented with no gaze palsy and preservation of adduction in the fellow eye.

Isolated abducens palsy as the presenting symptom of MS is rare. This case report adds to existing literature on the topic and supports the inclusion of MS in the differential diagnosis for an isolated abducens nerve palsy.

Ethics

Informed Consent: The patient provided written consent.
Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.J.G., A.N.E.S., Design: M.J.G., A.N.E.S., Data Collection or Processing: A.N.E.S.,

Analysis or Interpretation: M.J.G., A.N.E.S., Literature Search: M.J.G., Writing: M.J.G., A.N.E.S.

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