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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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CONTENTS

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EDITORIAL

## 2017 issue 4 at a glance:

In the age group of patients undergoing cataract surgery, benign prostate hypertrophy is another extremely common age-related health problem. Loss of iris tone caused by the alpha-blockers used to treat benign prostate hypertrophy gives rise to a condition called intraoperative floppy iris syndrome, which complicates cataract surgery. Though this is now questioned before cataract surgery, Acar et al. found that discontinuing alpha-blocker therapy 10 days before surgery resulted in no favorable changes in anterior segment parameters, including pupil dilation, in their ultrasound biomicroscopic evaluation of 31 eyes of 19 patients.

Biberoğlu et al. observed no significant differences in retinal nerve fiber layer or intraocular pressure (IOP) values before and after carotid artery stenting in 15 patients diagnosed with carotid artery stenosis (CAS) with no signs of Ocular Ischemic syndrome (OIS) when compared to 18 healthy male controls. As the effect of CAS treatment on IOP in the presence of OIS is well described in the literature, OIS emerges as a determinant of IOP levels post-stenting.

Tufan et al. compared the IOP reduction of eye drops vs. selective laser trabeculoplasty (SLT) in order to determine whether the procedure could replace medication and found that over a period of 6 months, 180 or 360 degree SLT lowered IOP comparably to medical therapy in eyes previously treated with timolol-containing fixed combination eye drops. Considering that preservative-free glaucoma medications are not available in our country and that compliance with eye drop therapy decreases with age and the number of drops to be applied, Tufan et al.'s study raises awareness of this replacement option and will impact the treatment preferences of patients and physicians.

Polat et al. investigated factors influencing compliance to intravitreal anti-vascular endothelial growth factor therapy among patients with wet type age-related macular degeneration (AMD). They determined the main factors leading to noncompliance to this therapy, which is probably the most expensive medical treatment in ophthalmology, were fear of injection, disbelief in the benefits of the treatment, financial limitations, continuation of treatment in another province, and systemic comorbidities. The authors state that raising the awareness of patients and their families may improve treatment compliance and success rates.

Erkan Turan et al. report that patients with similar strabismus diagnoses may exhibit different types of abnormal head position (AHP) and that patients may develop amblyopia or lack binocularity despite AHP. They conclude that attention to these details is required when diagnosing and treating patients with AHP.

In their screening study of schools for the visually impaired, Bingöl Kızıltunç et al. report that the causes of low vision and blindness was preventable in 27.6% and visual acuity improved with the use of low vision aids in 57.5% of 120 students, bringing attention to the serious deficiencies in the early diagnosis and rehabilitation of students in these schools.

In this issue's review, Özyol et al. compare the currently available intraocular lens materials in terms of uveal and capsular biocompatibility and review studies aimed at increasing the biocompatibility of intraocular lenses.

Serin et al. present two cases of molluscum contagiosum, a cause of unilateral chronic conjunctivitis. In their article, they include a valuable literature review on the differential diagnosis of unilateral chronic conjunctivitis, as well as discuss current treatment options for ocular molluscum contagiosum, which they diagnosed clinically and histopathologically.

Anterior segment optical coherence tomography (AS-OCT) is a relatively new imaging method primarily used in the assessment of anterior segment pathologies. Aslantürk Eren et al. evaluated AS-OCT findings such as lesion size, inner structure, degree of vascularity, and anterior and posterior surfaces in a patient diagnosed pathologically with spindle type iridociliary melanoma to determine whether AS-OCT can be used to distinguish benign and malignant tumors.

Koban et al. present what they believe to be the second case in the literature of mantle cell lymphoma with central nervous system involvement presenting with ophthalmoplegia. The authors remind us that ophthalmoplegia should also be considered among the initial signs of mantle cell lymphoma.

Cebeci et al. present a case of bullous type central serous chorioretinopathy (CSCR), which can often be confused with the ocular symptoms of acute Vogt-Koyanagi-Harada disease. Because corticosteroid therapy administered for a diagnosis of intraocular inflammation may exacerbate CSCR and lead to irreversible damage, the authors emphasize that atypical, bullous CSCR should be considered in the presence of serous retinal detachment.

Sarıgül Sezenöz et al. offer a detailed discussion of their use of ranibizumab to treat secondary choroidal neovascularization in a rare case of choroidal osteoma.

We believe that this issue will become a frequently used reference for our colleagues due to the original research articles, the results of which will inform our clinical practice and future studies, and the review article and case reports, which present updated literature summaries in their fields.

**Respectfully on behalf of the Editorial Board,**
**Sait Eğrilmez, MD**

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Original Article

# Evaluation of Anterior Segment Changes of Patients Taking Alpha1-Blockers by Ultrasound Biomicroscopy in the Drug-free Period

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## Abstract

**Objectives:** To evaluate and compare anterior segment changes in patients taking alpha-1 (α1) blockers (tamsulosin, terazosin, doxazosin, alfuzosin) for benign prostatic hypertrophy, during drug intake and drug-free period, using ultrasound biomicroscopy (UBM).

**Materials and Methods:** In this prospective study, UBM was done before and after pupil dilatation in 31 phakic eyes of 19 male patients taking α1-blockers. Undilated and dilated UBM was repeated before cataract extraction, after stopping the drug for 10 days. On ideal images, pupil diameter (PD), anterior chamber depth (ACD), anterior chamber angle (ACA), and angle opening distances at points 500 µm and 250 µm from the scleral spur (AOD500 and AOD250) values were noted and changes in parameters were evaluated to reveal any changes that occurred after discontinuing the drug. No patient in the study was previously or currently using any other α1-adrenergic antagonist medication. Exclusion criteria for all patients included a history of diabetes mellitus, systemic hypertension, glaucoma, pseudoexfoliation syndrome, chronic use of medicated eye drops, and previous ocular surgery.

**Results:** PD, ACD, ACA, AOD500 and AOD250 values measured before pupil dilatation in the drug-free period were not significantly different from those measured during α-blocker intake ($p>0.05$). In dilated eyes, the mean value of AOD500 was 0.35±0.08 mm during drug usage and 0.39±0.08 mm in the drug-free period. The mean value of AOD250 was 0.23±0.06 mm during drug usage and 0.26±0.07 mm after discontinuation. These increments were statistically significant ($p<0.05$, $z=-3.699$, $z=-2.984$). On the other hand, there were no significant differences in ACD, ACA, or PD values in dilated eyes after discontinuing α1-blockers ($p>0.05$).

**Conclusion:** The interruption of taking α1-blockers in patients who have benign prostatic hypertrophy does not seem to influence anterior segment parameters generally. However, further investigation is needed.

**Keywords:** Alpha1 blocker, anterior segment, ultrasound biomicroscopy

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## Introduction

Intraoperative floppy-iris syndrome (IFIS) associated with the usage of tamsulosin (Flomax®), first described by Chang and Campbell[1] in 2005, is defined by iris billowing, prolapse, and progressive pupil constriction during cataract surgery. Since then, several reports have confirmed IFIS and its relationship with tamsulosin. There is a wide spectrum of clinical expression of this syndrome, with some patients showing signs in one eye only or having asymmetric involvement between fellow eyes.[2,3] In addition, there are even several reports of patients developing IFIS for a long time after discontinuing tamsulosin.[1,4]

The pathophysiology of IFIS is not well described. Tamsulosin is an α1-adrenergic antagonist which is used to treat urinary retention from benign prostatic hypertrophy. Because of this, it is prescribed by urologists to block α1-receptors on the smooth muscle of the prostate, leading to muscle relaxation and relief of bladder outflow obstruction. Alpha1-adrenergic receptors are also found on the iris dilator muscle.[5,6] Recent studies suggest that iris dilator muscle thickness is reduced in individuals with a history of tamsulosin use.[7,8] It has been claimed that blocking the α1-adrenergic receptors on the iris dilator muscle leads to disuse atrophy, deficient mydriasis, and irregular iris behavior during intraocular surgery.

It is known that the risk of IFIS cannot be eliminated, but it can be reduced by discontinuing α-blockers. The biological half-life of tamsulosin is 48-72 hours.[9] Therefore, discontinuing the drug 4-7 days before surgery may be beneficial, but not able to completely prevent IFIS. There is no relationship between the duration of tamsulosin intake and IFIS.[1] IFIS associated with tamsulosin and other α-adrenoreceptor blockers seems to be a partially permanent pathology. Although pupil dilation improves and iris billowing decreases when tamsulosin is discontinued 1-2 weeks before cataract surgery, the risk of IFIS persists up to a year after discontinuation.[1,2] The current prospective study was designed to determine whether there are any preoperative changes in anterior segment (AS) parameters measurable by ultrasound biomicroscopy (UBM) after discontinuing α1-blocker.

## Materials and Methods

Approval for the study was obtained from the Ethics Review Committee of the İstanbul Training and Research Hospital (protocol number: 473). All research protocols adhered to the tenets of the Declaration of Helsinki and all volunteers went through a complete informed consent process. Patients were chosen from the list of those scheduled to have cataract surgery in the Ophthalmology Department of the İstanbul Training and Research Hospital in İstanbul, Turkey.

Phakic eyes of male patients with current use of tamsulosin (Flomax®, Boehringer Ingelheim), terazosin (Hytrin®, Abbott), doxazosin (Cardura®, Pfizer), or alfuzosin (Xatral®, Sanofi Aventis) were included in the study. No patient in the study was previously or currently using any other α1-adrenergic antagonist medication. Exclusion criteria for all patients included a history of diabetes mellitus, systemic hypertension, glaucoma, pseudoexfoliation syndrome, chronic use of medicated eyedrops (antiglaucomatous, steroids, non-steroidal anti-inflammatory drugs, antibiotics, etc.), and previous ocular surgery.

Patients using a α1 antagonist and scheduled for cataract surgery in our clinic underwent UBM (Sonomed-VuMax II®) both immediately before and 30 min after pupil dilatation with 2.5% phenylephrine (Mydfrin®, Alcon) and 1% tropicamide (Tropamid®, Bilim). Then they were requested to stop using the α1-blocker for 10 days. UBM was repeated on the day of surgery, both before and after pupil dilatation. Pupil diameter (PD), anterior chamber depth (ACD), anterior chamber angle (ACA), angle opening distances (AOD) at both 500 µm and 250 µm (AOD250) were measured from the UBM scans and evaluated to determine whether any significant changes occurred in the AS in the drug-free period.

All measurements were taken with the patient in supine position with dim ambient lighting to provide natural pupil dilation. Topical 0.5% propacaine HCl (Alcaine®, Alcon) was instilled before the procedure. For scanning, a silicone cup of the appropriate size (18, 20 or 22 mm) was gently placed between the superior and inferior fornices. Patients were instructed to keep their eyes open and look at a fixed point on the ceiling, sufficient saline was put in the cup for immersion, and the scan was initiated. Firstly, axial images of the AS were taken, radial section images of the angle on superior, inferior, lateral and medial quadrants were taken instantly. For the ideal images and to take consistent measurements, we took care to ensure axial and vertical alignment. While taking the axial section images, the probe was placed vertically to the limbus to get the best reflectance of iris. We also ensured the visibility of the scleral spur on all images.

Both the scans and measurements were taken by the same observer. All measurements were taken at least twice at different times by the same individual. PD, ACD, ACA, AOD500, and AOD250 were measured using the scales on the device software, consistent with the method suggested by Pavlin et al.[10] (Figure 1, 2, 3).

### Statistical Analysis

Mean and standard deviation were used in descriptive statistical analyses. Wilcoxon signed-rank test was used to analyze the repeated measurements in related groups at different times. Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, USA) software was used for all analyses.

## Results

Thirty-one phakic eyes of 19 male patients were included in the study. The mean age of patients was 71.3±0.7 years. Pupil diameters were analyzed first. The mean values of all other parameters and details are shown in Table 1. The mean non-dilated PD in the drug-free period was 3.45±0.72 mm. There was no difference in this value during α1-blocker use. The other

parameters also did not differ based on drug use in non-dilated eyes (p>0.05) (Table 2).

There were no significant differences in dilated PD, ACD, or ACA measurements after discontinuing α1 antagonists (p>0.05). However, the mean values of AOD500 and AOD250 with dilated pupils were statistically higher in the drug-free period. The mean value of AOD250 was 0.24±0.06 mm during α-blocker use and 0.26±0.07 mm in the drug-free period, and these values for AOD500 were 0.36±0.08 mm and 0.39±0.08 mm, respectively. The differences were statistically significant (p<0.05, z=-3.699, z=-2.984). Other measurements and statistical data are shown in Table 3.

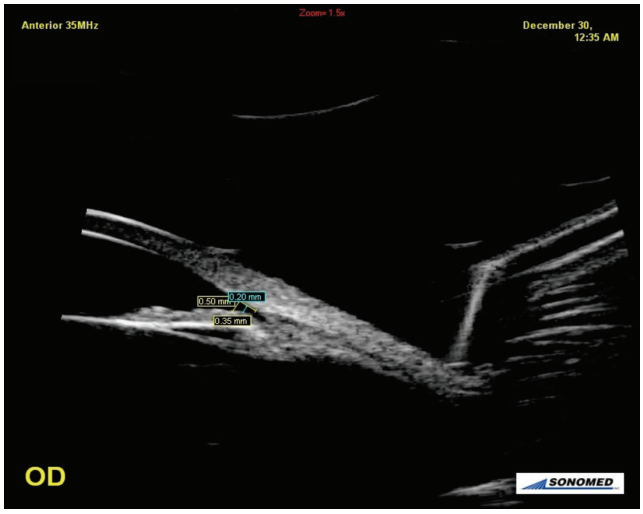


**Figure 1.** Angle opening distance (AOD) 500 and AOD250 measurements after pupil dilatation during alpha1 blocker usage (AOD500-250: AOD at points 500 µm and 250 µm away from scleral spur)
*OD: Right eye*


**Figure 2.** Angle opening distance (AOD) 500 and AOD250 measurements before dilatation after discontinuing alpha1 blocker (AOD500-250: AOD at points 500µm and 250µm away from scleral spur)
*OD: Right eye*

## Discussion

Since the first report of IFIS in 2005,[1] there has been a great deal of interest in better understanding this condition in order to ensure the safety of cataract surgery in patients taking tamsulosin. The pathophysiology of IFIS is not well understood, and current research is mostly focused on the direct effect of α1-adrenergic antagonists on the iris dilator muscle. Chronic receptor blockade could lead to iris vascular dysregulation, subsequent secondary atrophy of the iris dilator muscle, and finally, the anomalous iris behavior seen in IFIS. A recent prospective study has shown that not only α-blocker intake but benzodiazepines, quetiapine, and finasteride were all independently associated with IFIS.[11] Furthermore, Matsuo et al.[12] reported that they observed IFIS in 3 cases with a long-term history of using antipsychotic drugs such as haloperidol, risperidone, olanzapine, chlorpromazine, quetiapine, aripiprazol, without a history of using selective α1-blocker.

Chang and Campbell[1] construed that because of the long half-life of tamsulosin (48-72 hours), the iris dilator muscle became atrophic and this led to IFIS. But in other studies which investigated drug accumulation in melanocytes, while the accumulation of drugs like levofloxacin and chloroquine was shown in iris melanocytes, α1-blockers were not involved.[13] Goseki et al.[13] demonstrated that bunazosin, which is a selective α1 antagonist, accumulated in melanocytes and they proposed that this accumulation might lead to IFIS, as Chang et al.[4] stated.

The half-life of tamsulosin is 48-72 hours.[9] Therefore, it is believed that discontinuing the drug 4-7 days before the surgery may be beneficial. We wondered if there are any changes in AS parameters after discontinuing α-blocker for 10 days. Therefore, we decided to investigate this in the eyes of our cataract patients prior to surgery. We used UBM to evaluate AS parameters in this

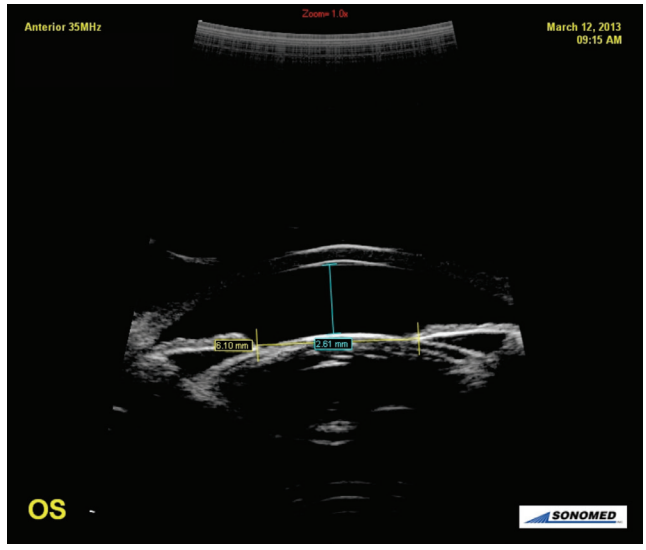


**Figure 3.** Anterior chamber depth and pupil diameter measurements after pupil dilatation during alpha1 blocker usage
*OS: Left eye*

study in order to determine whether there were any differences in eyes when the patients stopped taking α-1 antagonists.

Shtein et al.[14] used AS optical coherence tomography (AS-OCT) to assess iris morphology, including iris thickness and PD in patients using tamsulosin. Although some other studies using AS-OCT describe changes in iris thickness associated with tamsulosin use in patients with glaucoma,[8] similar to Tufan et al.,[15] they did not detect differences in iris thickness in their study. In contrast to the differences in pupil size seen by Tufan et al.[15] on AS-OCT, Shtein et al.[14] found that photopic pupil measurements on AS-OCT were not significantly different between patients who had taken tamsulosin and those who had not. Their clinical measurements of pharmacologically dilated pupil size before surgery found significantly smaller pupils in patients who had used tamsulosin than in control patients, in contrast to the findings in a study by Cooney et al.[16] They believed that their study used stronger pharmacologic pupil dilators because patients were being prepared for surgery rather than being dilated in the clinic. However, even in this study, preoperative pupil size was not directly associated with clinical manifestations of IFIS and thus provided no information that was predictive of intraoperative iris behavior.

Tufan et al.[15] found that scotopic PD was similar in patients using α-blocker and those who had never used an α-blocker (3.99±1.11 vs. 3.74±1.35, nonsignificant). They noted a significantly reduced photopic PD (2.89±0.55 vs. 3.62±0.64, p<0.001) and an increased scotopic/photopic PD (1.42±0.44 vs. 1.02±0.30, p<0.001) in the study group and concluded that evaluating changes in PD might be more useful for predicting IFIS than evaluating iris structural alterations.

Yuksel et al.[17] also investigated whether there were any differences in AS parameters between three patient groups: treated with tamsulosin, treated with doxazosin, and untreated. They used Pentacam to examine the patients in standard dim light conditions. They found that PD, ACD, and ACA were decreased in the first two groups, while central corneal thickness and corneal volume were similar in all groups.

**Table 1. The mean values of anterior segment parameters**

| | While α-blocker using | | Drugless period | |
|---|---|---|---|---|
| | **Non-dilated** | **Dilated** | **Non-dilated** | **Dilated** |
| PD | 3.34±0.64 mm | 6.50±1.47 mm | 3.45±0.72 mm | 6.61±1.29 mm |
| ACD | 2.64±0.34 mm | 2.66±0.32 mm | 2.63±0.32 mm | 2.65±0.33 mm |
| ACA | 23.16±3.67 mm | 20.41±4.22 mm | 23.52±3.79 mm | 20.63±4.40 mm |
| AOD250 | 0.25±0.06 mm | 0.24±0.06 mm | 0.27±0.08 mm | 0.26±0.07 mm |
| AOD500 | 0.38±0.07 mm | 0.36±0.08 mm | 0.40±0.08 mm | 0.39±0.08 mm |

PD: Pupil diameter, ACD: Anterior chamber depth, ACA: Anterior chamber angle, AOD: Angle opening distance

**Table 2. Anterior segment parameters Wilcoxon Signed-Rank test results (non-dilated)**

| **Parameters** | **With-without drug** | **n** | **Mean** | **Sum** | **z** | **p** |
|---|---|---|---|---|---|---|
| ACD | Negative rank | 11 | 17.59 | 193.50 | -0.805 | 0.42 |
| | Positive rank | 19 | 14.29 | 271.50 | | |
| | Equal | 1 | 0.00 | 0.00 | | |
| ACA | Negative rank | 9 | 14.22 | 128.00 | -1.267 | 0.21 |
| | Positive rank | 17 | 13.12 | 223.00 | | |
| | Equal | 5 | 0.00 | 0.00 | | |
| AOD500 | Negative rank | 12 | 11.58 | 139.00 | -1.706 | 0.09 |
| | Positive rank | 17 | 17.41 | 296.00 | | |
| | Equal | 2 | 0.00 | 0.00 | | |
| AOD250 | Negative rank | 11 | 15.41 | 169.50 | -1.043 | 0.30 |
| | Positive rank | 18 | 14.75 | 265.50 | | |
| | Equal | 2 | 0.00 | 0.00 | | |
| PD | Negative rank | 7 | 22.43 | 157.00 | -1.555 | 0.12 |
| | Positive rank | 23 | 13.39 | 308.00 | | |
| | Equal | 1 | 0.00 | 0.00 | | |

p<0.05, *Based on negative rank

PD: Pupil diameter, ACD: Anterior chamber depth, ACA: Anterior chamber angle, AOD: Angle opening distance

| Table 3. Anterior segment parameters Wilcoxon Signed-Rank test results (dilated) | | | | | | |
|---|---|---|---|---|---|---|
| **Parameters** | **With-without drug** | **n** | **Mean** | **Sum** | **z** | **p** |
| ACD | Negative rank | 14 | 11.46 | 160.50 | -0.301 | 0.76 |
| | Positive rank | 10 | 13.95 | 139.50 | | |
| | Equal | 7 | 0.00 | 0.00 | | |
| ACA | Negative rank | 9 | 10.00 | 90.00 | -0.572 | 0.57 |
| | Positive rank | 11 | 10.91 | 120.00 | | |
| | Equal | 9 | 0.00 | 0.00 | | |
| AOD500 | Negative rank | 4 | 7.63 | 30.50 | -3.699 | 0.00 |
| | Positive rank | 22 | 14.57 | 320.50 | | |
| | Equal | 3 | 0.00 | 0.00 | | |
| AOD250 | Negative rank | 7 | 8.36 | 58.50 | -2.984 | 0.00 |
| | Positive rank | 19 | 15.39 | 292.50 | | |
| | Equal | 3 | 0.00 | 0.00 | | |
| PD | Negative rank | 10 | 16.30 | 163.00 | -1.179 | 0.24 |
| | Positive rank | 19 | 14.32 | 272.00 | | |
| | Equal | 1 | 0.00 | 0.00 | | |

p<0.05, *Based on negative rank
PD: Pupil diameter, ACD: Anterior chamber depth, ACA: Anterior chamber angle, AOD: Angle opening distance

In our study we did not use AS-OCT or Pentacam, but ultrasound biomicroscopy, which is more subjective, so we ensured that all examinations and measurements were performed by the same physician under the same room light conditions. Unexpectedly, we did not find any significant differences after the patients stopped taking α1-blockers for 10 days. Including pupil diameters, none of the parameters except AOD250 and AOD500 changed after discontinuing the drug. However, the difference appeared only in dilated eyes. Perhaps AOD measurements increased after discontinuing in dilated eyes because of the effect of α1 antagonists on the pupil dilatation mechanism. But in contrast, there were no differences in pupil diameters. Our patients were dilated just before the cataract extraction, so strong pharmacological dilatation might cause that. There were, of course, significant increases in pupil diameters in some individuals after interruption of α1-blocker usage, but this variation in pupil diameters may be related to the duration of drug intake.

### Study Limitations

We could not find any other studies that investigated differences after discontinuing α-blockers. Therefore, more prospective studies using more objective AS imaging techniques are needed to compare our results. We used ultrasound biomicroscopy, which is subjective enough to affect the final measurements, so we took care that all measurements were done by the same physician under the same room light conditions. Another limitation was the insufficient number of patients included in the study.

## Conclusion

After stopping α1-blockers intake, there were no significant differences in AS parameters measured before pupil dilatation. Furthermore, of the measurements taken after pupil dilatation, only angle opening distances were increased after discontinuing the drugs.

### Acknowledgements

Thanks to Osman Kızılay and Yıldız Acar Ebcim for their contributions in data collecting.

### Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Review Committee of the İstanbul Training and Research Hospital (protocol number: 473). All research protocols adhered to the tenets of the Declaration of Helsinki.

Informed Consent: All volunteers went through a complete informed consent process.

Peer-review: Externally peer-reviewed.

### Author Contributions

Concept: Yeliz Acar, Kadir Eltutar, Design: Yeliz Acar, Kadir Eltutar, Data Collection and Processing: Yeliz Acar, Sibel Zırtıloğlu, Analysis and Interpretation: Yeliz Acar, Literature Search: Yeliz Acar, Writing: Yeliz Acar.

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

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Original Article

# Intraocular Pressure and Retinal Nerve Fibre Layer Thickness Changes After Carotid Artery Stenting

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## Abstract

**Objectives:** The aim of this study was to evaluate intraocular pressure (IOP) and retinal nerve fiber layer (RNFL) changes in patients with carotid artery stenosis (CAS) after carotid artery stenting.

**Materials and Methods:** This study was conducted as a cross-sectional, non-randomised clinical case series. Fifteen male patients (mean age: 63.6±9.1) with CAS and more than 70% carotid artery narrowing were included. All of the patients were followed in the department of neurology and were operated in the interventional radiology division. Eighteen healthy male subjects (mean age: 63.7±5.3) were included in the control group. All of the healthy subjects had a detailed ophthalmological examination and subjects with any chronic eye disease were excluded from the study. All of the participants had a detailed ophthalmological examination including tonometry using Goldmann applanation tonometry and RNFL analysis using optical coherence tomography (RTVue-100 5.1).

**Results:** There were no ocular ischemic symptoms in any of the participants. The mean IOP value was 15.1±2.1 mmHg in the control group and 16.6±2.4 mmHg before stent implantation, 16.4±2.2 mmHg at 1 week after implantation, 16.6±2.5 mmHg at 1 month after implantation, and 16.7±2.9 mmHg at 3 months after implantation in the CAS group. Mean RNFL thickness was 105±6 µm in the control group; in the CAS group, mean RNFL thickness values were 98±27 µm before stent implantation and 103±11 µm, 101±10 µm, and 101±11 µm at 1 week, 1 month, and 3 months after stenting. There were no significant differences between the CAS group and control group regarding IOP and RNFL thickness values ($p>0.05$). IOP and RNFL thickness also did not show any statistically significant changes from preoperative measurements in 3 months postoperative follow-up in the CAS group ($p>0.05$).

**Conclusion:** IOP and RNFL thickness remained unchanged after carotid stent implantation in carotid artery stenosis patients with no signs of ocular ischemic syndrome.

**Keywords:** Carotid artery stenosis, stenting, color Doppler ultrasound, intraocular pressure, retinal nerve fiber layer thickness

## Introduction

Carotid artery stenosis (CAS) is an important obstructive artery disease that can cause cranial ischemic infarction and stroke, and is the leading cause of ischemic stroke.[1] The main goal in the treatment of CAS is to eliminate internal carotid artery (ICA) stenosis and the risk of embolism after carotid endarterectomy and carotid artery stenting (CS), as well as to increase retinal circulation.[2] If ophthalmologic symptoms are assessed at an early stage, they can be managed prophylactically before reaching an irreversible stage and can be prevented at the onset, before the development of permanent blindness. At the same time, ophthalmologic findings can sometimes lead us to suspect CAS and facilitate the early diagnosis of stenosis before the patient develops symptoms like stroke.[3] Patients who develop ocular ischemia may exhibit an increase in intraocular pressure (IOP) due to neovascularization; however, aqueous humor production decreases in some patients due to ciliary body ischemia, resulting in no IOP increase.[4] Based on these data, in this study we aimed to compare changes in IOP and retinal nerve fiber layer (RNFL) thickness in patients who underwent CS.

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## Materials and Methods

The study included 15 male patients (mean age, 63.6±9.1 years) who were examined in the neurology department and diagnosed with CAS based on a finding of >70% narrowing of the carotid artery on color Doppler ultrasound (CDUS) and who underwent CS in the interventional radiology unit. Eighteen male participants (mean age, 63.7±5.3 years) were included as the control group. The study was conducted in accordance with the principles of the Declaration of Helsinki, informed consent forms were obtained from all participants, and approval was granted by the Ethics Committee for local clinical trials (protocol number: 09.2015.090 70737436-050.06.04).

The CS patients were asked specifically about hypertension, diabetes, and their alcohol and smoking history. Patients were ophthalmologically evaluated preoperatively and at postoperative 1 week, 1 month, and 3 months. All participants underwent a detailed eye examination. Best visual acuity was assessed using the Snellen chart. Snellen visual acuity values were converted to LogMAR values for statistical comparison. The anterior segment was assessed by slit-lamp examination. For IOP measurement, a mixture of 0.5% proparacaine and fluorescein was instilled into the eye and IOP was measured by Goldmann applanation tonometry. The average of three measurements was recorded. Optic nerve head (ONH) imaging was performed on all participants with the RTVue RT-100 spectral domain optical coherence tomography (Optovue Inc., Fremont, CA, USA) device in the ONH and 3D modes for glaucoma screening. The ONH program and three-dimensional disc program of the RT-100 were used for RNFL analysis. The ONH scanning protocol consisted of 12 radial images with a length of 3.7 mm, each making 455 scans transecting the center of the optic disc, and 13 concentric rings, each making between 425-965 scans and with diameters ranging from 1.3 to 4.9 mm. An RNFL thickness map was created from the RNFL thicknesses measured from the area within a 3.45 mm diameter of the disc center. The average and superior and inferior hemisphere RNFL thicknesses of the patients were evaluated (Figure 1).

The central corneal thickness (CCT) and axial lengths (AL) of all patients were measured by the same ophthalmologist using Haag-Streit International/LS 900 Lenstar. The lenses were evaluated for cataract after pupil dilation with tropicamide and phenylephrine eye drops. A detailed fundus examination including the entire retinal periphery was then conducted using a Volk SuperField NC lens. The eyes were evaluated for the presence of venous stasis retinopathy, iris neovascularization, glaucoma, optic nerve injury, vascular embolism, occlusion, and ocular ischemic syndrome (OIS).

Patients with visual acuity less than 6/10, spheric refraction exceeding -4 or +3 diopters (D), cylindrical refraction ≥±3 D, uveitis, glaucoma and retinal disease, optic disc damage, corneal and vitreal opacities, pupillary anomalies, history of ocular surgery other than phacoemulsification, cataract with NC<4, C<5, p<3 according to the LOCS II classification, systemic disease that may affect the measurements, or current drug treatment were not included in the study.

### Carotid Stenting Procedure

Before the procedure, patients were given detailed information about the treatment process and possible complications, and written consent forms were obtained. Patients whose procedures were planned were started on double antiaggregant therapy (75 mg clopidogrel + 100 mg acetylsalicylic acid twice daily) 3 days before the procedure. Patients who did not receive double antiaggregant therapy in advance and those undergoing emergency intervention were taken into surgery after being administered a loading dose of 450 mg clopidogrel. Hemogram, creatinine, and coagulation tests were performed as part of routine preparation. For these preoperative preparations, the patients were hospitalized the day before the procedure and monitored.

All procedures were conducted in an angiography unit equipped with a Siemens Artis Zee Bi-plain Angiography device, and all patients were monitored during CS. Electrocardiogram, oxygen saturation, and non-invasive arterial blood pressure were monitored during the procedure. In all patients, the right femoral artery was preferred as the entry site, and local anesthesia was applied to the area. At the beginning of the procedure, all patients were administered 5000 U of heparin intravenously.

After entering the femoral artery using the Seldinger technique, in 13 patients a 7F vascular sheath was inserted into the femoral artery and a 7F guiding catheter was advanced and positioned in the main carotid artery to be treated, while in 2 patients a 6F long vascular sheath was positioned directly in the main carotid artery. The guiding catheter and vascular sheath system was washed with pressurized isotonic serum throughout the procedure. Firstly, imaging of the neck and intracranial segments and intracranial branches of the carotid artery was performed to evaluate the hemodynamic changes that should occur in the intracranial vascular tree before and after the procedure and the possible presence of intracranial stenoses. Carotid angiography was then performed by administering contrast material via the catheter or vascular sheath placed in the main carotid artery to be stented, and a road map was obtained. Prior to the CS procedure, the guide wire of the protection filter was passed through the targeted stenosis and the filter was opened in a straight segment. Protection filters were routinely used in all patients; the Boston Scientific Filter Wire EZ Embolic Protection System was used in 13 patients and the Spider FX™ Embolic Protection Device was used in 2 patients. The monorail stent system was expanded above the guide wire carrying the filter, at the level of the lesion so as to encompass the area of stenosis determined using the road map. The Cristallo Ideale™ Carotid Stent System Self-Expanding stent was used in 11 patients and the Protege® RX Carotid Stent System Self-Expanding Nitinol stent was used in 4 patients. The stenosis was positioned high in 4 patients, so predilatation was performed with a 3x20 mm balloon prior to stenting in order to allow the stent to safely pass through at the level of the lesion.

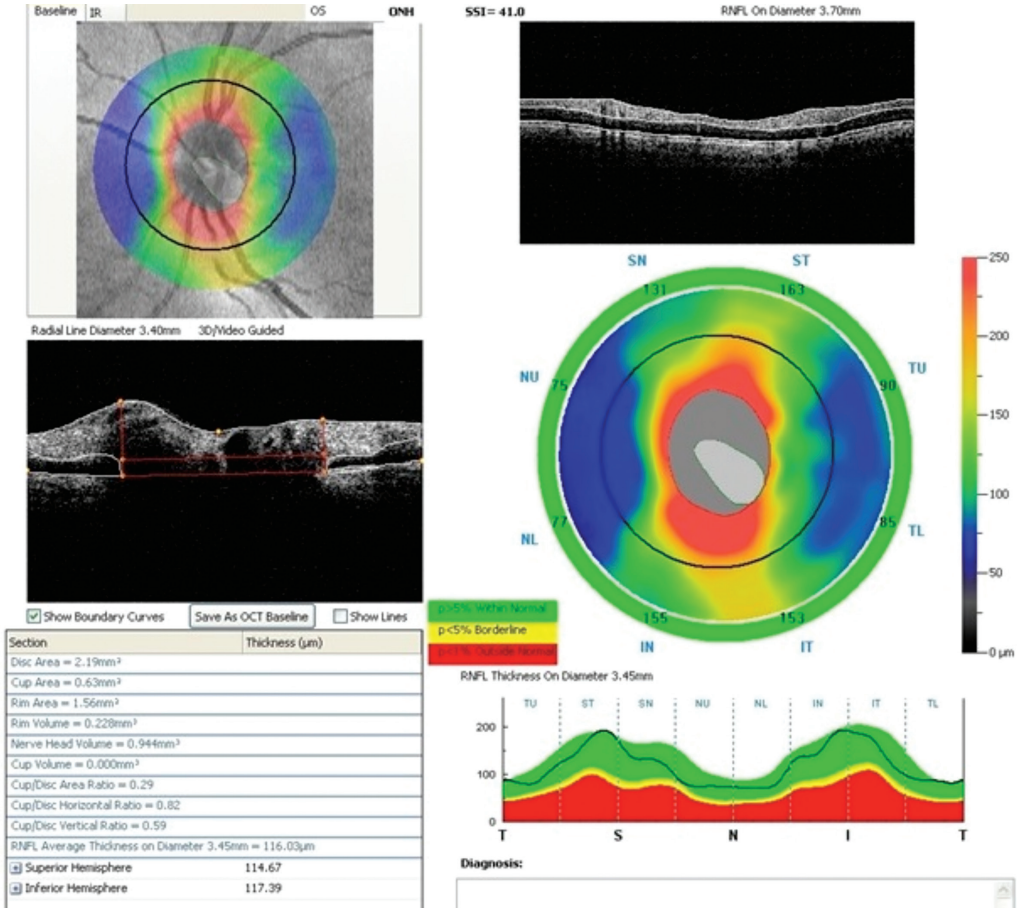


**Figure 1.** Optical coherence tomography output evaluating the average and superior and inferior hemisphere retinal nerve fiber layer thicknesses

Postdilatation was performed on all patients after expanding the stent to allow it to reach its optimal span. Postdilatation was performed using a 6x20 mm balloon in 6 patients and a 5x20 mm balloon in 9 patients. After the procedure was completed, contrast material was administered to reevaluate the neck and intracranial arteries.

In the postoperative period, double antiaggregant therapy (75 mg clopidogrel + 100 mg acetylsalicylic acid daily) was administered to the patients for 3 months, to be followed by lifelong 100 mg acetylsalicylic acid prophylaxis.

### Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows version 21.0 was used in statistical analysis of the study data. Mean ± standard deviation and percentage values were used for the descriptive statistics. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. Parametric tests were used to analyze numerical data with regular distribution, while nonparametric tests were used to analyze numerical data with irregular distribution.

Student's t-test and the Mann-Whitney U test were used for intergroup comparisons and the paired intragroup comparisons of means. The chi-square test was used in the analysis of proportional data. Correlation analyses were done with the Pearson test. The statistical significance level was accepted as $p<0.05$ in analyses in which there were no variables from similar categories. When variables from the similar category were analyzed together, the significance level was decided according to the Bonferroni correction based on $p<0.05$.

## Results

There were no significant differences between patients diagnosed with CAS and the control group in terms of mean age, spherical equivalents, visual acuity, CCT, or AL. A comparison of the patient and control groups' general findings is provided in Table 1 and the other clinical features of the patients are summarized in Table 2.

None of the patients had ocular pain, retinal hemorrhage, or glaucoma. No complications were observed in any of the patients in follow-up examinations after stenting.

No statistically significant differences were observed when the preoperative, postoperative 1 week, postoperative 1 month, and postoperative 3 month IOP values of patients in the study group were compared with the control group ($p<0.05$) (Table 3).

There were also no statistically significant differences when the preoperative (n=15), postoperative 1 week (n=14), postoperative 1 month (n=8), and postoperative 3 month (n=10) IOPs of the patients were compared (p=0.963) (Table 4).

No statistically significant differences were observed when the preoperative, postoperative 1 week, postoperative 1 month, and postoperative 3 month RNFL values of patients diagnosed with CAS were compared with the control group (p<0.05) (Table 5).

## Discussion

As the ophthalmic artery is a branch of the ICA, ocular involvement can occur in any case of ICA stenosis. Ocular involvement can range from transient unilateral acute blindness caused by emboli that break off from the atherosclerotic plaque in the stenosis, to chronic OIS due to persistent hypoperfusion or complete blindness due to occlusion of the central retinal artery or ophthalmic artery. OIS is characterized by ocular pain, decreased vision, patchy hemorrhages in the retina, and enlargement in the veins. Due to ocular hypoperfusion, any stenosis of the ICA can lead to ischemic retinopathy, neovascular glaucoma, ischemic optic neuropathy, retinal artery occlusions, cataract, and ocular hypotony. OIS and other findings also serve as indicators of cerebral ischemic disorders.

Microaneurysms, narrowing of the retinal arterioles, and venous dilation are observed on fundus examination due to decreased flow in the ophthalmic artery. When the ocular perfusion pressure lowers and approaches intraocular pressure, ischemia develops in both the posterior and anterior segments of the eye. Venous-stasis retinopathy limited to the posterior progresses to an OIS that also includes the anterior if the stenosis continues. Microproliferations that develop in the retinal vasculature and the iris form fibroadhesions. As a result, the anterior iridocorneal angle is occluded and intraocular pressure increases. If neovascularization is not treated, it can progress to neovascular glaucoma. After treating the carotid stenosis, these patients show improvements in their visual symptoms. In some patients, aqueous humor production decreases due to ciliary body ischemia, and there may be no increase in IOP.[4] Rubeosis iridis is sometimes the only symptom associated with carotid stenosis.[5] OIS is more common in carotid stenosis patients with weak collateral connections. The decrease in retrobulbar blood flow in patients with OIS can be demonstrated by CDUS. Retrograde flow, which is a predictor of high-grade carotid stenosis, can be seen in some patients. This retrograde flow leads to further exacerbation of ocular ischemia by further reducing retrobulbar blood flow due to the vascular steal phenomenon.[6,7,8] Decreased vision and pain due to increased IOP may occur in ocular ischemia. In some cases, these symptoms may be the first clinical signs of CAS.

Hemispheric neurological symptoms, amaurosis fugax, and Hollenhorst plaques detected in ophthalmologic examination are findings that require imaging in the diagnosis of CAS. Retinal artery occlusion and ischemic optic neuropathy may also be related to carotid stenosis, as mentioned above. However, the predictive value of ocular findings in diagnosing stenosis is a subject of debate. Over 3 years, McCullough et al.[3] evaluated 145 patients exhibiting these symptoms for carotid stenosis and found that amaurosis fugax had a 30% predictive value of clinical suspicion of carotid stenosis. Hollenhorst plaques were

**Table 1. A comparison of the general findings of the patient and control groups**

| | Study group (n=15) | Control group (n=18) | p value |
|---|---|---|---|
| Age (years) | 63.6±9.1 | 63.7±5.3 | 0.913 |
| Spheric equivalent | 0.30±1.6 | 0.33±0.7 | 0.986 |
| Mean VA (LogMAR) | 0.033±0.72 | 0 | 0.343 |
| Mean CCT (µm) | 534±25 | 546±62 | 0.376 |
| Mean AL (mm) | 22.89±0.86 | 23.41±0.95 | 0.065 |

VA: Visual acuity, CCT: Central corneal thickness, AL: Axial length

**Table 2. Clinical characteristics of the patient group**

| CAS severity | 80% (70-90) | Stroke | 9 (60%) |
|---|---|---|---|
| HT | 11 (73%) | Amaurosis fugax | 2 (13%) |
| DM | 5 (33%) | Cataract | 2 (13%) |
| Smoking | 13 (86%) | Venous filling | 12 (80%) |
| Alcohol use | 2 (13%) | Stage 1 HRP | 5 (33%) |
| TIA | 5 (33%) | Stage 2 HRP | 4 (26%) |

CAS: Carotid artery stenosis, HT: Hypertension, DM: Diabetes mellitus, TIA: Transient ischemic attack, HRP: Hypertensive retinopathy

**Table 3. Comparison of intraocular pressure values between the control and study groups**

| | Control group (n=18) | Study group (n=15) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | Control - Preoperative p value | Postoperative 1 week | Control - Postoperative 1 week p value | Postoperative 1 month | Control - Postoperative 1 month p value | Postoperative 3 months | Control - Postoperative 3 months p value |
| IOP (mmHg) | 15.16±2.05 | 16.6±2.4 | 0.084 | 16.4±2.2 | 0.104 | 16.6±2.5 | 0.093 | 16.7±2.9 | 0.193 |

IOP: Intraocular pressure

| Table 4. Comparison of pre- and postoperative intraocular pressures in the study group | | | | | |
|---|---|---|---|---|---|
| **IOP (mmHg)** | **Preoperative** | **Postoperative 1 week** | **Postoperative 1 month** | **Postoperative 3 months** | **p value** |
| | 16.6±2.4 | 16.4±2.2 | 16.6±2.5 | 16.7±2.9 | 0.963 |
| IOP: Intraocular pressure | | | | | |

| Table 5. Comparison of optical coherence tomography parameters between the control and study groups | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Control group (n=18)** | **Study group (n=15)** | | | | | | | |
| | | **Preoperative** | **Control - Preoperative p value** | **Postoperative 1 week** | **Control - Postoperative 1 week p value** | **Postoperative 1 month** | **Control - Postoperative 1 month p value** | **Postoperative 3 months** | **Control - Postoperative 3 months p value** |
| RNFL (µm) | 105±6 | 98±27 | 0.386 | 103±11 | 0.357 | 101±10 | 0.338 | 101±11 | 0.134 |
| RNFL: Retinal nerve fiber layer | | | | | | | | | |

detected in 22 eyes, but only 4 of these patients had more than 60% stenosis in the carotid artery. In the same study, the authors reported that the presence of Hollenhorst plaques was found to be positively correlated with CAS at a rate of 18.2%, that the predictive values of other ocular symptoms such as ischemic optic neuropathy, retinal artery and vein occlusion, and optic atrophy were weak, and that stenosis was observed in one out of 5 patients who underwent CDUS after venous stasis retinopathy was detected, and its predictive value was 20%. Ultimately, they stated that Hollenhorst plaques and venous stasis retinopathy were of moderate value in the prediction of CAS.[3] None of the patients in our study exhibited rubeosis iridis, neovascular glaucoma, or retinal artery or vein occlusion.

Studies show that the balance between ocular blood flow and IOP is important for ONH circulation. It has been demonstrated that as IOP increases, there is a decrease in the end diastolic flow rate and an increase in the resistance index of the arteries that supply the ocular structures, and end diastolic flow rate has been shown to negatively correlate with glaucoma progression.[9,10,11] We also evaluated patients' pre- and posttreatment IOP values in regards to possible CAS-related changes in ocular blood flow and the risk of glaucomatous optic neuropathy due to circulatory impairment, and observed no significant difference between the patient and control groups. In addition, no significant differences emerged when the pretreatment and posttreatment 1-week, 1-month, and 3-month IOP values of patients with CAS were compared with one another. This can be explained by the lack of patients with OIS in our patient group and the absence of ciliary body ischemia caused by stenosis, in which case there is no reduction in aqueous humor production.[12]

Sayin et al.[13] compared the RNFL values of 25 patients diagnosed with CAS and 25 age-matched healthy control subjects and found no significant differences. In contrast, Pavan[14] reported RNFL thinning in 8 CAS patients with over 70% stenosis. No difference was observed between our control group and patient group in terms of RNFL; however, there was also no change in the IOP and RNFL values of the patient group after stenting.

Ocular symptoms may be the first sign of serious carotid atherosclerotic disease. In this case, ophthalmologic examination is important for the prognosis of these patients. Patients at high risk for ischemic stroke can be referred for early intervention. In case of any retinal findings of OIS on ophthalmologic examination or a history of temporary monocular vision loss, the patient can be referred to the neurology clinic upon suspicion of CAS, thereby preventing ischemic neurological damage.

## Conclusion

In our study, there were no changes in baseline RNFL thickness and IOP values after stenting in patients with CAS who did not develop OIS. This finding must be supported by future studies including larger patient groups.

### Ethics

Ethics Committee Approval: Marmara University Ethical Commitee (protocol number: 09.2015.090 70737436-050.06.04).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

### Author Contributions

Concept: Esra Biberoğlu, Muhsin Eraslan, Feyyaz Baltacıoğlu, İpek Midi, Design: Esra Biberoğlu, Muhsin Eraslan, Feyyaz Baltacıoğlu, İpek Midi, Data Collection or Processing: Esra Biberoğlu, Muhsin Eraslan, Feyyaz Baltacıoğlu, İpek Midi, Analysis or Interpretation: Esra Biberoğlu, Muhsin Eraslan, Feyyaz Baltacıoğlu, İpek Midi, Literature Search: Esra Biberoğlu, Muhsin Eraslan, Writing: Esra Biberoğlu, Muhsin Eraslan, Feyyaz Baltacıoğlu, İpek Midi.

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Original Article

# Selective Laser Trabeculoplasty vs. Fixed Combinations with Timolol in Practice: A Replacement Study in Primary Open Angle Glaucoma

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## Abstract

**Objectives:** To evaluate the potential of selective laser trabeculoplasty (SLT) in two arms (360° vs. 180°) as a replacement for fixed combinations (FCs) with timolol in primary open angle glaucoma over 6 months.

**Materials and Methods:** Of 40 patients in a prospective, comparative, interventional case series, 18 eyes and 22 eyes were randomized to SLT 180º and SLT 360º groups, respectively, along with 40 fellow-control eyes. FC with timolol was discontinued on the day of treatment for the eye to be operated on, while ongoing therapy was not interrupted for the contralateral eye. Eyes were examined for intraocular pressure (IOP) elevation 1 hour and 1 day after SLT. The follow-up visits were then scheduled for 1 week, 1 month, 3 months, and 6 months after, during the which the IOP of both eyes and any possible complications were evaluated.

**Results:** There were no statistically significant differences in mean IOPs through 6 months among the groups with exception of postlaser 1 hour and postlaser 1 day ($p<0.001$ and $p=0.010$, respectively). Multiple comparison analysis showed significantly higher IOP in both SLT 180º and SLT 360º subgroups compared to their controls at postlaser 1 hour ($p=0.007$, $p<0.001$) but significantly lower IOP only in SLT 360º subgroup compared to the controls at postlaser day 1 ($p=0.013$).

**Conclusion:** SLT offers promising potential as a substitute equivalent to efficacy of FCs with timolol. However, SLT 360° may not achieve additional IOP reduction.

**Keywords:** Fixed combination antiglaucoma medications, intraocular pressure reduction rate, primary open-angle glaucoma, selective laser trabeculoplasty

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## Introduction

Glaucoma is the second leading cause of blindness worldwide and 74% of the patients have primary open angle glaucoma (POAG).[1] The current treatment paradigm aims to decrease intraocular pressure (IOP), initially with pharmacotherapy, performing laser trabeculoplasty as the second step, and resorting to incisional surgery as a final option.[2] However, medical treatment has some inherent drawbacks such as nonadherence, tachyphylaxis associated with chronic administration, and the financial burden imposed by high pharmaceutical costs.[3,4,5,6] As a consequence, one eye goes blind in 27% of patients receiving medical treatment for 20 years.[7] In order to maximize patient adherence and quality of life, several fixed combinations (FCs) of commonly used IOP-lowering medications have been developed recently, which include the topical beta-blocker 0.5% timolol combined with a prostaglandin analogue, alpha-adrenoceptor agonist, or topical carbonic anhydrase inhibitor.[8,9] A relatively recent meta-analysis evaluated 41 eligible randomized clinical trials on 53 arms investigating the efficacy of 6 FCs after medicine-free washout periods and reported the relative reductions for mean diurnal IOP as 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. However, from the statistical standpoint, the meta-analysis concluded that only latanoprost/timolol and travoprost/timolol are likely to achieve better IOP reduction among these combinations, and the comparisons mostly remain within the non-inferiority margin.[10]

Selective laser trabeculoplasty (SLT), described by Latina and De Leon[11], is a relatively novel therapeutic approach reported to be equally efficacious as both a first-line medication and argon laser trabeculoplasty (ALT).[12] SLT requires less than 1% of the energy used in ALT and thereby causes minimal thermal burn to the trabecular meshwork.[13,14] Since the IOP-lowering mechanism of SLT is associated with biochemical and cellular pathways rather than mechanical or thermal effects[15,16], it is considered to be possible to repeat the procedure over time, which enhances the potential cost-saving feature as opposed to medication.[17] With respect to therapeutic efficiency, there are several studies reporting relative IOP reductions from baseline ranging between 26.4% and 35.1%,[2,18,19,20,21,22,23,24] which are consistent with the IOP reduction rates of the 6 FCs mentioned above. However, to our knowledge only one study evaluating SLT as a replacement for medical therapy reported reduction in number of antiglaucoma medications by a mean of 2.0 at 6 months [95% confidence interval (CI) 1.8-2.3] while keeping the IOP within the target range.[25] As a result, SLT theoretically seems to reduce IOP comparable to FCs, which it may substitute for in practice.

Based on the assumption that all FCs reduce IOP within a non-inferiority margin, in this study we aimed to evaluate the potential of SLT as a replacement for FCs by comparing reduction in IOP over 6 months for POAG. We further compared the efficacy of SLT 360° and SLT 180° applications.

## Materials and Methods

This study was designed as a prospective, comparative, interventional case series and was conducted between December 2012 and June 2013. After obtaining the institutional ethics committee approval [Health Sciences University, Bakırköy Dr. Sadi Konuk Training and Research Hospital (2012-116)], patients' charts in the glaucoma unit of our tertiary referral hospital were reviewed and the following criteria were sought for recruitment:

a) Presence of bilateral POAG,

b) Both eyes receiving the same antiglaucoma medications and dosing which currently included an FC of 0.5% timolol maleate,

c) IOP of both eyes ≤23 mmHg (average of the last 3 measurements) and equal (difference between IOP of both eyes ≤2 mmHg in the last 3 measurements).

On chart reviews, glaucoma was confirmed on the basis of glaucomatous disc damage (vertical cupping, diffuse and focal neural rim thinning) with at least 2 reliable visual field (VF) tests (Humphrey Field Analyzer, Swedish Interactive Threshold Algorithm 24.2 test, Carl Zeiss Meditec, Dublin, CA, USA) which denote fixation losses <20% along with false positives and negatives <30%. Scotomas of 3 contiguous points at the level of 5% on the pattern deviation plot were sought on successive VFs. Alternatively, spectral domain-optical coherence tomography were referred to for at least 1 sector of peripapillary retinal nerve fiber layer (pRNFL) thinning at the level of 1% or 2 contiguous sectors of pRNFL thinning at the level of 5% on the temporal-superior-nasal-inferior-temporal plot conforming to disc changes at least on 2 occasions when reliable VFs were absent (RNFL 3.45 protocol, RTVue-100 OCT, Optovue Inc, Fremont, CA, USA). Thus, 44 patients meeting the abovementioned criteria were then interviewed and informed about the study and asked for verbal and written consent on a voluntary basis. Four of these patients were later excluded due to cataract surgery (1 patient), nonadherence to antiglaucoma medication use (2 patients) and loss to follow-up (1 patient). The study was conducted in accordance with the Declaration of Helsinki.

One eye of the patients was randomly selected for laser therapy and included in the intervention group while ongoing medical treatment was continued on the contralateral eye, which was included in the control group. The eyes in the intervention group were further randomized into SLT 180° or SLT 360° laser subgroups (by U.O.). Prior to laser therapy, both eyes underwent comprehensive ophthalmic examination in which medical and ophthalmic history, refraction, best corrected visual acuity, slit lamp biomicroscopy, IOP (Goldmann applanation tonometry) and fundoscopy were included in order to confirm the records on the charts. Gonioscopy was carried out using a 3 mirror lens (Design-OG3M-10, Ocular, Bellevue, WA, USA) to confirm angles of the eyes were open in 3-4 quadrants (Shaffer grades of 3-4) (by K.T.).

Patients with a history of previous intraocular operations or laser procedures, pseudoexfoliation or pigmentary glaucoma,

advanced glaucoma (vertical cup/disc ratio >0.8) were excluded. Eyes with signs of corneal and/or lens abnormalities that might preclude precise tonometry or visualization of the cup and optic disc were also excluded.

Q-switched, frequency-doubled Nd:YAG laser of 532 nm wavelength (Selecta 2, Lumenis, Coherent, Inc., Palo Alto, CA, USA) was used for treatment. The pulse duration and spot size were 3 ns and 400 µm, respectively. Following topical anesthesia with 0.5% proparacaine hydrochloride, pigmented trabecular meshwork was targeted and non-overlapping laser spots were evenly placed on either the inferior 180º or the entire 360º of the trabecular meshwork with a specifically designed SLT gonio lens (Latina, Ocular Instruments, Bellevue, WA, USA) (by U.Y.). By 0.1 mJ increments, the initial energy/pulse of 0.7 mJ was adjusted to the point that would induce a cavitation bubble and then kept constant throughout the procedure. Half an hour before and just after the SLT application, apraclonidine 1% was administered to prevent IOP spikes. No additional topical steroid or nonsteroid anti-inflammatory medication was prescribed for the postlaser period. Along with the generic name of the timolol maleate 0.5% combination used before the laser treatment (180° or 360°), the total number of laser spots and total energy exposure were also recorded.

Timolol maleate 0.5% combination therapy was discontinued on the day of treatment for the eye to be operated on, whereas ongoing therapy was not interrupted in the contralateral eye. Patients were examined for IOP elevation and anterior chamber reaction 1 hour and 1 day after intervention. Follow-up visits were scheduled for 1 week, 1 month, 3 months, and 6 months after the operation, during which the IOP of both eyes were evaluated with Goldmann applanation tonometry and any possible complications were noted and treated appropriately. IOP measurements were taken between 10:00 AM and 3:00 PM.

Timolol maleate 0.5% preparations were administered as one drop, once daily in the evening (8:00 PM) for FCs containing bimatoprost 0.03%, travoprost 0.004%, and latanoprost 0.005% and as one drop, twice daily (8:00 AM and 8:00 PM) for dorzolamide hydrochloride 2%, brinzolamide 1%, and brimonidine tartrate 0.2% combinations.

All data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Demographic features including age, gender, operated eye (right or left), number of antiglaucoma medications used before laser therapy (FCs are considered as 2 drugs), distribution of FCs of timolol maleate 0.5%, number of laser spots, and total energy applied were described with mean, standard deviation (mean ± standard deviation) and/or frequency, percentage values, and 95% confidence interval. Mean values of repeated IOP measurements were displayed on a plot as a function of time. Tukey's test along with analysis of variance (ANOVA) was used to correct for multiple comparisons of age, repeated IOP measurements and prelaser number of antiglaucoma medications among groups. Number of laser spots and total energy exposure between SLT groups were compared with Student's t test. Chi-square test was used for multiple comparisons of categorical variables such as gender and operated eye. Appropriate p values of significance are displayed on the relevant graphs or the tables.

## Results

A total of 40 patients were included in the study. There were 18 eyes in the SLT 180° group and 22 eyes in the SLT 360° group, along with 40 fellow-control eyes retained throughout the study. All subjects were Caucasian.

Table 1 shows the demographics and baseline characteristics of the patients. There were no statistically significant differences between the SLT 180° and SLT 360° treatment subgroups regarding age, gender, side, prelaser mean IOP, or prelaser number of antiglaucoma medications (p=0.986, 0.960, 0.817, 0.667, 0.696, respectively). However, number of laser spots along with total energy exposure were significantly different between the subgroups, as would be expected (p<0.001).

Table 2 shows the distribution of FCs of timolol maleate 0.5% used before the intervention between the SLT 180° and SLT 360° subgroups.

The mean IOPs in the SLT 180°, SLT 360° and control groups before laser and 1 hour, 1 day, 1 week, 1 month, 3 months, and 6 months after are shown in Table 3. There were no statistically significant differences among the groups with exception of postlaser 1 hour and postlaser 1 day (p<0.001 and p=0.010, respectively). Multiple comparison analysis with Tukey post hoc test showed significantly higher IOP in both the SLT 180° and SLT 360° subgroups compared to their controls at postlaser 1 hour (p=0.007, p<0.001) but significantly lower IOP only in SLT 360° subgroup compared to the controls at postlaser day 1 (p=0.013). Figure 1 shows the changes in mean IOP over time for the first 6 months. Accordingly, mean IOPs after SLT 180° and SLT 360° spiked remarkably at postlaser 1 hour and traced a slight trough at postlaser 1 day. However, no eyes had an IOP ≥30 mmHg or complications other than mild anterior chamber cells and flare (postlaser 1 hour) at any time. Moreover, there was no significant difference between repeated mean IOPs of control group (intraclass) through 6 months (p=0.191, ANOVA).

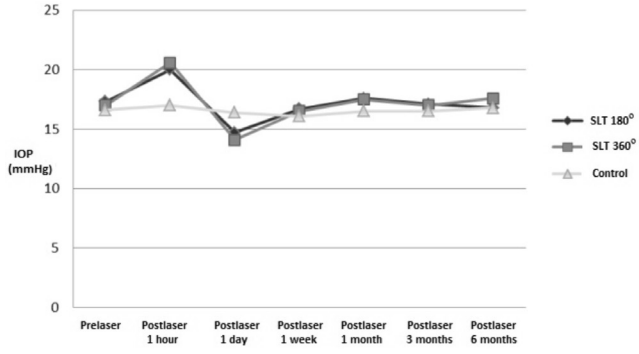


**Figure 1.** Course of mean intraocular pressures through six months
SLT: Selective laser trabeculoplasty, IOP: Intraocular pressure

**Table 1. Demographic data, pretreatment values, and treatment features of the study participants**

| | SLT 180° (n=18) | SLT 360° (n=22) | Control (n=40) | p |
|---|---|---|---|---|
| Age (years)<br>Mean ± SD (95% CI) | 54.2±12.4 (48.0 - 60.4) | 53.6±7.6 (50.2-57.0) | 53.9±9.9 (50.7-57.1) | 0.986* |
| Gender<br>Male<br>Female | <br>9 (50%)<br>9 (50%) | <br>10 (45.5%)<br>12 (54.5%) | <br>19 (47.5%)<br>21 (52.5%) | 0.960** |
| Eye<br>Right<br>Left | <br>8 (44.4%)<br>10 (55.6%) | <br>12 (54.5%)<br>10 (45.5%) | <br>20 (50%)<br>20 (50%) | 0.817** |
| Prelaser IOP (mmHg)<br>Mean ± SD (95% CI) | 17.3±2.3 (16.2-18.5) | 17.0±2.9 (15.7-18.4) | 16.6±2.6 (15.8-17.5) | 0.667* |
| Prelaser No.AGM<br>Mean ± SD (95% CI) | 2.2±0.4 (2.05-2.51) | 2.4±0.5 (2.19-2.63) | 2.3±0.4 (2.20-2.50) | 0.696* |
| Number of laser spots<br>Mean ± SD (95% CI) | 56.0±6.5 (52.8-59.2) | 97.5±11.5 (92.5-102.7) | - | <0.001[t] |
| Total energy (mJ)<br>Mean ± SD (95% CI) | 65.6±17.2 (57.1-74.3) | 116.0±31.7 (101.9-130.1) | - | <0.001[t] |

IOP: Intraocular pressure, SLT: Selective laser trabeculoplasty, No.AGM: Number of antiglaucoma medications, SD: Standard deviation
*ANOVA, **Chi-square test, [t]Student's t test

**Table 2. Distribution of fixed combinations with timolol maleate 0.5% used before the intervention between the treatment subgroups**

| Fixed combinations of timolol maleate 0.5% subject to replacement by | SLT 180° (n=18) | SLT 360° (n=22) |
|---|---|---|
| Timolol maleate 0.5% + Bimatoprost 0.03% | 7 (38.9%) | 5 (22.7%) |
| Timolol maleate 0.5% + Dorzolamide hydrochloride 2% | 7 (38.9%) | 12 (54.5%) |
| Timolol maleate 0.5% + Brinzolamide 1% | 1 (5.6%) | 2 (9.1%) |
| Timolol maleate 0.5% + Travoprost 0.004% | 0 (0%) | 2 (9.1%) |
| Timolol maleate 0.5% + Brimonidine tartrate 0.2% | 2 (11.1%) | 1 (4.5%) |
| Timolol maleate 0.5% + Latanoprost 0.005 % | 1 (5.6%) | 0 (0%) |

SLT: Selective laser trabeculoplasty

## Discussion

The SLT/Med study, which was a prospective, randomized, multicenter clinical trial evaluating SLT vs. prostaglandin therapy as an initial treatment option demonstrated mean IOP reductions of 26.4% and 27.8%, respectively, from baseline.[2] Lai et al.[21] with regards to SLT vs. medical therapy reported mean IOP reduction of 32.1% and 33.2% from baseline at the 5 year follow-up, whereas reduction rates were statistically insignificant between 4-6 months in a comparison of SLT 360° to latanoprost 0.005% by Nagar et al.[26,27] Two other prospective, nonrandomized studies by Melamed et al.[20] and McIlraith et al.[28] reported similar reductions from baseline with SLT as initial therapy. A retrospective study by Kara et al.[29] reported mean reduction of 22.5% in IOP at 1 year. On the other hand, the meta-analysis by Cheng et al.[10] evaluated 41 randomized trials and reported IOP reductions with timolol maleate 0.5% FCs that are comparable to the SLT trials mentioned above. Our results show that in patients receiving FCs, SLT may successfully sustain the same IOP levels at least for 6 months, which was consistent with a reduction in number of antiglaucoma medications by a mean of 2 at 6 months reported by Francis et al.[25]

With respect to safety, despite apraclonidine 1% administration for preventing IOP spikes, mean IOPs at postlaser 1 hour were significantly higher than contralateral control eyes in the study. Without prophylaxis, Helvacioglu et al.[30] reported IOP spikes of 3-4 mmHg in almost all eyes at 1 and 2 hours postlaser. Our finding, however, is consistent with the previous reports wherein IOP spikes of 3-5 mmHg were detected in 8.4-10.3% of the subjects at 1 and 2 hours postlaser after prophylactic apraclonidine 0.5% or 1% administration.[24,31,32] In addition, mean IOP course over 6 months revealed that SLT 180° and 360° achieved lower mean IOPs than that of the control group only at postlaser 1 day, with a statistically significant difference for SLT 360°. It should be noted that we did not set a washout period of 2-3 weeks before and discontinued the medications immediately after the laser procedure. Therefore, we attribute those lower IOPs at postlaser 1 day to the additive but not immediate IOP-reducing effect of SLT. Prophylactic apraclonidine 0.5% use just before SLT may also have reduced IOP additionally by a sustained effect.

The superiority of SLT 360° over SLT 180° in IOP-reducing efficacy is controversial. In patients with POAG, Nagar et al.[33] reported no statistically significant difference between SLT

**Table 3. Mean intraocular pressures before and after Intervention**

| IOP (mmHg) | SLT 180° (n=18) Mean ± SD (95% CI) | SLT 360° (n=22) Mean ± SD (95% CI) | Control (n=40) Mean ± SD (95% CI) | p* |
|---|---|---|---|---|
| Prelaser | 17.3±2.3 (16.2-18.5) | 17.0±2.9 (15.7-18.4) | 16.6±2.6 (15.8-17.5) | 0.667 |
| Postlaser 1 hour | 20.0±2.8 (18.6-21.4) | 20.6±4.3 (18.7-22.5) | 17.0±2.9 (16.1-18.0) | <0.001 |
| Postlaser 1 day | 14.7±2.4 (13.5-15.9) | 14.1±3.5 (12.6-15.7) | 16.4±2.8 (15.5-17.3) | 0.010 |
| Postlaser 1 week | 16.7±2.5 (15.5-18.0) | 16.5±3.5 (15.0-18.1) | 16.1±2.7 (15.2-17.0) | 0.732 |
| Postlaser 1 month | 17.6±2.7 (16.2-19.0) | 17.5±3.2 (16.0-18.9) | 16.5±2.6 (15.7-17.3) | 0.251 |
| Postlaser 3 months | 17.1±2.4 (16.0-18.4) | 17.0±3.0 (15.7-18.4) | 16.5±2.7 (15.7-17.4) | 0.670 |
| Postlaser 6 months | 16.8±2.4 (15.6-18.0) | 17.6±3.1 (16.3-19.0) | 16.8±2.4 (16.0-17.7) | 0.473 |
| p** | - | - | **0.191 | - |

IOP: Intraocular pressure, SLT: Selective laser trabeculoplasty, SD: Standard deviation, CI: Confidence interval
*ANOVA **Intraclass (control group) comparison (ANOVA)

180° and SLT 360°, while SLT 90° produced the least effective outcome. However, studies by Shibata et al.[34] and Prasad et al.[19] suggest that SLT 360° is more effective in achieving lower mean IOPs or more limited IOP fluctuations than with SLT 180°. Moreover, Song et al.[35] reported higher failure rates with SLT 180°. In our study, SLT 360° did not display a significantly higher IOP reduction over SLT 180° through 6 months.

A number of limitations should be kept in mind in the interpretation of our results. First, performing SLT on one eye and continuing the AGM therapy on the contralateral one may be associated with crossover effects for both treatment modalities. With SLT, McIlraith et al.[28] displayed approximately 10% reduction of IOP in the untreated contralateral eyes for up to 6 months. Similarly, on the medication arm, The Ocular Hypertension Treatment Study (OHTS) showed 5.8% - 12% reduction of IOP in the untreated eyes as a contralateral effect of topical ß-blockers.[36] However, we did not observe any findings in IOP suggesting crossover effects. Here we just speculate that crossover effects of AGM and SLT may either be masked or cancelling each other out in our study.

Measuring IOP during the daytime and only once per day in our study precludes drawing any conclusions about diurnal fluctuations or peak IOP levels. As diurnal fluctuation is an independent risk factor for progression of glaucoma,[37] before proposing as a primary therapy, SLT should be shown to decrease the fluctuation to some extent as medications do. With respect to that, Nagar et al.[26] reported success rates in fluctuation reduction as 50% for SLT and 83% for latanoprost.

The third and the most important limitation of this study was the assumption that all FCs reduce IOP similarly within a non-inferiority margin which indeed may not be the case. To our knowledge, there is no single clinical study comparing the efficacies of all beta-blocker timolol 0.5% combinations in IOP reduction. According to conclusions drawn from comprehensive review and meta-analysis manuscripts, prostaglandin-timolol FCs are likely to achieve better reduction in IOP than the other timolol combinations.[10,38,39] As a recent systematic review concludes, bimatoprost/timolol FC in particular seems to achieve better reduction of IOP compared to other prostaglandin-timolol combinations containing latanoprost or travoprost.[40] A clinical trial comparing all FCs to each other in terms of IOP reduction rate is therefore required to establish a reliable foundation.

In conclusion, FCs have provided improvement in patient compliance, reduction in level of preservatives, and thereby gained more preference recently. Alternatively, as our results suggest, SLT offers promising potential as a substitute for AGM equivalent to efficacy of FCs. One plausible argument remaining against SLT may be its diminishing effect over time.[23] However, Avery et al.[41] and Hong et al.[42] showed safe and similar IOP reduction rates for repeat SLT comparable to first treatment. In this case, SLT may even indicate longer AGM-free periods for certain patients lacking compliance and suffering from preservative-related side effects. Further prospective studies that follow more patients for longer durations will be necessary before reaching a definitive conclusion in the comparison of FCs and SLT.

## Conclusion

SLT offers promising potential as a substitute equivalent to efficacy of FCs with timolol. However, SLT 360° may not achieve additional IOP reduction.

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**Ethics**
Ethics Committee Approval: Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Board, (2012-116)
Informed Consent: Received.
Peer-review: Externally peer-reviewed.

**Authorship Contributions**
Surgical and Medical Practices: Fadime Ulviye Yiğit, Concept: İsmail Umut Onur, Design: İsmail Umut Onur; Fadime Ulviye Yiğit, Data Collection or Processing: Ali Kutlay Tufan, Analysis or Interpretation: Şenay Aşık Nacaroğlu, Literature Search: Ahmet Ağaçhan, Writing: İsmail Umut Onur.

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Original Article

# Factors Affecting Compliance to Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in Patients with Age-Related Macular Degeneration

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**Abstract**

**Objectives:** To determine factors influencing compliance in patients with neovascular age-related macular degeneration (n-AMD) undergoing intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

**Materials and Methods:** The files of n-AMD patients recommended treatment with ranibizumab were reviewed retrospectively. The treatment regimen was 3 consecutive monthly injections followed by monthly follow-up with intravitreal injections as needed (pro re nata, PRN). Demographic and ocular characteristics were recorded. The patients were categorized into 2 groups: full compliance to treatment, or incomplete loading schedule and/or irregular maintenance treatment. All patients were interviewed by phone about factors affecting continuation of treatment.

**Results:** Mean age of the 314 patients (160 female, 154 male) included in the study was 71.6±9.1 years. A total of 246 patients (78.3%) could complete 3 consecutive injections at 1-month intervals after the start of treatment; 57 patients (18.2%) did not attend monthly follow-up during the 1-year follow-up period following the 3 consecutive monthly injections. Overall, 39.8% of the patients were not able to fully comply with the ranibizumab treatment by PRN regimen for 1 year. Better visual acuity at baseline, smaller lesion size, living closer to the hospital, higher education and sociocultural level, and better financial status were determined as factors affecting patient compliance. The most frequent reasons to discontinue treatment were fear of injection, disbelief in the benefit of the treatment, financial limitations, continuation of treatment at another center, and comorbid systemic diseases.

**Conclusion:** Patient compliance and success rates of anti-VEGF therapy may be increased by determining the factors affecting patient compliance and raising awareness about n-AMD among patients and their relatives.

**Keywords:** Patient compliance, intravitreal injection, ranibizumab, treatment, age-related macular degeneration

## Introduction

Age-related macular degeneration (AMD) is a progressive and degenerative disorder of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris. It is the most common cause of central vision loss in people 65 years and older.[1] The incidence of AMD is increasing due to the growing elderly population, especially in developed societies, and this constitutes an important health problem today.[2] The wet (neovascular/exudative) form of AMD can cause rapid loss of useful vision, negatively affecting patients' daily lives and ability to meet their needs. Therefore, research regarding the management of this type of AMD has been extensive and is ongoing.[3,4,5,6]

The main underlying factor in the pathogenesis of wet AMD is the formation of new vessels in the choroid layer.[3] The introduction of vascular endothelial growth factor (VEGF) inhibitor therapy into clinical practice has dramatically altered the prognosis of wet AMD. Randomized clinical trials on AMD demonstrate a significant improvement in patients treated with ranibizumab compared to the placebo group, and ranibizumab

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therapy is recommended monthly to achieve the most effective visual outcomes.[4,5,6] However, as an alternative to monthly injections, many retina clinics prefer a regimen of 3 monthly intravitreal injections as a loading dose, followed by injections administered as necessary based on visual acuity, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA) findings, because this approach is more feasible in clinical practice.[7,8,9,10,11,12,13] Having to go to the hospital every month for injection or follow-up, depending on their clinical condition, negatively influences patient compliance for various reasons, therefore affecting the success and outcome of treatment.

The aim of this study was to determine patients' treatment compliance rates and the factors that affect compliance with treatment and follow-up in patients diagnosed with wet AMD and recommended for ranibizumab therapy.

## Materials and Methods

The medical records of patients examined and diagnosed with wet AMD between February 2009 and February 2012 were analyzed retrospectively. A total of 314 patients who were recommended intravitreal ranibizumab injection (IVRI) therapy and who provided consent after being informed of the treatment regimen and duration were included in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Afyon Kocatepe University, Ethics Committee for Clinical Trials (2013/4 Decision: 42). Informed consent forms were obtained from all patients.

The patients were diagnosed with AMD based on clinical, OCT, and FFA findings. Best corrected visual acuity (BCVA) was assessed using the Early Treatment Diabetic Retinopathy Study chart. All patients were informed that the first 3 injections were requisite, after which they would be examined monthly and injections would be repeated as necessary. At the follow-up appointments, all patients underwent ophthalmologic examination and OCT imaging, while FFA was performed only when needed. The treatment regimen consisted of 3 consecutive monthly injections followed by additional injections given when deemed necessary according to OCT and visual acuity findings.

Patients' demographic features and ocular characteristics were recorded from their records. We determined the number of patients who continued treatment and follow-up appointments for 1 year from the time of diagnosis and investigated the reasons for unsuccessful treatment and follow-up. All patients included in the study were contacted by phone and they or their relatives were asked predetermined questions in order to identify factors that may affect treatment compliance (Table 1). Patients who could not be reached by phone or whose medical records could not be accessed were not included in the study.

Patients were studied in 2 groups according to their compliance to IVRI treatment and the follow-up appointments for 1 year. Patients who regularly received 3 consecutive IVRI treatments after being diagnosed with wet AMD and were followed regularly for 1 year thereafter comprised the 'compliant group' (Group 1), while patients who did not regularly receive 3 consecutive IVRI treatments or could not be followed regularly for 1 year comprised the 'noncompliant group' (Group 2). Group 2 was further divided into 2 subgroups: patients who completed 3 consecutive months of IVRI treatment but who were unable to complete 1 year of follow-up and treatment (Group 2a), and patients who were unsuccessful in completing their 1 year of follow-up and treatment, including the initial 3 consecutive monthly IVRI injections (Group 2b).

### Statistical Analysis

The data obtained were recorded and analyzed using a statistics software package (SPSS for Windows, version 18.0, SPSS, Chicago, IL, USA). Because the data pertaining to factors affecting patient compliance were qualitative and grouped, chi-square test and chi-square automatic interaction detector (CHAID) analysis were used. P values below 0.05 were considered significant. The correlation between compliance and factors that may affect compliance was assessed using Cramer's V analysis.

## Results

The mean age of the 314 patients included in the study was 71.6±9.1 years; the study group comprised 160 female patients and 154 male patients. The number of patients who successfully completed 3 consecutive doses of IVRI treatment and were followed regularly for 1 year (Group 1) was 189 (60.2%), while 125 (39.8%) patients showed inadequate compliance to treatment and follow-up (Group 2). Subgroup analysis of Group 2 showed that 57 patients (18.2%) completed 3 consecutive months of IVRI treatment following diagnosis but did not complete 1 year of follow-up (Group 2a), while 68 patients (21.6%) were not able to comply with follow-up and treatments including the initial 3 consecutive months of IVRI treatment (Group 2b). According to this, 246 patients (78.3%) completed 3 consecutive months of regular IVRI treatment. However, 57 (18.2%) of these patients were not able to regularly attend follow-up after the 3 consecutive IVRI treatments. The number of patients who were able to fully comply with their treatment and follow-up was 189 (60.2%) (Figures 1 and 2).

In the correlation analysis of data obtained from responses provided by patients and/or their relatives during the phone interview, statistically significant relationships emerged between patient compliance with the 1 year follow-up and IVRI treatment and an increase or decrease in the visual acuity of patients after

**Table 1. Information collected from the patients**

| | |
|---|---|
| Age (years) | AMD laterality |
| Education level | Symptom duration |
| Employment status/occupation | Previous AMD treatment |
| Place of residence | Intravitreal injection time and duration |
| Comorbid systemic disease | Follow-up and treatment duration |
| Number of companions | Reasons for noncompliance |
| Fear of injections | AMD awareness level |

AMD: Age-related macular degeneration

treatment, the visual acuity in the affected eye at the time of diagnosis, how far from the hospital they lived, education level, sociocultural status, age, economic status, fear of injection, the size of the choroid neovascularization lesion detected with FFA, and retirement status ($p<0.05$). No statistically significant correlations were found between compliance with the 1 year follow-up and IVRI treatment and whether the patients were newly diagnosed or diagnosed in the past, whether they were previously diagnosed with or treated for age-related macular degeneration, the visual acuity level in the fellow eye at the time of diagnosis, the side and number of eyes involved, or patients' age and employment status (Table 2).

From the results of CHAID analysis, it was determined that the patients' treatment response in terms of visual acuity was the factor that may have the greatest effect on patient compliance with the 1 year follow-up and treatment. Compliance rates were high among patients whose visual acuity values increased or decreased following treatment, while visual acuity alone showed no positive effect on compliance when it remained unchanged (Table 3). In the second step of the CHAID analysis, it was determined that visual acuity at the time of diagnosis was the most influential factor in compliance among the patients whose visual acuity increased or decreased following treatment. In this group, patients with visual acuity values of 20/40 and higher at time of diagnosis had the highest compliance rates (Table 4). In the third step of the CHAID analysis, the factor that affected compliance in patients whose visual acuity was 20/40 and better was found to be the patients' place of residence. As the distance between patients' residence and the treatment center decreased, compliance rates increased.

The patients provided between 1 and 4 reasons for not complying with the recommended IVRI treatment and 1 year follow-up. Among the 232 reasons stated by the 125 patients who failed to comply with follow-up and treatment, the most common was a fear of intravitreal injection (29.6%). This was followed by disbelief that treatment would be beneficial/resignation to one's fate (21.6%), financial difficulty (20.8%), residing in another province or continuing with treatment in another province (20%), comorbid systemic diseases (18.4%), dissatisfaction with the outpatient clinic or operating room conditions (17.6%), lack of relatives to help the patient come to the hospital or not having enough time (16%), and difficulty in coming and going due to old age (16%) (Figure 3).

When we examined the less common reasons, we found that 7 patients (5.6%) stopped attending follow-up because of improved vision and reduced visual complaints after IVRI treatment, but 5 of those patients presented to our clinic again after an average of 6 months due to deteriorating vision and increased visual complaints. Six patients (4.8%) were lost to follow-up due to mortality. The cause of death was cerebrovascular events in 3 patients, heart attack in 2 patients, and traffic accident for 1 patient. Of the patients who were unable to appear regularly to follow-up appointments, 6 (4.8%) were unable to find time due to their job, 5 (4%) were unable to find time due to caring for their spouse who was ill or bedbound, 4 (3.2%) had had a traffic accident a short time before the appointment date, and 3 (2.4%) were unable to come due to severe winter weather conditions.

## Discussion

In this study, we observed that a significant portion of wet AMD patients did not comply adequately with the AMD treatment and follow-up protocol. The factors which had the greatest influence on whether patients continued their treatment were visual acuity change with treatment, visual acuity at the time of diagnosis, and distance to the treatment center.

Controlling angiogenesis with anti-VEGF therapy, which is now the standard treatment modality for wet AMD patients,

**Table 2. Correlation analysis of factors that may affect patient compliance**

| | r | p |
|---|---|---|
| Increase or decrease in BCVA in the affected eye | 0.431 | <0.001 |
| BCVA in the affected eye at time of diagnosis | -0.223 | <0.001 |
| Place of residence (distance from hospital) | -0.227 | <0.001 |
| Education level | 0.217 | <0.001 |
| Age | -0.176 | 0.002 |
| Marital status | 0.156 | 0.006 |
| Fear of injections | -0.141 | 0.013 |
| Size of choroidal neovascularization lesion | -0.131 | 0.020 |
| Employment status | 0.117 | 0.041 |
| Diagnosis status (previous/new diagnosis) | -0.047 | 0.405 |
| Treatment status | 0.045 | 0.427 |
| Laterality (right/left) | 0.036 | 0.528 |
| Sex | -0.022 | 0.697 |
| BCVA in the fellow eye at time of diagnosis | -0.019 | 0.734 |
| Comorbid systemic disease | 0.010 | 0.865 |

BCVA: Best corrected visual acuity

**Table 3. Patient distribution by final visual acuity**

| Patient group | Final VA increase | Final VA decrease | Final VA unchanged |
|---|---|---|---|
| Compliance | 95 (50.3%) | 70 (37%) | 24 (12.7%) |
| Noncompliance | 38 (30.4%) | 16 (12.8%) | 71 (56.8%) |

VA: Visual acuity

**Table 4. Compliance rates of patients whose best corrected visual acuity increased or decreased during treatment and follow-up, based on initial best corrected visual acuity**

| | Patient number (%) | |
|---|---|---|
| Visual acuity | Compliant | Noncompliant |
| <20/640 | 24 (77.4%) | 7 (22.6%) |
| 20/640-20/125 | 77 (74.0%) | 27 (26.0%) |
| 20/100-20/50 | 41 (66.1%) | 21 (33.9%) |
| >20/40 | 23 (100%) | 0 (0%) |

prevents further macular damage by inhibiting the growth of new vessels and thus stabilizes vision. However, since the underlying pathology continues, anti-VEGF injections need to be continued repeatedly to control angiogenesis. Clinical trials have reported the long-term outcomes of patients complying with the study protocol, and successful treatment outcomes have been achieved.[4,5,6] Unlike the monthly injections given in clinical trials, however, a regimen of monthly follow-up examinations and additional injections applied as necessary after the first 3 injections is more common in clinical practice worldwide. Some regimens use change in visual acuity during follow-up as the criterion for needing additional injections, while other clinics use the stabilization criterion. According to the stabilization approach, treatment is suspended if vision and anatomy have not shown further improvement in the last 3 follow-up visits, and is reinitiated and continued according to the stabilization criterion in the event of recurrence.[7,8,9,10,11,12,13] Because clinical practice requires patients to continue attending monthly follow-up, treatment compliance rates may vary depending on factors that push the limits of patients' compliance with treatment and patients' level of awareness in terms of the disease and its treatment. While anti-VEGF therapy is promising for AMD patients, the need for repeated intraocular injections makes it difficult to successfully implement. This affects the efficacy and outcomes of treatment.

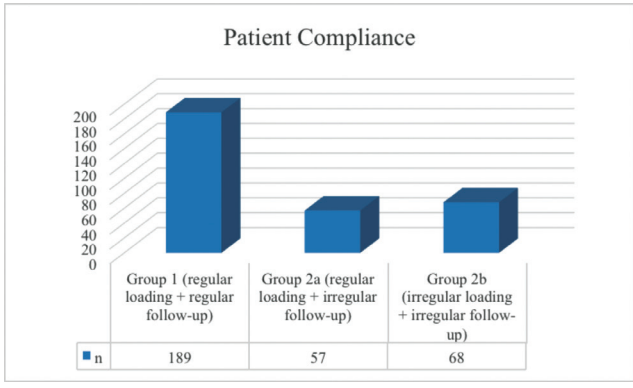


**Figure 1.** Distribution of patients by study group

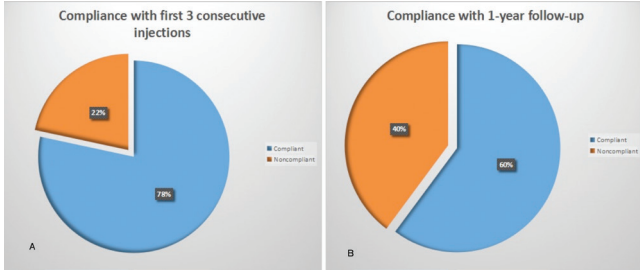


**Figure 2.** Rates of compliance with the first three consecutive ranibizumab injections (A). Compliance rates of the 57 patients who were unable to comply with the 1-year treatment and follow-up period despite complying with the first 3 injections (B)

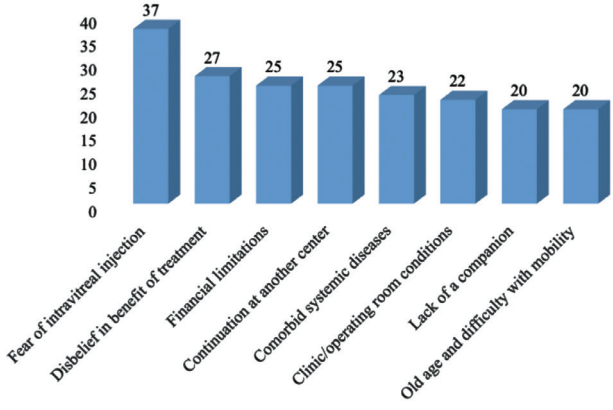


**Figure 3.** Reasons stated by patients for their lack of compliance

It has not been adequately addressed in the literature whether or not patients adequately comply with the intravitreal anti-VEGF treatment protocol in wet AMD due to the frequent and repeated injections. As far as we can determine, this subject has not yet been studied in our country, and the few studies conducted abroad have focused more on the reasons why patients discontinue treatment. Droege et al.[14] investigated the factors and problems affecting compliance with anti-VEGF treatment in AMD in real-life conditions and found a compliance rate of 81.1%. Reasons reported for inability to continue follow-up and treatment included not benefiting from treatment, severe comorbid systemic conditions, continuing treatment at another center, refusing treatment, and death. In addition, similar to our study, distance to the hospital and the necessity for a companion were found to be among the factors that made compliance difficult for patients. In another study with a similar purpose, compliance rates were reported as over 90% in the stabilization phase of treatment and 63.2% in the maintenance phase. Patient compliance was found to depend on the duration of treatment, visual acuity in the fellow eye, and functional outcomes of the initial treatment administered to the affected eye.[15] In their study investigating the reasons for discontinuing IVRI, Vaze et al.[16] found that 42.3% of the patients did not continue treatment for various reasons including their doctor ending treatment, frequent visits, difficulty of attendance and follow-up, financial limitations, pain, disbelief in the benefit of the treatment, and refusal of continuance of treatment due to comorbid systemic conditions. Other reasons given were continuing treatment at another center and being unable to continue treatment due to death.

In addition to factors that may affect patients' compliance with intravitreal injection therapy and follow-up, some studies on the efficacy of intravitreal injection therapy have investigated reasons why some patients terminate treatment as a subtopic.[8,17,18] These studies determined rates of discontinuing treatment or follow-up to be 4.2%, 8.1%, and 14.2%. When other studies are also considered, the rates of noncompliance with or discontinuation of treatment range between 4.2% and 42.3% in the literature. The differences in compliance rates between studies may be due to differences in the social and financial means and sociocultural levels of the patient populations and/

or differences in methodology and follow-up duration between studies.

Unlike in other studies, in the present study we attempted to investigate all factors that may have a positive or negative effect on compliance with IVRI treatment by examining not only the characteristics of patients who either discontinued treatment or did not comply adequately, but also the characteristics of patients who were adequately compliant with treatment and follow-ups, in order to identify solutions for increasing patient compliance.

While patients' financial means, education level, sociocultural values, disease awareness, and access to treatment are better in developed countries compared to developing or undeveloped countries, the tendency to live alone in old age is more common in developed countries due to the nature of society. This may cause the factors influencing patient compliance to differ from country to country. Health workers, especially ophthalmologists, patients themselves and their relatives, and the authorities that govern health policies all share the great responsibility of improving factors that may affect patient compliance. For example, fear of injection and not benefiting as expected from treatment were found to be the most common reasons stated by patients in our study for not complying adequately with the treatment and 1 year follow-up. This highlights the responsibility of ophthalmologists to properly inform patients about the pathogenesis, course, and treatment of AMD and what treatment responses they should expect.

In Turkey, patients with health insurance have to pay a certain portion of the price of ranibizumab. In addition to this, high transportation costs can be a serious problem for patients and their families whose financial means are limited. Due to the large numbers of patients, the amount of time allotted to patients in outpatient clinics and operating rooms is minimized. Major steps must be taken in the development of policies to ensure that these conditions positively affect patients' compliance with follow-up and treatment.

Due to its nature, AMD usually emerges in very old patients. Many patients with AMD have a comorbid systemic disease. In our study, 74.3% of the patients had comorbid conditions. In terms of compliance, systemic disease was present in 73.7% of the noncompliant patients and 74.6% of the compliant patients. Although this is not a statistically significant difference, it shows that comorbid systemic disease is the reason that a substantial proportion of patients in this age group were unable to comply adequately. Here again, important responsibility falls on ophthalmologists in terms of explaining every aspect of AMD to patients, and on family physicians in terms of informing patients that postponing their eye examinations may lead to a serious threat to their visual acuity or cause them to miss the effective window for treating AMD.

It is noteworthy that an increase or decrease in final BCVA in the affected eye following treatment emerged in statistical analysis as the most important factor affecting patient compliance. The positive aspect of this result may show that visual success is better in patients with a high level of compliance to treatment, which is expected. However, a decrease in the final BCVA has a positive effect on a patient's compliance with follow-up and treatment because it evokes the fear of possibly losing one's vision. Compliance is a necessary but not sufficient condition for successful visual outcomes. Hence, we found a group of patients in our study who did not comply adequately despite their visual acuity having improved with treatment. There may also be factors that make visual success difficult despite adequate compliance, such as disease severity and resistance. In these cases, it is clear that raising the patient's level of awareness should increase patient compliance. BCVA in the affected eye at time of diagnosis emerged as another important factor and was inversely proportional to compliance, indicating that patients with lower vision at the time of diagnosis were more compliant with treatment and monthly follow-up. This may also have been a result of fear of vision loss. Studies including larger case series that investigate all factors and reasons for noncompliance, in addition to those analyzed in this study, may help to increase patients' rate of compliance with intravitreal injection therapy.

The limitations of our study are its retrospective design and the subjective nature of the answers to the questions asked by phone. It is possible that the answers were incomplete or biased.

## Conclusion

In conclusion, although acceptance of and compliance with treatment seem to be relatively high initially in patients with wet AMD recommended for IVRI therapy, a significant proportion of these patients are unable to fully comply with the treatment regimen within the 1-year follow-up period due to the stated reasons. However, in the time period our study analyzes, intravitreal injection therapy was newly becoming common among AMD patients. The behavioral characteristics of patients with regard to compliance with treatment may have changed in subsequent years. A new study is currently being conducted in our clinic investigating how patient behavior has changed in later years. Determining the factors that may affect treatment compliance in wet AMD patients and raising the awareness of patients and their relatives may facilitate the improvement of treatment compliance and success rates.

### Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Afyon Kocatepe University, Ethics Committee for Clinical Trials (2013/4 Decision: 42).

Informed Consent: Informed consent forms were obtained from all patients.

Peer-review: Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Onur Polat, Sibel İnan, Serkan Özcan, Concept: Onur Polat, Sibel İnan, Serkan Özcan, Mustafa Doğan, Tuncay Küsbeci, Güliz Fatma Yavaş, Ümit Übeyt İnan, Design: Onur Polat, Serkan Özcan, Mustafa Doğan, Ümit Übeyt İnan, Data Collection or Processing: Onur Polat, Sibel İnan, Serkan Özcan, Güliz Fatma Yavaş, Analysis or Interpretation:

Tuncay Küsbeci, Güliz Fatma Yavaş, Ümit Übeyt İnan, Literature Search: Sibel İnan, Serkan Özcan, Mustafa Doğan, Writing: Onur Polat, Güliz Fatma Yavaş, Ümit Übeyt İnan.

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Original Article

# Ocular Causes of Abnormal Head Position: Strabismus Clinic Data

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## Abstract

**Objectives:** To determine the most common ocular causes and types of abnormal head position (AHP) and describe their clinical features.

**Materials and Methods:** Patients with AHP who had been followed in the strabismus unit were retrospectively reviewed. Demographic features and orthoptic characteristics were recorded.

**Results:** A total of 163 patients including 61 women (37.4%) and 102 men (62.6%), with a mean age of 19.9±18.3 were recruited. The most common causes of AHP were determined as fourth cranial nerve palsy (33.7%), Duane retraction syndrome (21.5%), sixth cranial nerve palsy (11%), nystagmus blockage syndrome (9.8%) and Brown syndrome (6.7%). Other less frequent causes were A-V pattern strabismus, comitant strabismus, thyroid orbitopathy and third cranial nerve palsy. The most common types of AHP were head tilt (45.4%) and face turn (36.8%). Out of 142 patients whose visual acuity could be evaluated, 28.2% had amblyopia. The frequency of amblyopia varied depending on the diagnosis ($p<0.001$), while there was no relation between amblyopia and different types of AHP ($p=0.497$). Stereopsis and fusion could be tested in 128 patients and 43.8% of them had stereopsis and fusion. The presence of stereopsis and fusion was found to be related with the diagnosis ($p=0.001$), whereas it was not related with the types of AHP ($p=0.580$). The presence of amblyopia was not significantly associated with fusion ($p=1.000$) or stereopsis ($p=0.602$).

**Conclusion:** There are many ocular pathologies that cause AHP. Patients with similar diagnoses may have different types of AHP. Patients may have amblyopia and impaired binocularity despite AHP. Therefore, all patients with AHP should be examined in detail and these points should be considered in the treatment plan.

**Keywords:** Abnormal head position, nystagmus, ocular, strabismus

## Introduction

Abnormal head position (AHP) refers to the head forming an angle with the body on horizontal, vertical or anteroposterior axis.[1] AHP may occur due to ocular, muscular, neurological, or vestibular causes.[2] When examining a patient with AHP symptoms in the clinic, the cause of the position can be distinguished from orthopedic and vestibular causes by simply having the patient close their eyes and observing the correction of the position.[2] Alterations in normal head alignment may manifest as the chin looking upwards or downwards, the face being turned to the right or left, the head being tilted right or left, or various combinations of these positions.[1] AHP of ocular origin includes head malpositions resulting from false information obtained from afferent vision paths, oculomotor nerves, or the vestibular aparatus.[1] Although the underlying causes of AHP vary, ocular AHP is a mechanism developed in order to increase visual acuity, optimize visual field, ensure single and binocular vision or fusion, and prevent diplopia.[3,4] Persistent

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AHP due to ocular pathology may lead to permanent deformities caused by muscular atrophy and musculoskeletal system changes secondary to the position.[5]

This study aimed to evaluate the AHP types and etiologies in AHP patients being followed in the strabismus unit, and to determine the relationship between AHP and clinical findings.

## Materials and Methods

This retrospective study was conducted in accordance with the principles of the 2013 Declaration of Helsinki and with the consent of the Hacettepe University Non-interventional Clinical Research Ethics Board. The medical records of patients being followed in the strabismus unit were reviewed. Patients who had a history of ocular surgery or whose AHP was of non-ocular origins were not included in the study. A total of 163 patients met these eligibility criteria and were included in the analysis. The patients' age, gender, AHP type, AHP degree (°), best corrected visual acuity, amount of deviation (prism diopters [PD]), ocular motility findings, and binocularity were recorded. Visual acuity was measured using Snellen or Lea chart and expressed in the decimal system. Strabismus measurements were made using the Krimsky test or prism cover test. In patients who complied with examination, fusion was assessed with the Worth 4 dot test and stereopsis with the Titmus stereo test. Fusion and stereopsis were assessed without AHP correction. AHP was measured on three axes using orthopedic goniometry.

### Statistical Analysis

Descriptive statistics were expressed in mean ± standard deviation for continuous numerical variables and in number and percentage for categorical variables. Correlations between categorical variables were assessed using chi-square test (Fisher's exact or Yates corrected chi-square). Statistical analyses were performed using IBM SPSS statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) software. P values less than 0.05 were considered statistically significant.

## Results

Of the 163 patients, 61 (37.4%) were female and 102 (62.6%) were male. The mean age was 19.9±18.3 years (1-73 years). The most common diagnoses in patients with AHP were fourth nerve palsy (33.7%), Duane retraction syndrome (21.5%), sixth nerve palsy (11%), nystagmus blockage syndrome (9.8%), and Brown syndrome (6.7%). The frequency distribution of the diagnoses and the ophthalmologic examination findings are summarized in Table 1. Among all patients, the AHP types in order of prevalence were head tilt (45.4%), face turn (36.8%), combined AHP (11.7%), chin up (5.5%) and chin down (0.6%). Each diagnostic group showed different AHP types with one being predominant. The mean degree of head tilt was 18.92±7.08° (10-45°) and the mean degree of face turn was 20.30±9.04° (5-40°). The mean degree of chin up position was 19.22±7.45° (8-35°), whereas the one patient with chin down position showed 10° tilt.

Of the 142 patients with measurable visual acuity, 40 (28.2%) had amblyopia. The average visual acuity was 0.83±0.22 (0.1-1.0). Amblyopia was most common in nystagmus blockage syndrome (100%) and least common in Duane retraction syndrome (16.0%). There was a significant correlation between diagnosis and the incidence of amblyopia ($p<0.001$). However, there was no significant difference in amblyopia prevalence among the various AHP types ($p=0.497$).

In primary gaze position, 14.7% of the patients were orthotropic. The most common type of strabismus was esotropia (28.2%). The mean amount of deviation was 24.18±15.81 PD (3-60 PD) in the 52 esotropic patients and 23.39±15.41 PD (3-65 PD) in the 43 exotropic patients. The mean amount of deviation was 14.86±7.74 PD (4-40 PD) in the 74 patients with vertical strabismus. Forty-five patients had diplopia. One hundred and thirty-nine patients (85.3%) exhibited varying degrees of ocular motility limitation. Twelve of those patients had clinically insignificant bilateral/symmetric minimal movement restriction, despite the absence of any paralytic or restrictive etiology.

Of the 128 patients who could be assessed for fusion and stereopsis, 43.8% had both fusion and stereopsis. There was no statistical difference in fusion or stereopsis rates among the various AHP types ($p=0.580$), but there was a significant difference according to diagnosis ($p=0.001$). Analysis of fusion and stereopsis in the diagnostic groups revealed significantly high rates of stereopsis and fusion loss (93.3%) in the sixth nerve palsy group ($p=0.001$). When fusion and stereopsis were considered separately, no significant difference was found among the various AHP types ($p=0.352$ for fusion, $p=0.702$ for stereopsis), but a significant difference emerged between diagnoses ($p<0.001$ for fusion, $p=0.013$ for stereopsis). Amblyopia was not significantly associated with the presence of fusion ($p=1.000$) or stereopsis ($p=0.067$). There was no significant correlation between the degree of AHP and fusion ($p=0.378$), stereopsis ($p=0.611$), or amblyopia ($p=0.065$).

## Discussion

The clinical detection of AHP due to ocular causes is very important for several reasons, including the possibility of developing secondary and permanent torticollis as a result of muscular and soft tissue changes due to delayed treatment, loss of binocularity that may occur if the AHP cannot be maintained, and development of amblyopia.[3,6] AHP is among the important diagnostic criteria for paralytic diplopia and nystagmus.[7] Various series evaluating the causes of AHP have listed the most common ocular causes. Mitchell[8] reported incomitant strabismus in 52.4%, nystagmus in 19%, and congenital esotropia in 10.9% of 630 patients with ocular torticollis. In the same study, the most common causes of incomitance were identified as A-V pattern, fourth nerve palsy, asymmetric surgery, Duane retraction syndrome, and Brown syndrome.[8] Incomitant strabismus was also a prominent cause of ocular AHP in the present study, and the five most common causes were fourth nerve palsy (33.7%),

Duane retraction syndrome (21.5%), sixth nerve palsy (11%), nystagmus blockage syndrome (9.8%), and Brown syndrome (6.7%). Dikici and Kızılkaya[9] found that AHP was a result of some type of strabismus in 80% of 187 patients, and 80% of all the cases were incomitant. In another study of 64 patients with Down syndrome and AHP, incomitant strabismus was reported as the most common identifiable cause (26.6%).[10] In their review of 2,701 participants who presented to an ophthalmology clinic due to any ophthalmologic complaint, Erkan Turan et al.[11] determined that 30 patients had AHP and emphasized that comitant strabismus, nystagmus, and Duane retraction syndrome were the most common causes of AHP.

The presence and the type of AHP is important in diagnosing ocular disease.[12] Boricean and Bărar[13] determined face turn to be the most common type of AHP in a study of children. However, in our study, head tilt was the most common (45.4%), followed by face turn (36.8%). The diagnostic distribution of the patients included in a study is the most important factor influencing the frequency of AHP. Head tilt was the most common type of AHP in the present study because the most common diagnosis in our

**Table 1. The frequency of abnormal head positions and examination findings according to diagnosis (n=163)**

| Diagnosis | Frequency % (number of patients) | AHP type (%) | Amblyopia % (number of patients) | Presence of binocularity % (number of patients) | Deviation in primary position (%) |
|---|---|---|---|---|---|
| Fourth nerve palsy | 33.7 (55) | Head tilt (87.3)<br>Combined (7.3)<br>Face turn (3.6)<br>Chin down (1.8) | 16.0 (8/50) | Stereopsis 65.9 (31/47)<br>Fusion 51.1 (24/47)<br>Stereopsis + fusion 44.7 (21/47) | Vertical deviation (45.5)<br>Exotropia + vertical deviation (38.2)<br>Esotropia + vertical deviation (5.5)<br>Exotropia (5.5)<br>Orthotropia (3.6)<br>Esotropia (1.7) |
| Duane retraction syndrome | 21.5 (35) | Face turn (82.9)<br>Head tilt (14.2)<br>Combined (2.9) | 13.8 (4/29) | Stereopsis 77.8 (21/27)<br>Fusion 77.8 (21/27)<br>Stereopsis + fusion 70.4 (19/27) | Esotropia (62.9)<br>Orthotropia (14.3)<br>Exotropia (14.3)<br>Exotropia + vertical deviation (5.7)<br>Esotropia + vertical deviation (2.9) |
| Sixth nerve palsy | 11.1 (18) | Face turn (77.8)<br>Head tilt (11.1)<br>Combined (11.1) | 27.8 (5/18) | Stereopsis 40.0 (6/15)<br>Fusion 6.7 (1/15)<br>Stereopsis + fusion 6.7 (1/15) | Exotropia (94.1)<br>Esotropia + vertical deviation (5.9) |
| Nystagmus blockage syndrome | 9.8 (16) | Combined (31.3)<br>Head tilt (31.3)<br>Face turn (25.0)<br>Chin up (12.4) | 100 (12/12) | Stereopsis 60.0 (6/10)<br>Fusion 60.0 (6/10)<br>Stereopsis + fusion 60.0 (6/10) | Orthotropia (75.0)<br>Exotropia (12.5)<br>Esotropia (6.3)<br>Exotropia + vertical deviation (6.3) |
| Brown syndrome | 6.7 (11) | Head tilt (45.4)<br>Chin up (27.3)<br>Combined (27.3) | 25.0 (2/8) | Stereopsis 83.3 (5/6)<br>Fusion 66.7 (4/6)<br>Stereopsis + fusion 50.0 (3/6) | Orthotropia (45.5)<br>Vertical deviation (18.2)<br>Exotropia + vertical deviation (18.2)<br>Esotropia (9.1)<br>Esotropia + vertical deviation (9.1) |
| A-V pattern deviation | 6.1 (10) | Face turn (70.0)<br>Head tilt (30.0) | 37.5 (3/8) | Stereopsis 33.3 (3/9)<br>Fusion 11.1 (1/9)<br>Stereopsis + fusion 11.1 (1/9) | Esotropia (50.0)<br>Exotropia (50.0) |
| Vertical concomitant deviation | 3.1 (5) | Head tilt (60.0)<br>Chin up (20.0)<br>Combined (20.0) | 40.0 (2/5) | Stereopsis 75.0 (3/4)<br>Fusion 75.0 (3/4)<br>Stereopsis + fusion 75.0 (3/4) | Vertical deviation (100) |
| Vertical and horizontal concomitant deviation | 3.1 (5) | Head tilt (40.0)<br>Face turn (20.0)<br>Chin up (20.0)<br>Combined (20.0) | 25.0 (1/4) | Stereopsis 60.0 (3/5)<br>Fusion 40.0 (2/5)<br>Stereopsis + fusion 20.0 (1/5) | Exotropia + vertical deviation (80.0)<br>Esotropia + vertical deviation (20.0) |
| Thyroid-associated orbitopathy | 3.1 (5) | Chin up (40.0)<br>Head tilt (20.0)<br>Face turn (20.0)<br>Combined (20.0) | 20.0 (1/5) | Stereopsis 100 (4/4)<br>Fusion 50.0 (2/4)<br>Stereopsis + fusion 25.0 (1/4) | Vertical deviation (80.0)<br>Esotropia + vertical deviation (20.0) |
| Third nerve palsy | 1.8 (3) | Face turn (66.7)<br>Combined (33.3) | 66.7 (2/3) | Stereopsis 0 (0/1)<br>Fusion 0 (0/1)<br>Stereopsis + fusion 0 (0/1) | Exotropia (100) |

AHP: Abnormal head position

patient group was fourth nerve palsy. In their study presenting the clinical characteristics and surgical treatment of 75 patients with Duane retraction syndrome, Kalevar et al.[14] reported that 86% of esotropic patients and 80% of the exotropic patients had AHP in primary position, while there was no AHP in the orthotropic patient group. Biler Demirkılınç et al.[15] reviewed patients with Duane retraction syndrome and emphasized that the most common clinical finding was AHP. Suh et al.[16] reported that 12 of 13 patients with Brown syndrome had AHP and classified the cases as slight, medium, or severe depending on the amount of AHP and the presence of vertical strabismus in the gaze positions. In their study presenting the surgical outcomes of patients with unilateral superior oblique palsy, Tenlik et al.[17] detected AHP in 97.3% of 37 patients. In our study, we observed that different types of AHP can occur in patients with the same diagnosis (Table 1). Therefore, all diagnoses should be considered and investigated in patients presenting with AHP.

As AHP is a compensating mechanism, it is believed that fusion capacity and visual acuity that stimulates fusion are both necessary. Consequently, patients with amblyopia or suppression may not be expected to develop AHP.[18] Similarly, a heterotropia that cannot be balanced with position or fusion amplitudes can be considered a factor that causes amblyopia.[6] While we did not find a significant correlation between the presence of amblyopia and binocularity and the type of AHP, we found that the prevalence of amblyopia and binocularity vary depending on diagnosis. Stereopsis is a high-order binocular function.[19] Stereopsis may be absent despite motor and sensory fusion, and stereopsis may be present, though rarely, without motor fusion.[19] We did not evaluate motor fusion in the present study because we had a very wide age range in our patient group. However, since stereopsis and fusion are cortical functions at different levels, we assessed their mutual interaction with AHP individually and found that AHP was not significantly correlated with either of them. Although not common, AHP may accompany comitant strabismus. In cases of infantile esotropia, amblyopia, and severe fixation preference, head position can be improved, especially in reading and focused gaze positions.[7] In pattern strabismus, a position that minimizes strabismus and provides binocularity may be preferred.[20] AHP can also be observed in non-strabismus cases such as uncorrected refractive error.[21] It should be kept in mind that the group of patients in the study did not have a homogenous diagnosis distribution and that binocular function could not be assessed in all patients. Furthermore, we measured fusion using the Worth 4 dot test and stereopsis with the Titmus test. Using different tests for these measurements may yield different results. Therefore, these findings may not be sufficient to explain the origin of AHP in all patients sharing the same diagnosis, and cannot be generalized to all strabismus patients. In order to determine whether the presence of AHP is protective with respect to amblyopia and loss of binocularity and to explain AHP pathogenesis on an individual basis, studies should be conducted on AHP and non-AHP patients with the same diagnosis. Patients without AHP were not included in our study.

**Study Limitations**

Our study has the limitations of any retrospective work. In this study, we evaluated patients with AHP who were being followed in the strabismus unit. Therefore, it is not possible to generalize the results to include all patients having AHP. Because it was not possible to evaluate binocularity and visual acuity in all of the patients included in the study, these analyses do not encompass all patients. In order to individually examine why patients with different diagnoses use AHP, studies that include larger patient groups and obtain detailed and reliable fusion and stereopsis measurements from patients with and without AHP are needed.

## Conclusion

Different types of AHP may occur in patients with the same diagnosis. Patients with AHP should be examined for different diagnoses. It should be kept in mind that predictions regarding amblyopia and the presence of binocularity cannot be made based on AHP type, and that the patient's diagnosis should also be considered during evaluation. Another thing to remember is that the presence of amblyopia may not always be accompanied by loss of binocularity.

**Ethics**

Ethics Committee Approval: This study was approved by the Hacettepe University Non-interventional Clinical Research Ethics Board.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Kadriye Erkan Turan, Hande Taylan Şekeroğlu, Emin Cumhur Şener, Ali Şefik Sanaç, Concept: Kadriye Erkan Turan, Hande Taylan Şekeroğlu, Design: Kadriye Erkan Turan, Hande Taylan Şekeroğlu, Data Collection or Processing: Kadriye Erkan Turan, Esra Vural, Analysis or Interpretation: Kadriye Erkan Turan, Hande Taylan Şekeroğlu, İrem Koç, Jale Karakaya, Literature Search: Kadriye Erkan Turan, İrem Koç, Writing: Kadriye Erkan Turan, Hande Taylan Şekeroğlu, İrem Koç, Jale Karakaya.

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Original Article

# Results of Screening in Schools for Visually Impaired Children

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## Abstract

**Objectives:** The aim of this study was to identify the causes of visual impairment in children attending schools for students with visual impairment and to identify children suitable for treatment and rehabilitation.

**Materials and Methods:** All students were examined in our department by a pediatric ophthalmologist and an ophthalmologist experienced in low vision and visual rehabilitation. The children's medical histories were recorded. All children underwent ophthalmological examination including visual acuity measurement, anterior segment and dilated fundus evaluation, retinoscopy with cycloplegia, and intraocular pressure measurement. The causes of visual impairment were grouped as avoidable and unavoidable. Children with residual visual acuity better than 20/1250 were included in the low vision rehabilitation programme.

**Results:** A total of 120 patients were evaluated and 79.2% were legally blind (visual acuity less than 0.05), 18.4% had low vision (visual acuity between 0.05 and 0.3), and 0.8% had normal vision (>0.3). The main causes of visual impairment were retinal dystrophies (24.2%) and retinopathy of prematurity (17.5%). Of all diseases related to visual impairment, 27.6% were avoidable. Improvement in visual acuity was achieved with low vision aids in 57.5% of all patients.

**Conclusion:** The incidence of visual impairment due to avoidable causes can be decreased by ophthalmic screening. Treatment of these children in the early stages of visual development can improve visual acuity. Even in cases with delayed diagnosis, low vision aids are important for visual and neurobehavioral development, and these programmes may improve quality of life and education in these children.

**Keywords:** Blindness, low vision, low vision aids, visual acuity, visually impaired

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## Introduction

The estimated number of blind people around the world is 45 million.[1] This number is expected to increase to 76 million by 2020.[2] In 1999, it was estimated that there were 1.4 million blind children and each year 500,000 children are becoming blind.[3] Most of them have treatable or preventable causes. In 1999, VISION 2020: The Right to Sight initiative was launched by the World Health Organization (WHO; Geneva, Switzerland) with the International Agency for the Prevention of Blindness (London, England).[4,5] This global movement aims to eliminate avoidable blindness by the year 2020 and avoidable childhood blindness is one arm of this project.

The aim of this study was to identify the profile of children going to schools for students with visual impairment in Ankara, the capital city of Turkey, to determine the causes of low vision and blindness, and to identify children suitable for treatment and rehabilitation.

## Materials and Methods

There are two schools in Ankara for visually impaired children, the Gören Eller and Mitat Enç Schools for the Visually Impaired. A total of 120 students attending these schools were examined in a period of 6 months and all of the students were included in the study. Ethics Committee approval was obtained from Ankara University.

A detailed medical history was obtained from the students' parents. The gestational age and weight, family history of eye diseases, consanguinity, any accompanying neurological diseases, and presence of other sensory disabilities such as deafness and speech disability were recorded.

Visual acuity (VA) was measured with Early Treatment Diabetic Retinopathy Study chart if possible; in younger or uncooperative children, Lea symbols were used, and if VA was not measurable with these methods, light perception, projection, and hand movements were tested and noted. The anterior segment was examined using slit-lamp biomicroscopy. Posterior segment examination with indirect ophthalmoscopy and retinoscopy were performed after cycloplegia and dilatation of pupil with 1% cyclopentolate. Intraocular pressure was measured with Tonopen tonometer.

Before pupil dilatation and cycloplegia, low vision aids were tried in all students who had VA more than 20/1250. Electro-optical and telescopic systems were used to evaluate near and distance visual acuities. Colored filters were also tested to reduce light sensitivity and enhance contrast sensitivity.

Visual loss was classified according to the 2010 WHO definition of visual impairment (Table 1).[6] Blindness and low vision were defined as visual impairment.

The causes of visual impairment were classified according to whether the loss of visual ability was due to avoidable reasons. Prenatal/perinatal infections, trauma, retinopathy of prematurity (ROP), congenital glaucoma, congenital cataract, uveitis, and refractive errors were accepted as avoidable causes. Other diseases such as retinal/corneal dystrophies, congenital eye anomalies, and cortical blindness were grouped as unavoidable causes.

## Results

A total of 120 children were included in the study. Sixty-nine (57.5%) of them were male and 51 (42.5%) were female and the mean age was 11.5±2.84 years. The ages of the youngest and oldest children attending these schools were 6 and 20 years respectively.

Of all 120 patients, 95 (79.2%) were legally blind, 22 (18.4%) had low vision, and 1 (0.8%) had normal vision. VA could not be assessed in 2 patients (1.6%) due to mental retardation (Table 2). Of the 95 legally blind patients, 69 (72.6%) had only light perception.

The etiological classification of visual impairment is shown in Table 3. The main causes were retinal dystrophies and ROP, with 29 (24.2%) and 21 (17.5%) patients, respectively. A history of consanguinity was present in 48 patients (40%). Among these, the most common disease was retinal dystrophies (19 patients, 39.6%). The other common diseases were congenital eye anomalies and congenital glaucoma, with 7 (14.6%) and 6 (12.5%) patients, respectively. In addition, 24 patients (20%) had family history of visual impairment. The diagnoses of patients with family history and consanguinity were shown in Table 3.

Nineteen (15.8%) patients had associated neurological diseases. Fourteen (73.7%) had epilepsy, 2 (10.5%) mental retardation, 2 (10.5%) cerebral palsy, and 1 (5.3%) had craniofacial anomalies.

Deafness and speech disorders were other sensory disabilities accompanying visual impairment; 6 patients (5%) had speech disorders and 2 (1.7%) were also deaf.

Of all diseases related to visual impairment, 27.6% were avoidable whereas 72.4% were unavoidable. Forty-three patients (35.8%) were using spectacles before examination. Glasses were prescribed to an additional 28 patients after examination. Four patients (3.3%) were scheduled for surgery. These operations

**Table 1. Classification of visual impairment according to the 2010 World Health Organization definition**

| WHO category | Level of vision |
|---|---|
| Normal vision | 0.3≤ |
| Low vision | 0.05≤, <0.3 |
| Blindness | <0.05 |

WHO: World Health Organization

**Table 2. Distribution of the patients according to their visual acuities**

| Visual acuity | Patients, n (%) |
|---|---|
| Blindness (<0.05) | 95 (79.2%) |
| Low vision (≥0.05, <0.3) | 22 (18.4%) |
| Normal vision (≥0.3) | 1 (0.8%) |
| Unable to assess | 2 (1.6%) |

**Table 3. Causes of visual loss, numbers of consanguinity and family history in students attending to the school for students with visual impairment, in Ankara**

| Etiology of visual impairment | Patients, n (%) | Consanguinity, n (%) | Family history, n (%) |
|---|---|---|---|
| Retinal dystrophies | 29 (24.2) | 19 (39.6) | 9 (37.4) |
| Retinopathy of prematurity | 21 (17.5) | 5 (10.4) | - |
| Congenital eye anomalies | 17(14.2) | 7 (14.6) | 4 (16.7) |
| Congenital glaucoma | 14 (11.7) | 6 (12.5) | 4 (16.7) |
| Cortical blindness | 12 (10) | 1 (2.1) | - |
| Congenital cataract | 7 (5.8) | 3 (6.2) | 3 (12.5) |
| Albinism | 7 (5.8) | 2 (4.2) | 4 (16.7) |
| Other (refractive error, uveitis, etc.) | 13 (10.8) | 5 (10.4) | - |
| Total | 120 (100) | 48 (100) | 24 (100) |

were keratoplasty (2 patients), combined keratoplasty and lens extraction (1 patient) and strabismus surgery (1 patient); however, only 1 patient consented to the surgery. Bilateral keratoplasty was performed with the diagnosis of corneal dystrophy. In both eyes, VA was counting fingers before the surgery and increased to 0.1 (Snellen) after the surgery.

The visual acuities of 69 patients (57.5%) increased with low vision aids. Low vision aids used for near and far distances were electro-optical and telescopic systems. Of all 120 patients, 26 (21.7%) had an increase in VA with only electro-optical systems, while 43 (35.8%) used both electro-optical and telescopic systems. The types of telescopic systems used are shown in Tables 4 and 5.

Eight patients (6.6%) had improvement in VA with infrared and/or ultraviolet filter glasses (6 with albinism, 1 dyschromatopsia, 1 rod-cone dystrophy).

**Table 4. Telescopic systems used for far vision**

| Types of telescopic systems for far vision | Patients, n (%) |
|---|---|
| 4.2x Keplerian | 37 (30.8) |
| 2.5x Galilean - fix focus | 4 (3.3) |
| 6.0x Keplerian | 2 (1.7) |

**Table 5. Telescopic systems used for near vision**

| Types of telescopic systems for near vision | Patients, n (%) |
|---|---|
| 4.2x | 37 (30.8) |
| Bright field magnifiers 3x | 5 (4.2) |
| Spectacle clip-on magnifier | 1 (0.8) |

## Discussion

Childhood blindness accounts for about 4% of all blindness.[7] Scoring systems like the disability-adjusted life year can estimate the lifelong burden of a disease (http://wwwwhoint/healthinfo/statistics/GlobalDALYmethods_2000_2011pdf). Although childhood blindness seems to be rarer than adult blindness, it results in a similar or higher disability score than adult blindness, so prevention programs for childhood blindness and early diagnosis/treatment of these children are crucial for quality of life and improving visual and neurobehavioral development.

The WHO uses both an anatomical and etiological classification system for causes of childhood blindness[8] and these causes are also grouped as preventable, treatable, unpreventable and untreatable causes. The major preventable causes of childhood blindness are vitamin A deficiency, measles, ophthalmia neonatorum, and the harmful use of traditional eye care methods. The major treatable causes are cataract, ROP, and glaucoma.[9]

Both the prevalence and causes of childhood blindness vary according to the socioeconomic development of the countries. Three-quarters of blind children live in the poorest countries such as Africa and Asia.[10] The prevalences of childhood blindness in developed and developing countries are 0.3/1000 and 1.5/1000, respectively.[11] The main causes of childhood blindness are different in developed and undeveloped countries. While genetic and hereditary diseases seem to be the most frequent causes in developed countries, infectious/contagious diseases and nutritional deficiencies are the most common causes in undeveloped countries.[12]

According to the etiological classification, the main causes are corneal diseases and cataract in undeveloped countries, ROP in developing countries, neurological diseases in developed countries.[13]

Santos-Bueso et al.[12] evaluated the main causes of childhood blindness in a developed (Morocco) and an undeveloped (Ethiopia) country. Hereditary pathologies and refractive errors were the main causes in the Moroccan population, while corneal diseases and trauma were predominant in the Ethiopian population. Heijthuijsen et al.[14] showed that the main anatomical site of severe visual impairment and blindness was the retina (in 33.8% of cases) in the Republic of Suriname, a middle-income country.

One of the important avoidable causes of childhood blindness in developing countries is pediatric cataract. After controlling measles and vitamin A deficiency in developing countries, the number of childhood blindness due to cataract increased. The rate of lens blindness in different regions is estimated as 22% in Africa, 5.8% in the Americas, 13.2% in the Eastern Mediterranean, 15.2% in Europe, 13.6% in Southeast Asia, and 21.3% in the Western Pacific.[15] Aghaji et al.[16] evaluated

124 children with severe visual impairment and blindness in Southeast Nigeria. They found that the lens was the most common anatomical site of blindness (33.9%), 38.6% of cases were treatable, and 73.4% of all blindness was due to avoidable causes.

In the United Kingdom, the most common diseases were cortical visual impairment, retinal disorders such as ROP, and optic nerve disorders, with rates of 48%, 29%, and 28%, respectively.[17] Similarly, Kong et al.[15] determined that the 3 leading causes of childhood blindness in the United States were cortical visual impairment, optic nerve hypoplasia, and ROP, with rates of 18%, 15%, and 14%, respectively.

Various studies have described the results of childhood blindness in Europe.[18,19,20] In developed European countries, the leading causes were lesions of the central nervous system, congenital anomalies, and retinal disorders. In the middle-income countries of Europe, these causes were congenital cataract, glaucoma, and ROP.

There are many studies evaluating children with low vision and blindness in Turkey. Cetin et al.[21] found the rate of avoidable and preventable causes of childhood blindness as 69.4%. In contrast, other studies reported lower frequencies of preventable causes.[22,23,24] The main causes identified by Özen Tunay et al.[23] were hereditary macular dystrophy and cortical blindness, while Idil[22] determined the main causes to be hereditary macular degenerations, albinism, and optic atrophy, and hereditary pathologies were shown as the main causes of childhood blindness by Turan et al.[24] Our results were similar to these studies; the main causes were retinal dystrophies (24.2%), ROP (17.5%), and congenital eye anomalies (14.2%) in our study. Avoidable causes accounted for 27.6% of all cases. These findings are consistent with results in developed countries. Neonatal and early childhood ophthalmic screening tests performed by pediatricians, family practitioners, or ophthalmologists will help to diagnose avoidable diseases earlier, and early treatment will decrease the number of visually impaired children. In children with visual impairment due to delayed treatment or untreatable diseases, visual rehabilitation with low vision aids will increase visual acuity, and this improvement in vision will facilitate the education of these children.

Another important problem in Turkey is consanguinity; retinal dystrophies and congenital eye anomalies are more common in the Turkish population due to high consanguinity rates. The rate of consanguinity in blind children was found as high as 40%. Increasing public awareness about consanguinity may help to decrease the incidence of these diseases.

### Study Limitations

The main limitation of this study is the study population. In this study, we only evaluated the children going to the target schools. Most children with low vision or blindness do not have the chance to go to these schools, so this is not a community-based study. For this reason, more extensive studies involving children who cannot attend school should be undertaken.

## Conclusion

In our study population, most of the children achieved significant improvements in vision with rehabilitation, so attempting visual rehabilitation with low vision aids may give some of these children an opportunity to receive education with their peers without social isolation.

### Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from Ankara University.

Informed Consent: It was taken from the parents.

Peer-review: Externally peer-reviewed.

### Authorship Contributions

Concept: Aysun İdil, Huban Atilla, Ayşen Topalkara, Design: Aysun İdil, Huban Atilla, Ayşen Topalkara, Data Collection or Processing: Aysun İdil, Huban Atilla, Pınar Bingöl Kızıltunç, Cem Alay, Analysis or Interpretation: Aysun İdil, Huban Atilla, Pınar Bingöl Kızıltunç, Cem Alay, Literature Search: Pınar Bingöl Kızıltunç, Cem Alay, Ayşen Topalkara, Writing: Pınar Bingöl Kızıltunç, Aysun İdil, Huban Atilla.

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Review

# Biocompatibility of Intraocular Lenses

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**Abstract**
The performance of an intraocular lens is determined by several factors such as the surgical technique, surgical complications, intraocular lens biomaterial and design, and host reaction to the lens. The factor indicating the biocompatibility of an intraocular lens is the behavior of inflammatory and lens epithelial cells. Hence, the biocompatibility of intraocular lens materials is assessed in terms of uveal biocompatibility, based on the inflammatory foreign-body reaction of the eye against the implant, and in terms of capsular biocompatibility, determined by the relationship of the intraocular lens with residual lens epithelial cells within the capsular bag. Insufficient biocompatibility of intraocular lens materials may result in different clinical entities such as anterior capsule opacification, posterior capsule opacification, and lens epithelial cell ongrowth. Intraocular lenses are increasingly implanted much earlier in life in cases such as refractive lens exchange or pediatric intraocular lens implantation after congenital cataract surgery, and these lenses are expected to exhibit maximum performance for many decades. The materials used in intraocular lens manufacture should, therefore, ensure long-term uveal and capsular biocompatibility. In this article, we review the currently available materials used in the manufacture of intraocular lenses, especially with regard to their uveal and capsular biocompatibility, and discuss efforts to improve the biocompatibility of intraocular lenses.
**Keywords:** Uveal biocompatibility, capsular biocompatibility, cataract surgery, hydrophilic acrylic intraocular lens, hydrophobic acrylic intraocular lens

## Introduction

Biocompatibility is an important feature of intraocular lenses (IOL) which may influence their clinical performance in the short and long term. Biocompatibility may be broadly defined as the physical, chemical, and biological compatibility between a biomaterial and the body tissues, and the optimum compatibility of a biomaterial to the body's mechanical behavior. Ideally, a fully biocompatible IOL is expected to exhibit the following features: elicits no foreign-body reaction, is accepted by the surrounding tissues, has good compatibility with the capsular sac, and provides satisfactory vision over the lifetime of the patient without any further intervention. Although the most important determinant of biocompatibility is the implanted IOL, biocompatibility is also affected by characteristics of the host and the surgical technique. However, the main features involved in the biocompatibility of IOLs themselves are the lens material properties, the optic edge design, lens surface properties, and haptic-optic combination.

Although the biocompatibility of IOL lenses should be evaluated as a whole, the biological impact of an implanted IOL is at the uveal and capsular levels. Therefore, IOL biocompatibility is classified as uveal and capsular biocompatibility.[1] Uveal biocompatibility is determined by the inflammatory reaction to the IOL formed in the eye. Disruption of the blood-aqueous barrier during cataract surgery and IOL implantation results in a rapid inflow of protein and cells to the anterior chamber. The immediate consequence of this is protein deposition on the lens surface. This accumulation depends on the surface properties and chemical structure of the IOL material. Protein deposition on

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the IOL surface also facilitates the accumulation of other cells on the lens surface. Via activation of the compliment system, inflammatory cells are transformed into macrophage and giant cells, resulting in a foreign-body reaction against the IOL. This cellular response includes two different types of cells; the first are small, circular, fibroblast-like cells that peak in the first month, while the second are foreign-body giant cells that peak in the third month. The giant cells later degenerate and leave an acellular proteinous membrane on the IOL surface.[2] Uveal biocompatibility is evaluated based on the aqueous flare resulting from these pathophysiological events and the cellular deposition on the IOL.

Poly(methyl methacrylate) (PMMA) is the first intraocularly implemented IOL material. PMMA has important advantages including very good tissue tolerance, low foreign-body inflammatory response, high uveal biocompatibility, relatively higher refractive index, and good optical properties.[1] However, because of PMMA's intolerance to high temperature and pressure and its rigidity, foldable IOLs are currently preferred.

The foldable IOLs used today pose no problems with regard to uveal biocompatibility when evaluated clinically. In all of the previous studies in the literature, the levels of aqueous flare and cellular deposition on the IOL surface were not clinically significant, and these studies focused only on comparing IOLs being used. It has been reported that cellular accumulation on the IOL was not clinically significant even in uveitic eyes, where uveal reaction may be more pronounced, in diabetic patients, and in eyes with pseudoexfoliation syndrome.[3,4,5,6,7] Classifying the currently used foldable IOLs as hydrophobic and hydrophilic according to material properties revealed that hydrophilic IOLs have better uveal biocompatibility compared to hydrophobic ones.[8] The better tissue compatibility of hydrophilic materials is due to the high water content. In a study comparing aqueous flare caused by a hydrophobic IOL and a heparin-coated hydrophobic IOL over a 3-month follow-up period, no significant difference was found except on the first postoperative day.[9]

Foldable silicone lenses have hydrophobic surfaces. Silicone lenses offer an advantage in terms of uveal biocompatibility because of the very low levels of cellular deposition on the IOL surface.[10] In a study comparing hydrophilic, hydrophobic, and silicone IOLs, it was found that the amount of aqueous flare increased in all three types of IOL in the first month compared to preoperative levels; however, the amount of aqueous flare observed with the hydrophobic IOL was significantly higher than with the other types of IOLs. The authors reported that the amount of aqueous flare decreased after the first month and there was no significant difference among the IOLs during 18 months of follow-up.[6]

Early inflammatory cell deposition on the IOL is dominated by the small, circular cell type, which are an indicator of the blood-aqueous barrier disruption. The foreign-body giant cells which dominate later are an indicator of extended inflammation and are more responsible for uveal biocompatibility pathogenesis. Less inflammatory cell deposition occurs on hydrophilic IOLs compared to hydrophobic ones. It was found that accumulation of foreign-body giant cells predominates on hydrophobic IOLs, whereas accumulation of small circular cells is more prevalent on silicone IOLs. However, in long-term follow-up, it has been reported that there is no difference between IOLs with regard to cellular deposition.[4]

The pathogenesis of capsular biocompatibility involves proliferation and migration of lens epithelial cells. Lens epithelial cells form a single-cell lining beneath the anterior capsule and extend towards the equatorial lens curve. These cells exhibit mitotic activity, with maximum mitotic activity in the germinative zone encircling the pre-equatorial area of the anterior lens capsule. The newly formed cells proceed towards the equator, growing in volume and differentiating into a fibrillary structure. The epithelial cells located under the anterior capsule and those at the equator differ in function, growth pattern, and pathological processes. The lens epithelial cells under the anterior capsule do not proliferate, but rather exhibit fibrotic reaction. The cells in this area are the largest epithelial cells in the lens. The lens epithelial cells located on the equator tend to migrate along the posterior capsule in pathological cases and, instead of exhibiting fibrotic reaction, generally transform into large cellular structures called Elschnig pearls. Therefore, indicators considered in the clinical evaluation of IOL capsular biocompatibility are posterior capsule opacification resulting from the proliferation and migration of lens epithelial cells, anterior capsule opacification, or ongrowth of lens epithelial cells onto the anterior surface of the IOL.[11]

Posterior capsule opacification is the most common postoperative complication after successful cataract surgery and is the most important parameter of capsular biocompatibility. The development of posterior capsule opacification depends more on the optical edge design of the lens than on the IOL material. Studies have shown that a 360° sharp posterior optic edge significantly reduces posterior capsule opacification.[12,13,14,15] The sharp posterior edge creates a barrier that prevents the advancement of lens epithelial cells along the posterior capsule. A meta-analysis evaluating 66 prospective, randomized, controlled studies compared IOLs of the same material with sharp and rounded edge designs and revealed that IOLs with a sharp-edge design lead to less posterior capsule opacification.[16] In terms of IOL material characteristics, posterior capsule opacification occurs more frequently with hydrophilic compared to hydrophobic IOLs because a hydrophilic surface provides a foundation for lens epithelial cell proliferation and migration, whereas a hydrophobic surface adheres tightly to the posterior capsule due to its highly bioadhesive nature.[5,17,18,19,20,21] Another important cause of posterior capsule opacification in hydrophilic IOLs is that their high water content does not allow as sharp a posterior edge as can be achieved in hydrophilic IOLs.[22] Differentiation of lens epithelial cells from fibroblast-like cells causes opacification of the anterior capsule. This opacification is often clinically insignificant because it does not encroach on the optical axis. However, contraction of the capsulorhexis orifice as a result of fibrosis may cause IOL dislocation and associated refractive changes. With regard to material properties, the

reported rate of anterior capsule opacification is lower for hydrophilic acrylic lenses compared to hydrophobic acrylic lenses.[23] In terms of IOL optic edge design, it has been shown that contrary to posterior capsule opacification, a rounded or sharp posterior edge does not affect the degree of anterior capsule opacification.[24] On the other hand, it was reported that the angled haptic-optic junction leaves a clearance between the posterior capsule and the IOL optic, which influences posterior capsule opacification.[23] Although the removal of lens epithelial cells from under the anterior capsule during surgery could not be associated with the development of posterior capsular opacification, it has been shown to reduce anterior capsule opacification and contraction.[23,25]

The highly fibrotic reaction encountered in silicone IOLs is caused by lens epithelial cell proliferation being overstimulated by the silicone material. Dense fibrosis may result in posterior capsule opacification, anterior capsule opacification, and in some cases extreme fibrotic reaction which may cause IOL decentration.[11] In addition, contact between silicone lenses and intravitreal gases and silicone oil causes the lens to lose transparency.

Ongrowth of lens epithelial cells onto the IOL occurs as a result of the proliferation of lens epithelial cells from the capsulorhexis edge towards the anterior surface of the IOL. It usually does not lead to opacification or vision loss. It is mostly seen in hydrophilic acrylic lenses.[26,27]

In parallel to the recent technological developments in cataract surgery, there have also been important advancements in IOL technology. IOL innovations include efforts to increase patients' visual satisfaction, short- and long-term clinical performance, and IOL biocompatibility. Attempts to increase biocompatibility have often focused on modifying the surface or material properties of the IOLs.

Hybrid hydrophobic IOLs, developed by altering the properties of hydrophobic IOL material, have recently been introduced into clinical use. These hybrid hydrophobic IOLs are hydrophobic lenses that have a hydrophilic component. They have 4-5% water content and are stored in 0.9% saline solution. In a study comparing anterior capsule opacification scores in rabbit eyes with a hydrophobic IOL and a hybrid hydrophobic IOL over a 4-week follow-up period, a significantly lower anterior capsule opacification score was reported for the hybrid hydrophobic IOL.[28] An important feature of this class of IOLs is that they exhibit practically no glistening formation, which is a problem encountered in hydrophobic IOLs.[29] Glistenings are fluid-filled vacuoles within the IOL material. They are a consequence of the difference in refractive index that occurs when the crosslinks between hydrophobic IOL copolymers are filled with fluid. It usually does not affect visual acuity, but may have an impact on the quality of vision.[30] It is believed that hybrid hydrophobic IOLs prevent glistening formation because they have tighter crosslinks and their hydrophilic structure provides water balance in the IOL material.

Other work aimed at improving IOL biocompatibility focused on changing the IOL surface properties. Considering the fact that hydrophobic IOLs have good capsular biocompatibility and hydrophilic surfaces have good uveal biocompatibility, several molecules are being used to add hydrophilic surface properties to hydrophobic lenses. IOL surface properties are often provided by surface treatment, surface coating, and adding molecules to the surface. Heparin is clinically used as a surface-coating molecule to increase biocompatibility. In previous years, it was used in the surface coating of PMMA lenses in order to improve biocompatibility in uveitic, diabetic, and pediatric patients with greater likelihood of postoperative inflammation. Studies have demonstrated that PMMA with heparin surface modification reduces early postoperative inflammation.[31,32,33] Heparin surface coating gives the IOL surface a more hydrophilic character, thereby reducing inflammatory cell adhesion. Heparin coating of foldable hydrophobic IOL surfaces is also reported to effect changes in the clinical parameters of uveal biocompatibility.[9]

Various molecules have been used experimentally to imbue hydrophobic IOLs with hydrophilic surface properties. Polyethylene glycol is a molecule that increases uveal biocompatibility by reducing attractive forces between the lens surface and proteins.[34] In another study, the posterior surface of a hydrophobic IOL was coated with N-vinyl pyrrolidone, a hydrophilic monomer, in order to obtain a hydrophilic posterior surface, and it was reported that the hydrophilic posterior surface increased uveal biocompatibility while the hydrophobic anterior surface increased capsular biocompatibility.[35] Tissue growth factor beta-2 (TGF-β2) is an important factor in the stimulation of lens epithelial cells to form anterior capsule opacification. It was reported that a hydrophobic lens with anti-TGF-β2 surface modification both decreased lens epithelial cell ongrowth and increased lens surface hydrophilicity in experimental conditions.[36]

The biocompatibility features of IOL materials are summarized in Table 1 and the material properties of IOLs commonly used in Turkey are summarized in Table 2.

## Conclusion

Biocompatibility is an important property of an implanted IOL which reflects its long- and short-term clinical performance. With regard to IOL material properties, a sharp-edged anterior optic design and a hydrophobic surface are important for capsular biocompatibility, while a hydrophilic anterior surface is important for uveal biocompatibility. However, as the uveal biocompatibility of current foldable IOLs is not an important clinical problem even in the majority of eyes with higher risk of inflammation, it seems more clinically meaningful to prioritize capsular biocompatibility. While the material, surface properties, and optic design of IOLs are the main factors determining biocompatibility, other host and surgical factors should also be considered. Therefore, instead of choosing a single IOL with ideal biocompatibility for all patients, biocompatibility should be evaluated separately for each patient, also taking into account the nature of the planned surgery.

**Table 1. Comparison of the biocompatibility of intraocular lens materials**

| IOL Material | Advantage | Disadvantage |
|---|---|---|
| **Hydrophilic acrylic** | Higher tissue compatibility due to high water content<br>Low aqueous flare<br>Low rate of inflammatory cell accumulation on the lens surface | Insufficient posterior sharp-edged design due to the high water content<br>High rate of posterior capsule opacification<br>High rate of anterior capsule opacification<br>Greater lens epithelial cell ongrowth on the lens surface |
| **Hydrophobic acrylic** | Material compatible with a posterior sharp-edged design<br>Low rate of posterior capsule opacification<br>Low rate of anterior capsule opacification<br>Low rate of lens epithelial cell ongrowth on the lens surface | High aqueous flare*<br>Inflammatory cell accumulation on the lens surface* |
| **PMMA** | Good tissue compatibility<br>Low aqueous flare<br>Low rate of inflammatory cell accumulation on the lens surface | Foldable<br>High rate of posterior capsule opacification |
| **Silicone** | Low rate of inflammatory cell accumulation on the lens surface<br>Low rate of posterior capsule opacification | Increased fibrotic reaction due to lens epithelial cell stimulation<br>Lens surface opacification due to contact with intravitreal air<br>Difficulty visualizing the retina due to interface formed with silicone oil used in vitreoretinal surgery |

*Not at a clinically significant level
PMMA: Poly(methylmethacrylate), IOL: Intraocular lenses

**Table 2. Intraocular lenses commonly used in Turkey and their commercial names***

| Intraocular lens material | Commercial product name | Manufacturer |
|---|---|---|
| ***Hydrophobic acrylic*** | Sensar | Abbott Medical Optics, USA |
| | Tecnis® | Abbott Medical Optics, USA |
| | Acrysof IQ | Alcon Lab, USA |
| | Akreos | Bausch&Lomb, USA |
| | enVista | Bausch&Lomb, USA |
| | Eyecryl ASHF | Biotech, India |
| | Aktis SP | Nidek, Japan |
| | Nex-Acri™ | Nidek, Japan |
| | Focus Force | Zaraccom, Turkey |
| | Domilens | Zaraccom, Turkey |
| ***Hydrophilic acrylic*** | Eyecryl EYC600 | Biotech, India |
| | Lentis$^{\beta}$ | Oculentis, Germany |
| | C-flex® | Rayner, England |
| | Superflex® | Rayner, England |
| | Acriva$^{UD\,\beta}$ | VSY, Turkey |
| | Ocuva | VSY, Turkey |
| | CT ASPHINA$^{\beta}$ | Zeiss, Germany |
| ***PMMA*** | Biovision | Biotech, India |
| | Optima Edge | Biotech, India |
| | Freedomlens™ | Freedom, India |
| | Ecomed | Omnilens, India |
| | USIOL | USIOL, USA |
| | LiteFit | Visiontech, USA |
| | Focus Force | Zaraccom, Turkey |

Intraocular lenses are listed in alphabetical order by manufacturer in each section
$^{\beta}$: Hydrophobic surface properties, PMMA: Poly(methylmethacrylate)

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**Authorship Contributions**
Concept: Pelin Özyol, Design: Pelin Özyol, Erhan Özyol, Fatih Karel, Data Collection or Processing: Pelin Özyol, Erhan Özyol, Analysis or Interpretation: Pelin Özyol, Erhan Özyol, Fatih Karel, Literature Search: Pelin Özyol, Erhan Özyol, Writing: Pelin Özyol.

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Case Report

# Eyelid Molluscum Contagiosum Lesions in Two Patients with Unilateral Chronic Conjunctivitis

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**Abstract**
Molluscum contagiosum (MC) is a viral infection of the skin and mucosal tissues characterized by skin-colored or transparent round nodules with a dimple or pit in the center. The infection is caused by a DNA poxvirus called the MC virus. Although MC generally occurs in children, it has also been reported in immunocompromised and atopic patients. The virus is transmitted by skin contact or sexual intercourse. The lesions disappear spontaneously within several months in most cases. However, excision, cryotherapy, cauterization, topical chemical and antiviral agents, and/or oral cimetidine are used in refractory cases or to accelerate the healing process. Herein, we discussed the clinical findings and our treatment of two patients with unilateral chronic conjunctivitis associated with eyelid MC lesions in light of the literature.
**Keywords:** Molluscum contagiosum, eyelid lesions, chronic conjunctivitis

## Introduction

Molluscum contagiosum (MC) is characterized by papular lesions in the skin and mucous membranes caused by the *Molluscum contagiosum* virus, a DNA virus from the poxvirus group.[1,2] Humans are the only known host. The virus is transmitted through skin contact and sexual intercourse. It is particularly common in hot, developing countries and in communities with poor personal hygiene.[1,2,3,4] Signs of MC infection have been reported in about 4.5% of children under 10 years old. In developed countries, infections are sometimes acquired from swimming pools, saunas, and sports centers. In addition, it can also be seen in immunosuppressed patients (e.g. with AIDS or using drugs such as corticosteroids, TNF-α antibodies, and methotrexate), and in patients with atopic dermatitis, sarcoidosis, and Wiskott-Aldrich syndrome.[5,6,7,8] Diagnosis is usually based on clinical findings, and histopathological examination and laboratory tests are often not necessary.

The lesions, located on the skin and mucosa, typically appear as small (between about 2-6 mm), raised, flesh-colored or clear papules and there is pearly white caseous material in the pitted center.[1,2,3,9] The papular lesions, usually found in clusters, are often seen on the face, head, torso, and extremities in children, and in the genital area, lower abdomen, and upper legs in young adults in whom the infection is sexually transmitted.

Ophthalmic MC lesions are often located on the eyelids.[1,2,8,9,10] Viral proteins shed from the lid lesions into the tear film can lead to a hypersensitivity reaction with secondary chronic follicular reaction, punctate keratopathy in the conjunctiva, and in some cases subepithelial opacities and pannus. Rarely, primary MC lesions are seen in the conjunctiva and cornea. While the lesions usually resolve spontaneously within a few months, treatments such as excision, incision and curettage, cryotherapy, cauterization, topical chemical agents, and oral cimetidine can be used in refractory cases and to speed up the healing process.[1,11,12,13,14]

In this case report, the clinical findings and treatment of two patients who were admitted with unilateral chronic conjunctivitis and were found to have eyelid MC lesions are discussed in light of the literature.

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## Case Reports

### Case 1

A 5-year-old female patient who had raised lesions on her right eyelid for about 3 months and complaints of redness and watering in her right eye was admitted to our clinic. It was learned that she had previously been seen by three different ophthalmologists and had been treated with topical ofloxacin (Exocin® 4 times daily), olopatadine HCl (Patanol® 2 times daily), and dexamethasone sodium phosphate (Dexa-sine® 3 times daily) for 2 months. Visual acuity measured with E chart was 20/20 in both eyes. Intraocular pressure (IOP) was 12 mmHg in both eyes. On anterior segment examination, 2 pitted papular lesions were detected on the right upper eyelid 2 mm from the lash line and a similar lesion was noted 5 mm from the lash line on the lateral aspect of the lid (Figure 1A). The conjunctiva was hyperemic and there was intense follicular reaction in the lower fornix (Figure 1B). Suspecting MC, the existing treatment was discontinued and topical ganciclovir (Virgan® gel 3 times daily), lubricant treatment (Tears Naturale Free® drops 5 times daily), and eyelash cleansing were recommended. Complete blood count and immunoglobulin levels were normal. The family was informed that the lesions may spontaneously regress, and would be surgically excised if they did not. We observed in follow-up examination 1 month later that the lesions and symptoms had not regressed, so the papular lesions were excised preserving the integrity of the cyst wall and cryotherapy was applied to the base of the lesions. The detection of inclusion bodies in the material sent to pathology confirmed a diagnosis of MC (Figure 1C, 1D). The patient was treated postoperatively with topical moxifloxacin (Vigamox®) drops 5 times daily for 2 weeks and lubricant eye drops (Tears Naturale Free® 5 times daily). At 1-month follow-up, the lid lesions had disappeared and the follicular reaction was reduced. The patient remains under follow-up and no recurrence has been seen for 6 months (Figure 1E, 1F).

### Case 2

A 24-year-old female patient presented to our clinic with complaints of swelling of the right upper eyelid and redness in the eye for 2 months. Her visual acuity was 20/20 in both eyes and IOP was 14 mmHg. On anterior segment examination, there was a pitted papular lesion 2x2 mm in size on the medial aspect of the right upper eyelid at a distance of 4 mm from the lash line, and another small papule just below the eyebrow (Figure 2A). There was conjunctival hyperemia in the right eye and a mild to moderate degree of follicular reaction in the conjunctiva (Figure 2B). Serological tests for HIV and hepatitis A, B, and C viruses were negative. Immunoglobulin levels and lymphocyte subtype values were within normal limits. To reduce the viral load in the patient's eye, a half-strength dilution of betadine (5%) was instilled and washed out after 30 seconds. Treatment was initiated with topical moxifloxacin (Vigamox® drops 3 times daily), topical ganciclovir (Virgan® gel twice daily), and lubricant therapy (Tears Naturale Free® drops 5 times daily).

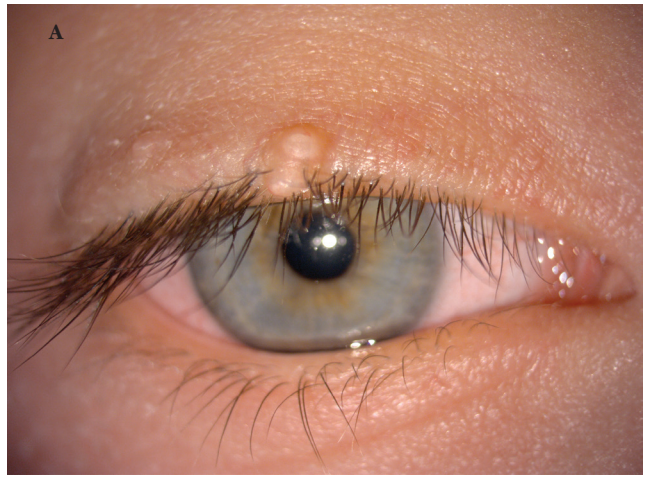



**Figure 1A.** Image of patient 1 showing 2 pitted papular lesions situated 2 mm from the lash line of the right upper lid and a similar lesion 5 mm from the lash line on the lateral aspect of the lid

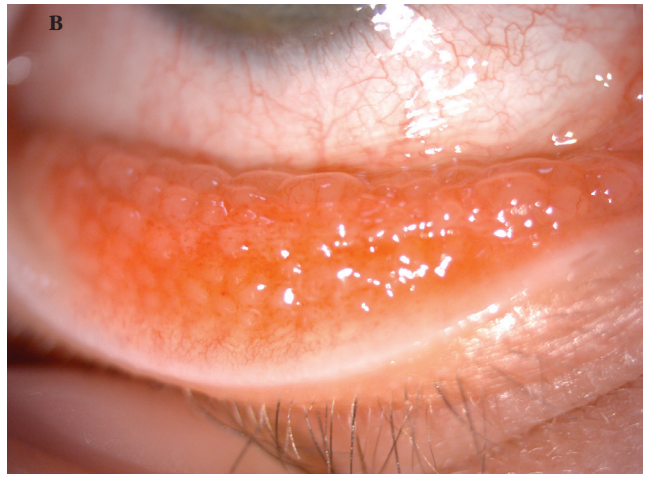



**Figure 1B.** Image of patient 1 showing conjunctival hyperemia and intense follicular reaction at the lower fornix

Follow-up examination 3 weeks later showed that the lesion and ocular symptoms had not regressed, so the larger papule was excised preserving the integrity of the cyst wall and cryotherapy was applied to the base of the lesion. Cryotherapy was applied directly to the smaller papule. Histopathological examination revealed inclusion bodies (Figure 2B). At postoperative 1 month follow-up, the lid lesions had disappeared and the conjunctival follicular reaction was reduced (Figure 2D, 2E). Follow-up is ongoing and no recurrence has been observed for approximately 5 months.

## Discussion

Ocular involvement of MC presents with round, small, hard papules on the eyelids. The virus proliferates in epithelial cells. After the lesions reach about 3-5 mm in diameter, a central depression forms due to the cellular damage mechanism and

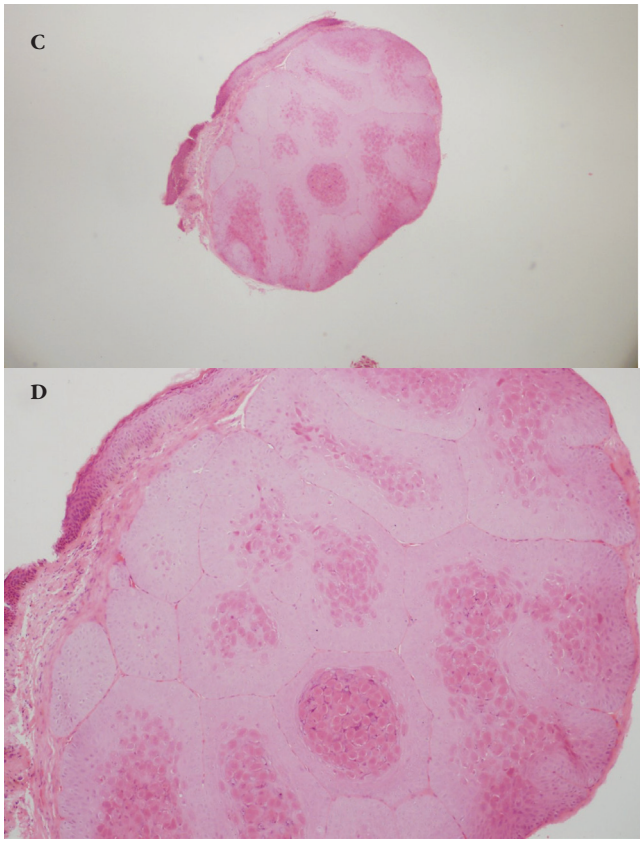



**Figure 1C, 1D.** Pathological specimen showing excised papule and eosinophilic intracytoplasmic viral inclusion bodies (hematoxylin & eosin, x20 and x100)

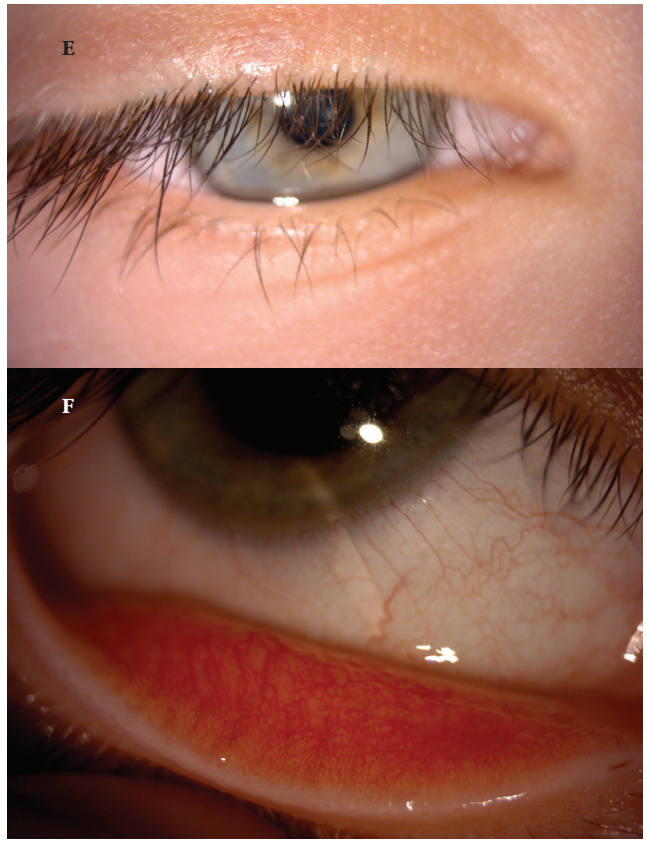



**Figure 1E, 1F.** Postoperative images of patient 1 show the eyelid lesion has disappeared and the follicular reaction in the conjunctiva has completely regressed

they typically develop the appearance of whitish lesions filled with caseous material and having a dimple or pit in the center.[1,2]

Although the diagnosis is made clinically when these characteristic MC lesions are evident on the lids, half of patients cannot be diagnosed at the first examination. Both of our patients presented with a 2- to 3-month history of red eye and lid edema. The first case had previously seen several ophthalmologists, but the lid lesions were overlooked and her condition had been treated as infectious conjunctivitis. Charteris et al.[2] examined the clinical and immunopathologic features of 35 MC cases and found that only 60% of the patients were diagnosed at the time of initial presentation. Histopathologic sections showed increased numbers of T lymphocyte cells and macrophages in the epidermis and dermis around the molluscum lesion.

In recent years, the increased incidence of MC among adults has been associated with AIDS.[1,2,5,6] HIV-related lesions are usually numerous and at least 5 mm in size. They respond poorly to treatment and recurrence is common. Blood testing of our patients revealed no significant systemic pathology or immunodeficiency.

The differential diagnosis of lid lesions can include basal cell carcinoma, papilloma, chalazion, sebaceous cyst, keratoacanthoma, blepharitis, wart, eczema, obstructed nasolacrimal duct, and ectropion. However, the typical

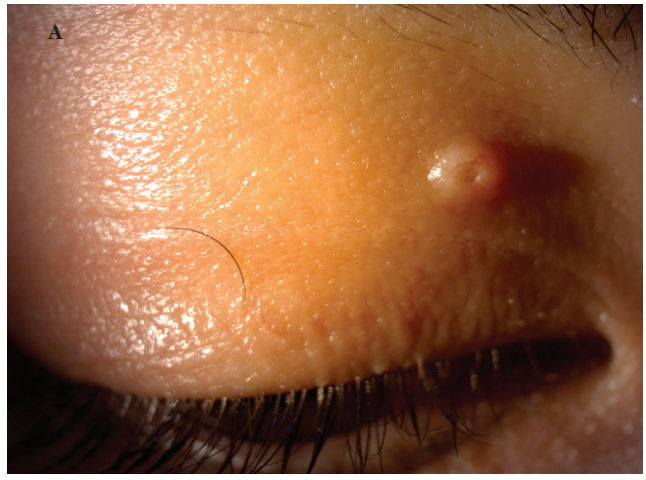



**Figure 2A.** Image of patient 2 showing a pitted papular lesion 2x2 mm in size situated 4 mm from the lash line on the medial aspect of the right upper eyelid

appearance of papular lesions is consistent with MC. Allergic, bacterial, viral, and chlamydial conjunctivitis may be considered in the differential diagnosis of the follicular reaction in patients with conjunctival involvement. For patients with corneal pannus, it may be necessary to rule out chlamydia and rosacea keratitis in the differential diagnosis.

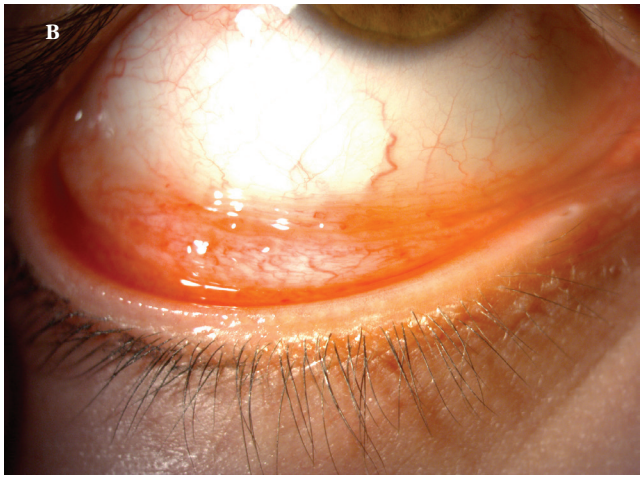



**Figure 2B.** Image of patient 2 showing conjunctival hyperemia and mild to moderate follicular reaction in the tarsal conjunctiva

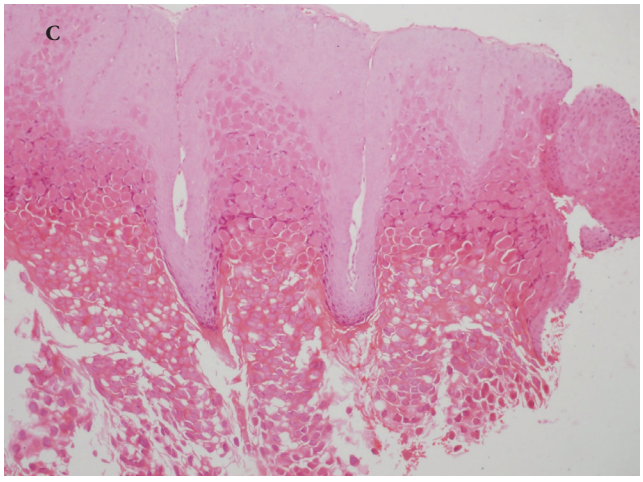
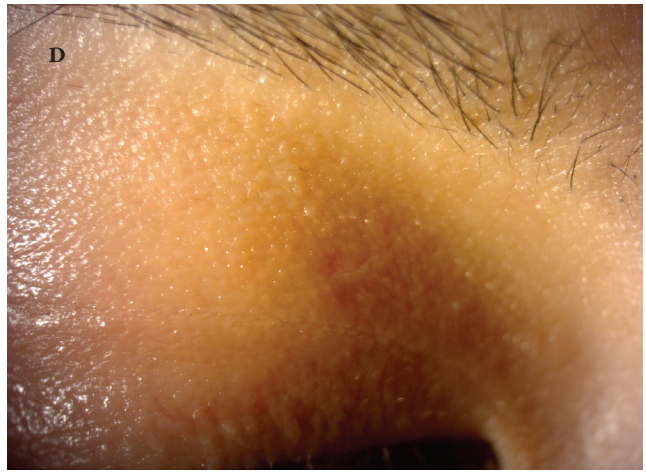



**Figure 2C.** Eosinophilic inclusion bodies are observed in the cytoplasm of squamous cells in the stratum granulosum layer (hematoxylin&eosin, x100)

Chlamydial conjunctivitis is defined as inclusion conjunctivitis occurring in adulthood. Ocular involvement may occur in 0.3-2% of patients with urogenital manifestation.[15] Ocular findings emerge within 5-14 days after contagion. Follicular response appears in the lower fornix and palpebral conjunctiva. In chlamydial infection, history and clinical findings facilitate diagnosis, and treatment is systemic.[15]

Although MC resolves spontaneously within months in healthy, immunocompetent individuals, it requires treatment in refractory cases.[1] It should be kept in mind that progressive corneal neovascularization and scarring may develop, especially in patients with chronic conjunctivitis and corneal involvement. Conjunctivitis and keratitis show rapid improvement after skin lesions are eradicated. There is no known antiviral treatment specific for MC. While topical ganciclovir is approved for use in acute herpetic keratitis, its efficacy has also been demonstrated against cytomegalovirus and some strains of adenovirus, while



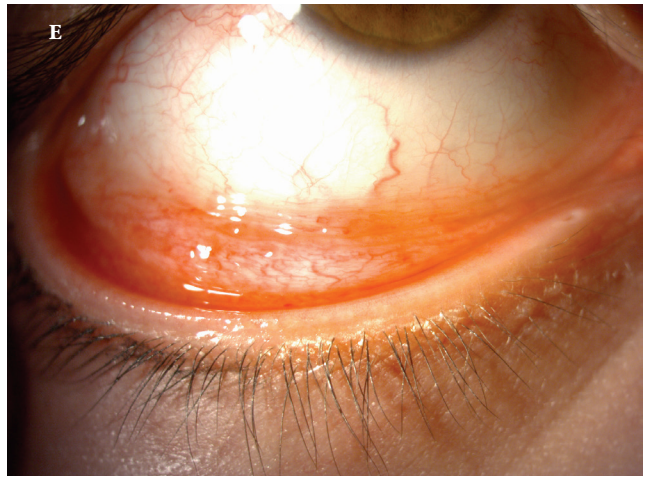




**Figure 2D, 2E.** Postoperative images of patient 2 show the lesion on the eyelid has disappeared and the follicular reaction in the conjunctiva is decreased

systemic administration of ganciclovir is effective against HIV.[16] Although there are no previous studies showing that topical ganciclovir is effective against MC, we initially administered it to both of our patients considering its broad-spectrum antiviral activity, but no improvement was achieved.

Surgical techniques include cryotherapy with liquid nitrogen, cauterization, needle aspiration, photodynamic therapy, and various laser therapies.[1,11,12,13,14] Silver nitrate, phenol, and trichloracetic acid are used as chemical agents, while treatment options for immunocompromised patients with refractory lesions include topical cidofovir (5%), intralesional or systemic interferon, imiquimod cream (5%), salicylic acid, glycolic acid, tretinoin, tazarotene, 5% sodium nitrate, podophyllotoxin, liquefied phenol, cantharidin, potassium hydroxide, 1% adenine cream, and oral cimetidine. Eyelid scarring, depigmentation, and eyelash loss may occur after these treatments. Karabulut et al.[11] reported dramatic improvement in dense eyelid lesions with only physical drainage in an immunocompetent pediatric patient with MC. Weller et al.[14] compared esthetic appearance after chemical ablation with phenol versus emptying the lesion by squeezing and reported that although there was no

significant difference, phenol treatment caused more scarring. In our cases, we demonstrate that surgical excision of the papules and cryotherapy applied to their bases and margins resulted in complete disappearance of the lesions with no scarring or recurrences within the 6-month follow-up period, and the chronic conjunctivitis also resolved completely.

**Ethics**

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Banu Bozkurt, Şansal Gedik, Concept: Banu Bozkurt, Design: Banu Bozkurt, Şule Serin, Data Collection and Processing: Şule Serin, Ayşe Bozkurt Oflaz, Analysis and Interpretation: Banu Bozkurt, Pınar Karabağlı, Şansal Gedik, Literature Search: Şule Serin, Ayşe Bozkurt Oflaz, Writing: Şule Serin, Ayşe Bozkurt Oflaz, Banu Bozkurt.

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

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Case Report

# Evaluation of Iris Melanoma with Anterior Segment Optical Coherence Tomography

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**Abstract**

Anterior segment optical coherence tomography (AS-OCT) is a relatively new imaging modality that allows assessment of anterior segment structures. AS-OCT enables the differentiation of benign and malignant tumors through the evaluation of lesion size, internal structure, degree of vascularity, and anterior and posterior surfaces. Herein, we discuss the AS-OCT findings of a patient with spindle type iridociliary melanoma diagnosed in pathologic examination.

**Keywords:** Iris, melanoma, optical, coherence, tomography

## Introduction

Uveal melanomas are the most common primary intraocular malignancy in adults, and iris melanomas account for 3-10% of uveal melanomas.[1] Iris melanoma, the most common malignancy of the iris, originates from the melanocytes of the iris stroma and its prognosis is better than that of choroid and ciliary body melanomas. With the examination techniques currently available, the diagnosis of uveal melanomas has reached 99%.[2] Uveal melanoma differs in this respect from other systemic cancers, for which biopsy is the diagnostic gold standard. Slit-lamp examination, transillumination, digital photography, A-scan ultrasonography, B-scan ultrasonography (USB), ultrasonic biomicroscopy (UBM), fluorescein and indocyanine green angiography, and anterior segment optical coherence tomography (AS-OCT) are methods utilized in diagnosis.

Using anterior segment imaging methods to visualize lesion features such as location and thickness and to determine whether lesions are solid or cystic, limited to the iris or involve the ciliary body are important for diagnosis and treatment planning in patients with iris or iridociliary lesions. One of these methods, AS-OCT, enables the acquisition of cross-sectional images of the tissues with low coherence interferometry.

Evaluation of the anterior segment with OCT was first performed in 1994 by Izatt et al.[3] AS-OCT (developed from retinal OCT, which acquires images using 830 nm wavelength light[3]) is a noncontact method that provides high-resolution anterior segment images using 1310 nm wavelength light.[4] In this report, we share a case in which an iris mass was detected in routine eye examination, partial lamellar sclerouvectomy (PLSU) was planned following AS-OCT imaging, and a diagnosis of malignant melanoma was histopathologically confirmed.

## Case Report

A 56-year-old female patient presented to our clinic with complaints of decreased vision in both eyes for the past several months. Her best visual acuity was 3/10 in the right eye and 4/10 in the left eye. Biomicroscopic examination revealed no pathology other than nuclear cataract in the right eye. In the iris of the left eye, a hyperpigmented mass approximately 4x2.5x1.5 mm in size was observed situated between 14:30-15:30 clock hours and extending to the iris root and anterior chamber (Figure 1).

Secondary cataract was present in the left eye; intraocular pressure measured by Goldmann applanation tonometer was 13 mmHg in both eyes and fundus examination was normal in both eyes. Further inquiry into the patient's history revealed that she

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had been aware of the iris spot since childhood but had never consulted an institution or doctor because she did not consider it important. There was nothing remarkable in her personal or family histories.

AS-OCT (Visante OCT/Zeiss) examination revealed that the mass was 2.30x1.32 mm in size, was raised with distinct borders and a smooth anterior surface, was solid and heterogeneous (with a vascular component), and extended to the ciliary body. While the anterior surface of the mass was defined by high reflectivity, the posterior surface boundaries could not be distinguished (Figure 2A, 2B). Based on the biomicroscopy and AS-OCT findings, a prediagnosis of malignant melanoma was made and iridogoniocyclectomy through PLSU was planned. Under hypotensive general anesthesia, surgery was placing the patient in reverse Trendelenburg position. Intraoperative transillumination to determine the location of the tumor showed that it did not extend beyond the pars plana region, and iridogoniocyclectomy was performed via PLSU. The tumor was excised with wide surgical margins and was sent to pathology. There were no intraoperative or postoperative complications. Postoperative examination revealed no residual mass (Figures 3, 4). Histopathological diagnosis was reported as mixed spindle A and B type melanoma. The patient was followed without additional treatment and no recurrence was detected during 23 months of follow-up. Phacoemulsification with posterior chamber intraocular lens implantation was performed on the left eye in the postoperative 12th month due to cataract. After 22 months of follow-up, the patient later developed rhegmatogenous retinal detachment and underwent a pars plana vitrectomy with silicone tamponade. The patient was in stable clinical condition at 1-month follow-up after vitreoretinal surgery.

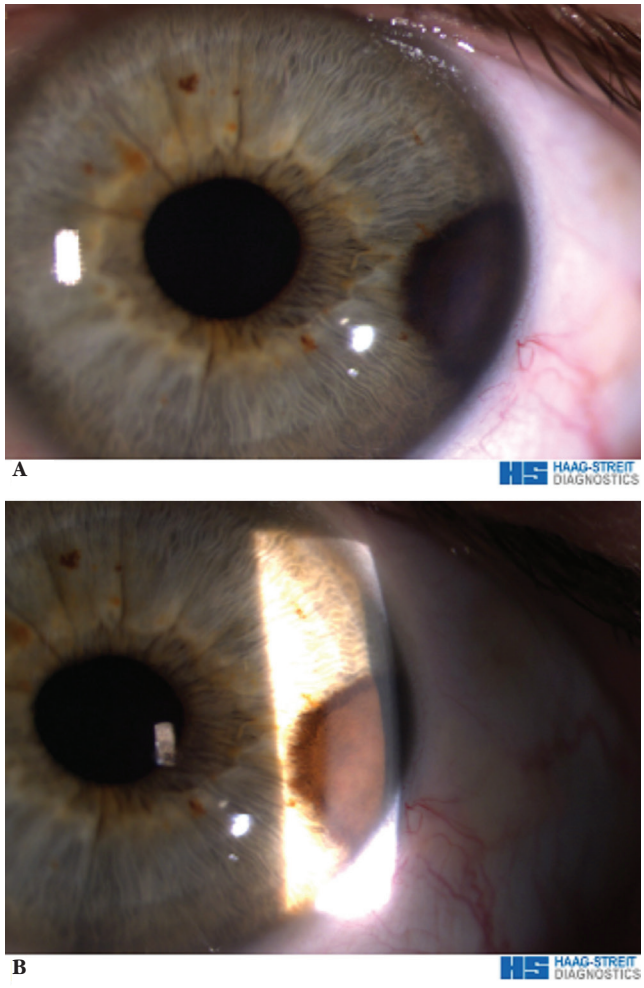


**Figure 1.** A) A raised brown mass extending to the iris root is visible on the peripheral iris surface between the 14:30-15:30 clock hours. B) Biomicroscopic view of the mass

## Discussion

In iris melanomas, the most common symptoms at admission are a blotch or color change in the iris. Iris melanomas can vary in appearance, ranging from amelanotic to brown, and are usually located in the lower half of the iris. They usually grow locally on the surface of the iris or toward the anterior chamber, though they can also extend toward the anterior chamber angle or the ciliary body.

Findings that suggest iris melanoma include vascularization of a mass on the surface of the iris, retraction of the pupil toward the lesion, a mass surface that is uneven and nodular instead of homogenous, invasion of the iridocorneal angle, and pigment covering the trabecular meshwork.[5]

Transillumination, anterior segment photographs, USB, UBM, AS-OCT, and fluorescein and indocyanine green

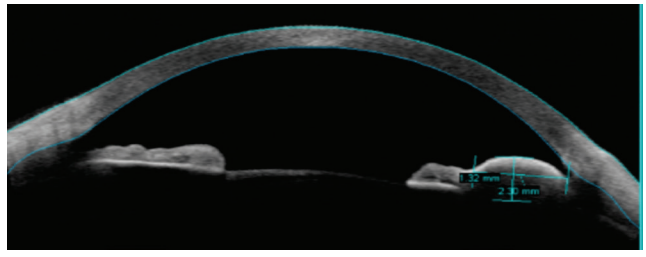

**Figure 2A.** An iris mass measuring 2.30x1.32 mm extending to the angle is observed on anterior segment optical coherence tomography. The anterior aspect of the mass appears highly reflective (enhanced anterior segment single)

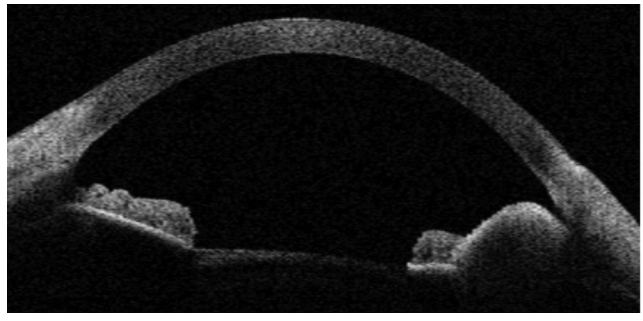

**Figure 2B.** Shadowing is observed in anterior segment optical coherence tomography due to poor visibility of the posterior surface of iris (raw image mode)


**Figure 3.** Postoperative anterior segment photograph of the patient. A) Iris coloboma developed postoperatively. B) Biomicroscopy image

angiography are utilized to visualize the anterior segment. UBM provides valuable information about the anterior segment because it has high penetration strength, can demonstrate extension to the ciliary body, is unaffected by pigmentation, and allows clear imaging of a tumor's posterior margin. Marigo et al.[6] used UBM to determine lesion size, internal structure, and extension toward the ciliary body or surrounding tissues and compared these findings with the lesions' histopathologic appearance after excision. They found that there was similarity between UBM findings and histopathological findings.

AS-OCT is an imaging technique used in different areas of ophthalmology such as cornea, refractive surgery, glaucoma, and ocular tumors, and its use has steadily increased over the last 10-20 years. AS-OCT provides high-resolution cross-sectional images without contact with the eye.[7]

The instrument can acquire a 256 A-Scan low-resolution image in 125 ms or 512 A-Scan high-resolution image in 250 ms. Thus, the resolution can be approximately 18 µm axial with 3-6 mm depth of penetration, and it is used in the

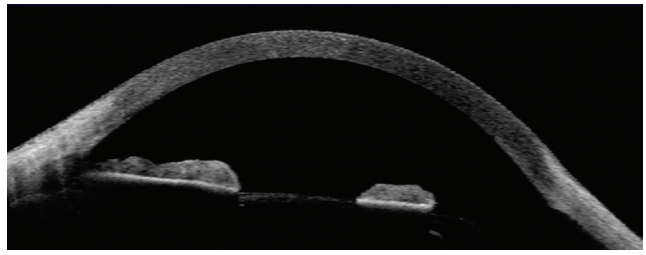

**Figure 4.** The iris periphery does not appear on postoperative anterior segment optical coherence tomography due to the surgery (enhanced anterior segment single). There is no residual mass

imaging of many pathological conditions such as iris cysts, iris nevi, and iris/ciliary body melanomas. There are many studies comparing AS-OCT with other anterior segment imaging methods. Pavlin et al.[8] demonstrated that AS-OCT is useful in small hypopigmented tumors limited to the iris but that UBM is superior to AS-OCT in imaging highly pigmented and ciliary body tumors due to its high tissue penetration.

Hau et al.[9] compared USB with AS-OCT in the examination of 126 eyes with iris or iridociliary body lesions. They demonstrated that the axial resolution was higher in AS-OCT compared to USB and that AS-OCT was superior in visualizing lesions involving the lateral and anterior aspects of the iris.

In contrast, they demonstrated that USB is superior in showing tumor configuration and internal structure in pigmented iris melanomas or lesions extending posteriorly because sound waves provide better penetration into pigmented lesions than light energy.

In AS-OCT images, reflectivity is correlated with the degree of tissue pigmentation. In a normal iris, the stroma is moderately reflective and the anterior surface is highly reflective. The iris pigment epithelium forms a highly reflective border on the posterior surface of the iris. Melanotic lesions show greater reflectivity on AS-OCT, while the reflectivity of amelanotic lesions is equal to or lower than that of the stroma. In one study, it was observed that iris nevi show high reflectivity, while iris melanomas contained areas of varying degrees of reflectivity dispersed throughout the thickness of the mass.[10] In the same study, it was reported that AS-OCT, especially in high-resolution mode, provided information comparable to UBM about lesion location, internal structure, and extension to the anterior chamber. Iris nevi and melanomas show low-to-moderate reflectivity on UBM, independent of the degree of pigmentation.[11]

In our case, the base diameter of the lesion was measured as 2.30 mm and its thickness as 1.32 mm with anterior segment OCT. The internal structure of the lesion appeared heterogeneous due to the vascular component and the posterior border of the pigmented lesion was not distinguishable. It has been stated in earlier studies that a melanotic lesion of the iris that has a diameter greater than 3 mm and a thickness greater than 1 mm or shows documented growth during follow-up may be interpreted as malignancy.[12,13,14] Small and slow-growing melanomas can be

monitored, but surgery is indicated for iridociliary melanomas that shed pigment on surrounding tissues, have pronounced vascularity, and increase in thickness and size.[15,16] Without the need for further imaging, a prediagnosis of melanoma was made and surgery was planned based on the clinical presentation and AS-OCT findings regarding the size, internal structure, and extension of the lesion. AS-OCT utilizing 1310 nm wavelength light for image acquisition has less tissue penetration than UBM, but provides higher image resolution. For this reason, it is more useful in the evaluation of superficial lesions located in the anterior aspect of the iris.

Most ophthalmology clinics use USB or AS-OCT more than UBM. However, the resolution of AS-OCT is reduced in large, densely pigmented lesions that extend to the ciliary body and cause shadowing.

In summary, AS-OCT is a noninvasive, convenient, high-resolution imaging modality which is useful in the preliminary diagnosis stage of iris or angle masses with no marked ciliary body involvement.

**Ethics**

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Concept: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Design: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Data Collection or Processing: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Özlenen Ömür Gündüz, Analysis or Interpretation: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Literature Search: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz, Writing: Mehtap Arslantürk Eren, Ahmet Kaan Gündüz.

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Case Report

# Mantle Cell Lymphoma Presenting with Acute Bilateral Ophthalmoplegia

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**Abstract**
A 72-year-old woman presented with acute onset of double vision, bilateral complete blepharoptosis, and nearly complete ophthalmoplegia. Orbital and brain magnetic resonance imaging were normal. Further investigation revealed bicytopenia with hepatosplenomegaly. Liver biopsy revealed mantle cell lymphoma. Cytology later showed the presence of mantle cells in cerebrospinal fluid analysis. Her ophthalmoplegia improved from her first cycle of systemic and intrathecal chemotherapy. To the best of our knowledge, this is the second case in the literature of mantle cell lymphoma with central nervous system involvement presenting with ophthalmoplegia. This symptom should be considered one of the initial signs of mantle cell lymphoma.
**Keywords:** Mantle cell lymphoma, ophthalmoplegia, blepharoptosis

## Introduction

Mantle cell lymphoma (MCL) comprises 5% of non-Hodgkin lymphoma. In general, patients are typically Caucasian (about 2:1), male (about 2.5:1), and elderly (median age of onset, 68 years), and they usually present with extensive disease, including widespread lymphadenopathy, bone marrow involvement, splenomegaly, circulating tumor cells, and bowel infiltration.[1] Central nervous system (CNS) involvement is an unusual form of extranodal involvement in the course of MCL. We present a rare case of MCL with CNS involvement with ophthalmoplegia and negative imaging studies. To the best of our knowledge, this is the second reported case in the literature.

## Case Report

A 72-year-old woman presented with a 1-week history of progressive blepharoptosis and diplopia. On examination, she had bilateral complete blepharoptosis and right exotropia in primary gaze position. There was nearly complete ophthalmoplegia in both eyes except minimal abduction (Figure 1). The right pupil was 2 mm and reacted sluggishly to direct light. The left pupil was 4 mm and nonreactive. Assessment of motility revealed noticeable underaction of both superior oblique muscles. Corneal sensation was intact bilaterally. Visual acuity was 20/20 in both eyes. All other aspects of the ophthalmologic and neurologic examinations were normal. Orbital and cranial computerized tomography were also normal. Her past medical history and family history were unremarkable.

Following an evident loss of weight estimated to be about five kilograms in three months, the attending physician requested a blood test which revealed deterioration in the liver function tests and bicytopenia. Computerized tomography scan of the chest, abdomen, and pelvis revealed hepatosplenomegaly. There were interstitial changes in the lung bases along with left pleural effusion. There was no lymphadenopathy. A magnetic resonance imaging (MRI) study of the brain was unremarkable.

The liver biopsy revealed diffuse infiltration by a MCL (CD20+, CD5+ and cycline D1+). She was then referred to the hematology department.

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CNS invasion of MCL was suspected on the basis of clinical features, but no abnormalities were detected in serial contrast-enhanced MRI studies. Lumbar puncture revealed normal opening pressure and showed exaggerated lymphocytic pleocytosis, a protein level of 174 mg/dL, and glucose level of 51 mg/dL. Cytology later showed the presence of mantle cells in cerebrospinal fluid analysis. Combined systemic and intrathecal chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) was administered for eight cycles in parallel with intrathecal injections of methotrexate and cytarabine. After the first cycle, her ophthalmoplegia and blepharoptosis improved. Recurrent ophthalmoplegia and blepharoptosis were not observed during the treatment process. The patient was followed by the internal medicine department and was referred to a tertiary cancer center for further treatment.

## Discussion

MCL is a very aggressive subtype of non-Hodgkin lymphoma and is unique among lymphomas in its clinical, biologic, and genetic properties. Nearly 70% of cases are diagnosed in advanced stages of the disease and most cases exhibit a relatively aggressive course. Median life expectancy ranges from 3 to 7 years. Because of its unresponsiveness to medical treatment as well as its aggressive nature, MCL is generally considered incurable.[2]

MCL usually involves the lymph nodes, spleen, and bone marrow. Extranodal involvement is often seen in the gastrointestinal tract and Waldeyer's ring. In most cases, the abovementioned organs are diffusely involved and the disease is generally diagnosed in later stages. The disease may also affect the breasts, lungs, soft tissues, salivary glands, and orbit. CNS involvement is seen mostly in recurrent disease and is rare at first presentation.[3]

Cheah et al.[4] presented the largest series of patients with MCL and CNS involvement reported to date. This study showed that the crude incidence of CNS involvement was 4.1%, with 0.9% having CNS involvement at diagnosis. The most frequent clinical manifestations of CNS involvement included signs and symptoms related to high intracranial pressure or meningeal infiltration, and mainly consisted of mental status changes, headache, cranial nerve palsies and diplopia. Symptoms at presentation varied, but they noted ocular disturbance in 20% of 57 patients with MCL and CNS involvement.[4,5]

We report the case of a 72-year-old woman with MCL having partial bilateral third, fourth, and sixth nerve palsy. Although there have been some rare cases reported with blepharoptosis and restricted eye movements as symptoms of non-Hodgkin lymphoma, to the best of our knowledge, ours is the first case of MCL presenting with bilateral ophthalmoplegia and blepharoptosis and the second case in the literature that has shown MCL with CNS involvement manifesting with ophthalmoplegia and negative imaging studies.[6,7,8]

Then and Patel[8] presented a unique case of a 65-year-old woman diagnosed with stage 4A Kappa restricted B Cell MCL who presented with acute-onset double vision, skew deviation of the eyes, left eye ptosis, right horizontal gaze palsy, right facial droop, dysarthria, and dysphagia 2 months after the lymphoma diagnosis. Orbit computerized tomography and brain MRI were normal. However, as in our case, lumbar puncture showed exaggerated lymphocytic pleocytosis and cytology showed the presence of mantle cells on cerebrospinal fluid analysis.

MRI is the best way to investigate the degree of CNS infiltration, whether intraparenchymatous or meningeal.[9] Ophthalmoplegia with normal MRI may occur via paraneoplastic encephalomyelitis and leptomeningeal metastasis (lymphomatous meningitis).[10,11]

Neoplastic meningitis, a particular manifestation of CNS recurrence, results from the infiltration of metastatic cells into the cerebrospinal fluid and meninges. Neoplastic meningitis is also referred to as lymphomatous meningitis in patients with

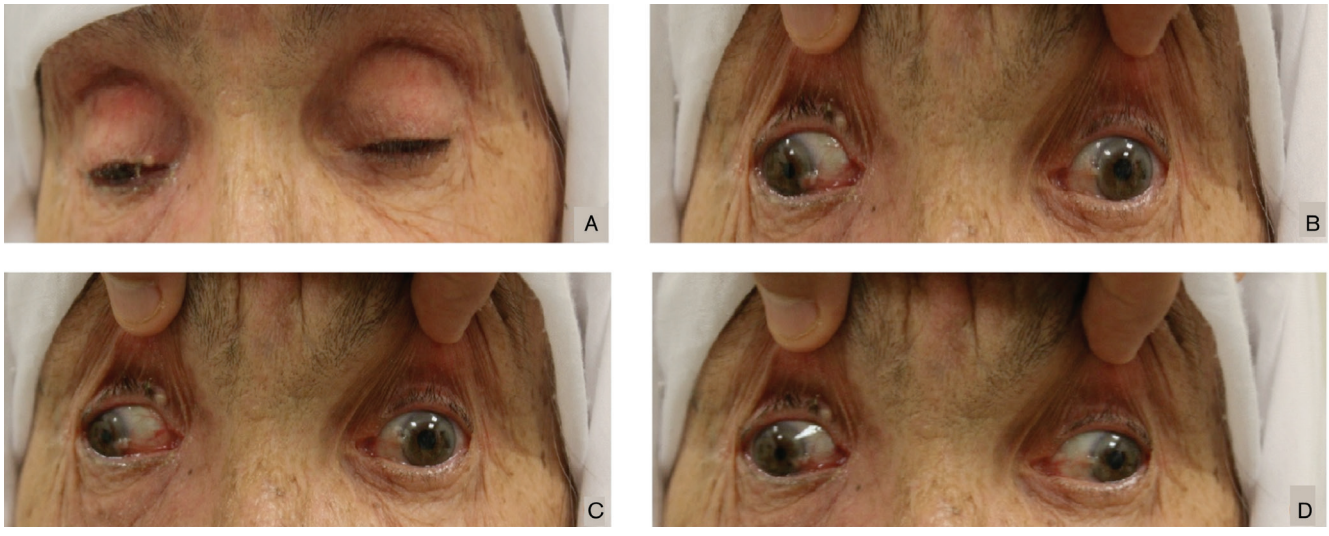


**Figure 1.** A) Bilateral complete ptosis and B) right exotropia in primary gaze position; C, D) Nearly complete ophthalmoplegia in both eyes except minimal abduction

lymphoma. Lymphomatous meningitis symptoms can reflect involvement at any level of the neuroaxis, which consists of the meninges (the three-layered sheath enclosing the organs of the nervous system), brain, spinal cord, and cerebrospinal fluid.[12,13] The analysis of cerebrospinal fluid has made it possible to confirm CNS infiltration. Cerebrospinal fluid cytology is positive in 86% of MCL patients with CNS involvement, and flow cytometry is positive in 91%.[4,14]

Common causes of acute complete bilateral ophthalmoplegia include Miller Fisher syndrome, Guillain-Barre syndrome, posterior-circulation (brainstem) stroke, myasthenia gravis, drug toxicity (e.g. phenytoin), and trauma.[15] MCL also should be added to the causes of rapidly progressive bilateral ophthalmoplegia. As in other B-cell lymphoma cases, improvement after chemotherapy suggests that early treatment with chemotherapy may effectively treat ophthalmoplegia associated with MCL.

**Ethics**

Informed Consent: Patient provided written informed consent.

Peer-review: Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Yaran Koban, Hatice Özlece, Concept: Yaran Koban, Hatice Özlece, Design: Yaran Koban, Mustafa Koç, Data Collection or Processing: Yaran Koban, Hüseyin Çelik, Zeliha Yazar, Analysis or Interpretation: Yaran Koban, Mustafa Koç, Orhan Ayar, Ayşe Burcu, Literature Search: Mustafa Koç, Orhan Ayar, Writing: Yaran Koban, Hatice Özlece, Orhan Ayar, Mustafa Koç.

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Case Report

# Atypical Central Serous Chorioretinopathy

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**Abstract**

Bullous central serous chorioretinopathy (CSCR) is a rare variant of CSCR characterized by severe serous retinal detachment which especially involves the inferior quadrants. Corticosteroid therapy administered for systemic or ocular misdiagnoses may induce and exacerbate CSCR. The purpose of this study was to report diagnosis and treatment results of an unusual case of bullous CSCR induced by systemic and periocular corticosteroid therapy received at another medical center due to a misdiagnosis of Vogt-Koyanagi-Harada disease.
**Keywords:** Central serous chorioretinopathy, Vogt-Koyanagi-Harada disease, corticosteroid

## Introduction

Central serous chorioretinopathy (CSCR) is an idiopathic chorioretinal disease which causes serous detachment in the neurosensory retina, which may also be accompanied by pigment epithelium detachment.[1] Compared to the acute and chronic types of CSCR, bullous CSCR is rarely reported and is characterized by bullous retinal detachment in the inferior quadrants of the fundus.[2,3,4] Although its pathophysiology is unknown, corticosteroids are known to be one of the major risk factors in the development of CSCR.[1,5,6,7,8] The use of corticosteroids, especially in the treatment of systemic or ocular conditions may lead to acute emergence or exacerbation of CSCR.[5,6,7,8,9] Atypical, bullous, or chronic type CSCR may be confused with other diseases that can cause intraocular inflammation such as Vogt-Koyanagi-Harada (VKH) disease, posterior scleritis, sympathetic ophthalmia, multifocal choroiditis, and serpiginous choroiditis.[5,9] Corticosteroid treatment due to the misdiagnosis of posterior uveitis leads to the exacerbation of CSCR symptoms.[9]

In the present study, we present the follow-up and treatment response of a patient diagnosed with bullous CSCR who was treated for an extended period with corticosteroids for a diagnosis of VKH.

## Case Report

A 28-year-old female patient presented to our clinic for progressive decrease in vision, first the right eye and later the left eye, for the past year. Her medical history was unremarkable in terms of systemic disease. She reported going to another center one year earlier for reduced vision where she was diagnosed with VKH and treated 3 times with high-dose corticosteroid and finally with an injection in her right eye. At time of presentation, the patient was using oral methylprednisolone 16 mg/day, oral cyclosporine 150 mg/day, and oral azathioprine 75 mg/day. Physically, she exhibited cushingoid appearance and complained of excessive weight gain and hair growth on the body. On examination, her visual acuity was light perception with projection in the right eye and 0.6 in the left eye. Anterior segment examination of both eyes was normal except for white accumulations consistent with corticosteroid in the inferior subconjunctival region of the right eye. Intraocular pressure measurement was 13 mmHg in the right and 15 mmHg in the left eye with dorzolamide hydrochloride-timolol maleate twice daily. Fundoscopic examination revealed no cells in the vitreous and exudative retinal detachment from the inferior quadrants to the superotemporal arcade in the right eye. In the left eye, there were no cells in the vitreous, while exudative

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retinal detachment was observed in the inferior periphery and subretinal fibrin accumulation was noted at the superotemporal and inferotemporal arcades and nasal to the optic disc (Figure 1A, B). Ultrasonographic imaging (USG) was compatible with exudative retinal detachment in the right and left eyes (Figure 1C, D). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) in the right eye revealed hypofluorescence in the region corresponding to the exudative retina detachment, as well as early hyperfluorescence increasing in later phases at the peripheral superotemporal arcade surrounded by multiple localized hypofluorescent foci. In the left eye, FA and ICGA revealed early hyperfluorescence increasing in later phases in the macula, superior and inferior temporal arcades, and nasal of the optic nerve (Figure 2A-H). Enhanced depth imaging-optical coherence tomography (EDI-OCT) revealed subretinal fluid and a hyperreflective band located subretinally in the section taken at the peripheral superotemporal arcade in the right eye; in the left eye, EDI-OCT showed subretinal fluid on the section passing through the macula, and subretinal hyperreflective material with a hyporeflective field and irregularity in retinal pigment epithelium (RPE) in the section taken at the level of the superotemporal arcade (Figure 2I-K). Subfoveal choroidal thickness in the left eye was determined as 591 µm on EDI-OCT (Figure 2J). Neurologic and otorhinolaryngologic examinations were normal; however, dermatologic examination revealed findings consistent with hirsutism. Based on the results of ophthalmologic examination and auxiliary imaging techniques, the patient was diagnosed with bullous type CSCR exacerbated by corticosteroid therapy. After consultation with endocrinologists, the patient was diagnosed with Cushing's syndrome associated with systemic corticosteroid use, and gradual methylprednisolone tapering was recommended. Therapy with cyclosporine and azathioprine was discontinued. The subconjunctival corticosteroid particles were removed from the patient's right eye. After consultation with endocrinology and obtaining the patient's consent, treatment was initiated with oral mineralocorticoid receptor antagonist eplerenone 25 mg twice daily. Low fluence photodynamic therapy (PDT) (25 J/cm$^2$, 300 mW/cm$^2$) was applied to areas of leakage seen on FA and ICGA in the macula and superotemporal arcade in the left eye due to the potential threat to the macula. Focal laser photocoagulation was applied to areas of leakage in the left nasal and inferotemporal arcades. Exudative detachment was reduced in the right eye and had completely regressed in the left eye at 1-month follow-up. At month 4, visual acuity was counting fingers from 1 meter in the right eye and had improved to 0.7 in the left eye. Anterior segment examination was normal in both eyes. Fundus examination in the right eye revealed regression of the exudative detachment to the inferotemporal arcade and the presence of subretinal fibrosis at the peripheral superotemporal arcade; in the left eye, subretinal fibrosis was observed at the inferior and superior temporal arcades (Figure 3A, B). EDI-OCT examination revealed subretinal fluid in the right and left maculas, and subfoveal choroidal thickness was 537 µm in the right eye and 335 µm in the left eye (Figure 3C, D). The patient was lost to follow-up after the fourth month because she moved to another country.

## Discussion

Although it is not fully understood how corticosteroids induce or exacerbate CSCR, various mechanisms have been implicated in the development of the disease. Exogenous or endogenous hypercortisolemia elevates catecholamine levels, creates a mineralocorticoid effect, or induces thrombocyte aggregation, which increase choriocapillaris permeability and RPE decompensation, leading to CSCR.[1,9] The development of CSCR is independent of the corticosteroid type, dose or route of administration.[9] Gass and Little[5] reported bilateral bullous CSCR in a patient who was administered systemic and sub-Tenon corticosteroid due to a misdiagnosis of choroiditis; the serous detachments regressed after discontinuing the drug and treating with laser photocoagulation. In a series reporting the

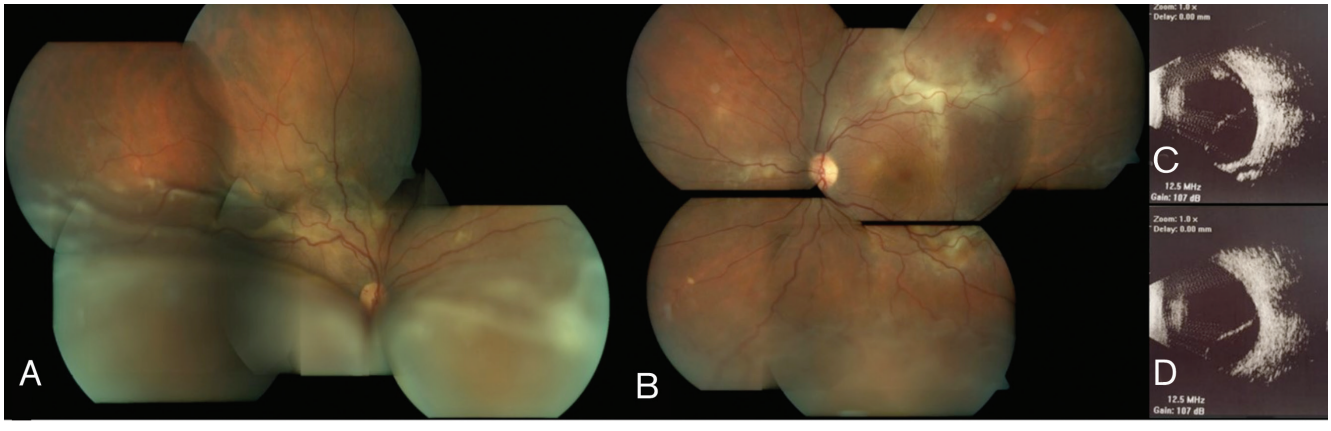


**Figure 1.** Fundus photography and ultrasonography (USG) images from the patient's right and left eyes. A) Bullous retinal detachment extending to the superotemporal vascular arcade in the right eye; B) Serous retinal detachment in the inferior periphery and subretinal fibrin visible at the inferior and superior temporal arcades and in the nasal quadrant in the left eye; C) Retinal detachment in the inferior and superior quadrants on the USG in the right eye; D) Retinal detachment in the inferior quadrant on USG in the left eye

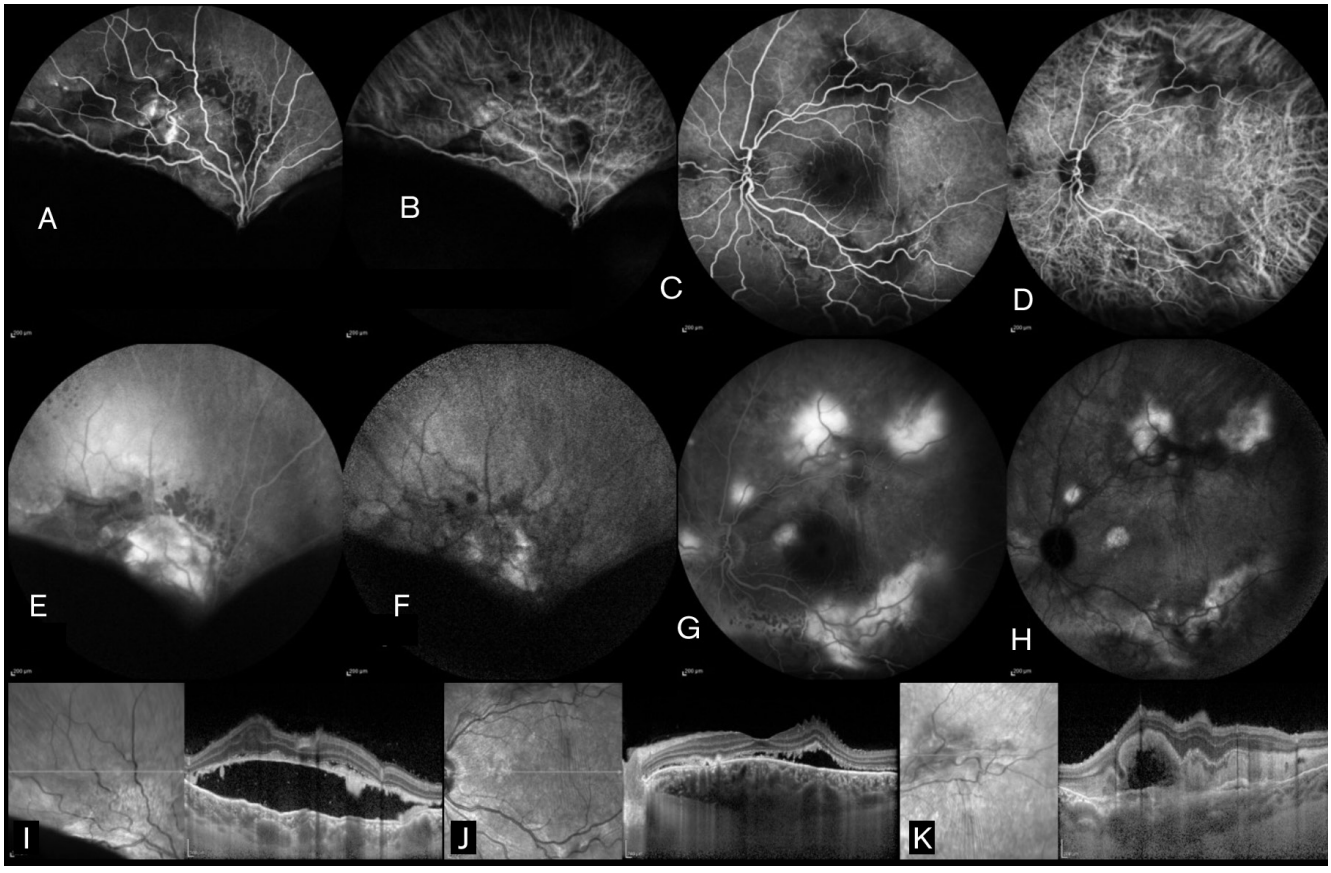


**Figure 2.** A) Fluorescein angiography (FA) in the right eye revealed an area of early hypofluorescence in the inferior quadrants and hyperfluorescence at the superotemporal vascular arcade; B) Indocyanine green angiography (ICGA) in the right eye revealed early hypofluorescence in the inferior quadrants and dilated choroidal vessels at the superotemporal arcade; C) FA in the left eye revealed early hypofluorescence at the superior and inferior temporal arcades and in the nasal quadrant; D) ICGA in the left eye revealed dilated choroidal vessels at the level of the temporal vascular arcade; E) FA in the right eye showed hyperfluorescence at the superotemporal vascular arcade due to leakage and hypofluorescence in the inferior quadrants at late phases; F) ICGA in the right eye showed late hyperfluorescence at the superotemporal arcade and hypofluorescence in the inferior quadrants; G) left eye revealed increased hyperfluorescence in late phases in the macula, superotemporal and inferotemporal arcades, and nasal quadrant; H) ICGA in the left eye showed hyperfluorescence in the macula, superotemporal and inferotemporal vascular arcades, and nasal quadrant in late phases; I) In the right eye, subretinal fluid and a subretinal hyperreflective band are visible on enhanced depth imaging-optic coherence tomography (EDI-OCT) from the section passing through the superotemporal vascular arcade; J) In the left eye, the macular EDI-OCT section reveals subretinal fluid, retinal pigment epithelium irregularities, internal limiting membrane folds, and a subfoveal choroid thickness of 591 µm; K) In the left eye, the OCT cross-section taken at the level of the superotemporal arcade reveals subretinal accumulation of hyperreflective material and a hyporeflective space

long-term follow-up outcomes of 25 patients with bullous CSCR, 4 patients (16%) developed this severe form of CSCR in which the areas of serous detachment healed with residual scarring or atrophy after drug discontinuation and treatment.[4]

The findings of bullous CSCR may be confused with uveal effusion, metastatic carcinoma or lymphoma, rhegmatogenous retinal detachment, and diseases that cause inflammation such as VKH disease, multifocal choroiditis, and sympathetic ophthalmia, and misdiagnosis results in unnecessary tests and treatments.[5,9] Kang et al.[10] observed progression of bullous detachment in a 47-year-old male patient who was treated with systemic corticosteroids for a prediagnosis of VKH; they subsequently discontinued the medication and successfully treated the patient with vitrectomy and internal subretinal fluid drainage. Gao and Li[11] reported a patient with a previous history of CSCR whose disease converted to the bullous form after being treated with systemic methylprednisolone due to misdiagnosis of VKH. A multimodal imaging approach utilizing FA, ICGA, and spectral domain-OCT is important in the differential diagnosis and follow-up of the disease.[12] CSCR is most commonly mistaken for the exudative retinal detachment seen in the acute phase of VKH. Findings that facilitate the diagnosis of CSCR are an absence of cells in the anterior chamber or vitreous and no sign of optic disc edema on examination; no choroidal thickening in USG; an absence of optic disc staining in late phases of FA; and observing multifocal hyperpermeability instead of diffuse hyperpermeability and the absence of hypofluorescence spots or optic disc staining on ICGA.[9] Other findings that support CSCR diagnosis are the presence of dome-shaped serous detachment on OCT, subretinal precipitates, localized fibrin reaction, presence of RPE detachment and irregularities, no visible subretinal septa, fundus autofluorescence showing hypoautofluorescence in the

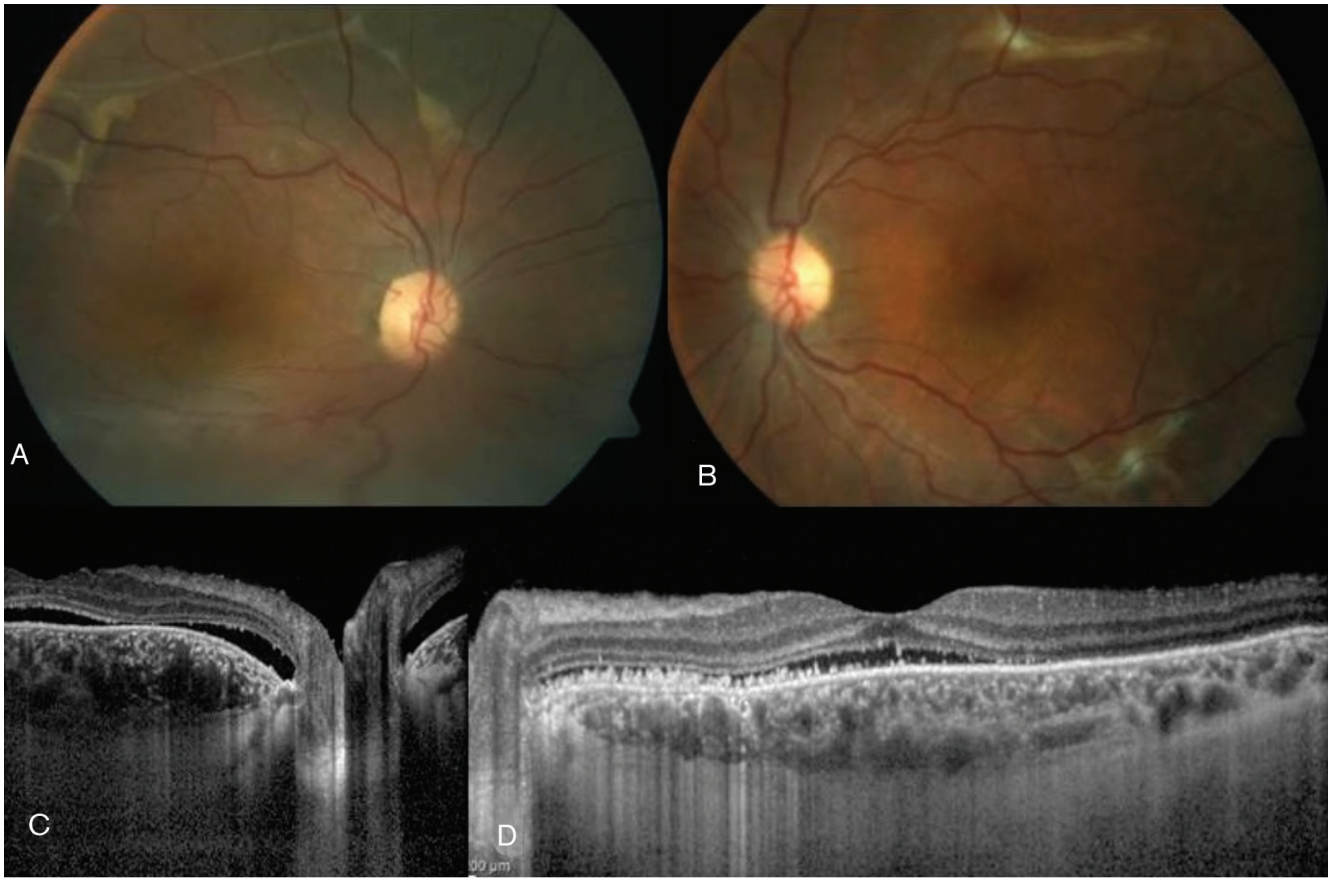


**Figure 3.** Fundus images from the left and right eyes taken 4 months after treatment. A) In the right eye, serous retinal detachment regressed to the level of the inferotemporal arcade, while a subretinal band is apparent at the level of the superotemporal arcade; B) In the left eye, subretinal fibrosis is apparent at the superior and inferior temporal arcades; C) Enhanced depth imaging-optic coherence tomography (EDI-OCT) in the right eye shows subretinal fluid and subfoveal choroid thickness of 537 µm in the section taken at the macula; D) EDI-OCT in the left eye revealed subretinal fluid in the macula, hyperreflective material in subretinal area, and subfoveal choroid thickness of 335 µm

area of subretinal fluid, and hyperautofluorescence corresponding with areas of leakage on FA.[9] Because choroid thickness increases in both VKH disease and CSCR, noninvasive EDI-OCT examination is not useful for differentiating between these two entities.[13] However, corticosteroid treatment provides favorable results in VKH ocular involvement, but may exacerbate ocular symptoms in CSCR.[9] In our study, our patient also received an initial diagnosis of VKH due to the presence of presumed serous retinal detachment, and was administered systemic and periocular corticosteroid therapy for one year. These treatments not only exacerbated the CSCR and induced its transformation to the bullous form, but also caused systemic problems such as Cushing's syndrome.

Due to its angio-occlusive effect, PDT leads to narrowing of the choroidal vessels and thereby a reduction in choroidal exudation, as well as reshaping of choroidal vessels.[14] Low-fluence or low-dose PDT is used in CSCR to avoid the potential complications of standard PDT, such as RPE atrophy, choroidal ischemia, and secondary choroidal neovascularization. Successful outcomes have been reported in studies using these techniques.[15,16] Although there are no randomized, controlled studies in the literature, some studies have shown that oral eplerenone, a mineralocorticoid receptor antagonist, decreases subretinal fluid in chronic CSCR and is a promising treatment method for the future.[17,18] Because our patient had very advanced stage disease, we combined available treatment methods such as low-fluence PDT, focal laser photocoagulation, and oral eplerenone, and the patient responded well within a short period.

In conclusion, bullous type CSCR may be confused with ocular symptoms of acute VKH disease. Corticosteroid therapy administered for a misdiagnosis of intraocular inflammation may exacerbate CSCR and lead to irreversible damage. Atypical bullous CSCR must be considered in cases of serous retinal detachment, and the use of multimodal imaging methods in addition to detailed ophthalmologic and systemic examinations will facilitate an accurate diagnosis before giving corticosteroids.

**Ethics**

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Zafer Cebeci, Merih Oray, Nur Kır, Concept: Zafer Cebeci, Merih Oray, Design: Zafer Cebeci, Merih Oray, Data Collection or Processing: Zafer Cebeci, Merih Oray, Şerife Bayraktar, Analysis or Interpretation: Zafer Cebeci, Merih Oray, Şerife Bayraktar, İlknur Tuğal-Tutkun, Nur Kır, Literature Search: Zafer Cebeci, Merih Oray, Şerife Bayraktar, Writing: Zafer Cebeci, Merih Oray.

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Turk J Ophthalmol 2017;47:243-246

Case Report

# Choroidal Osteoma and Secondary Choroidal Neovascularization Treated with Ranibizumab

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**Abstract**

A 47-year-old female patient presented with a complaint of decreased vision in the right eye. Her visual acuity was 0.16 in the right eye and 1.0 in the left eye. Fundus examination revealed a slightly elevated, yellowish-white lesion with regular borders at the macula of the right eye. Early and late hyperfluorescence related with choroidal neovascularization (CNV) was detected in the right eye on fundus fluorescein angiography. B-scan ultrasonography revealed a hyperechoic choroidal lesion with acoustic shadowing. The lesion was diagnosed as choroidal osteoma. The patient received 3 injections of intravitreal ranibizumab. After 4 months, the visual acuity of the right eye was 0.9 and the CNV had regressed. Follow-up at about 7 months revealed reduced visual acuity in the right eye with an increase in subretinal fluid. An additional ranibizumab injection was administered. In this case report, we discuss the findings and treatment of a rare case of choroidal osteoma with secondary CNV.

**Keywords:** Choroidal osteoma, choroidal neovascularization, intravitreal ranibizumab

## Introduction

Choroidal osteoma is a rare ossifying benign tumor with unknown pathogenesis.[1] It was first identified in 1978 by Gass et al.[2] The tumor is generally unilateral and located in juxtapapillary and macular region. Although it occurs more frequently in young women, men and middle-aged people may also be affected.[3,4] Despite being a benign tumor, it may cause serious vision loss due to pigment epithelium atrophy, serous retinal detachment, and most commonly choroidal neovascularization (CNV).[3,5] While patients usually present with blurred vision, metamorphopsia, photophobia, and vision field defects, 8-30% of patients are asymptomatic.[3,4] Choroidal osteoma is diagnosed by clinical examination. It appears in fundus examination as a slightly elevated, yellowish-white or orange-colored vascularized lesion with well-defined borders and pigment epithelium changes.[3,4,6] Fundus autofluorescence, computed tomography, ultrasonography (USG), magnetic resonance imaging, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA) assist diagnosis. Treatment targets complications. Here, we aimed to discuss a patient diagnosed with choroidal osteoma and secondary CNV who was treated with intravitreal ranibizumab.

## Case Report

A 47-year-old female patient presented with complaints of decreased vision in her right eye. On examination, her visual acuity was 0.16 in the right eye and 1.0 in the left eye. Slit-lamp anterior segment examination and intraocular pressures were normal in both eyes. Fundus examination revealed a yellowish-white lesion that had well-defined borders and was slightly raised from the surface of the retina located at macula of the right eye, while the left eye was normal (Figure 1A, B). FFA revealed early hyperfluorescence increasing in later stages and CNV in the region compatible with the lesion in the right eye (Figure 2A, B). B-scan USG in the right eye revealed a hyperechoic choroidal lesion causing acoustic shadowing (Figure 3). Spectral domain OCT revealed subretinal fluid in the right eye (Figure 4). Based on those findings, the patient was diagnosed with choroidal osteoma and secondary CNV. The patient was administered 3 intravitreal ranibizumab injections at 1-month intervals. In

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follow-up examination at 4 months post-injections, visual acuity had improved to 0.9 and OCT imaging showed regression of the subretinal fluid (Figure 5). Although the patient's vision was stable during that period, a decline in visual acuity was observed 3 months later. An additional intravitreal ranibizumab injection was administered when the visual acuity in the right eye reached 0.4. At final follow-up 2 months after the injection, OCT revealed that the subretinal fluid had regressed, and visual acuity had improved to 0.8. The patient's condition was stable during the 2-year follow-up period and no additional injections were required.

## Discussion

The main causes of vision loss in choroidal osteoma are the development of CNV, subfoveal fluid, and photoreceptor degeneration.[5] CNV is seen more frequently among patients exhibiting a combination of hemorrhage and surface irregularities.[5] Shields et al.[3] observed CNV development in 31% of their 61 choroidal osteoma patients, while Aylward et al.[4] reported the incidence as 47% in their study of 36 patients. Although the mechanism by which CNV develops is not well understood, researchers have suggested that retinal pigment epithelium damage CNV in the underlying choroid, or that osteoma itself has neovascular membrane extensions.[1,7] FFA and OCT are useful methods for identifying CNV.

There is no standard method for the treatment of choroidal osteoma. Patients must be followed regularly and secondary complications must be treated as appropriate. In the management of CNV secondary to choroidal osteoma, partial success has been achieved using thermal laser photocoagulation and photodynamic therapy (PDT) for extrafoveal lesions, and transpupillary thermotherapy and PDT for subfoveal lesions. However, some studies showed that these treatment methods might leading to tumor decalcification, thus increasing retinal damage.[8,9,10]

It is believed that laser photocoagulation may not have adequate efficacy in cases of CNV secondary to choroidal osteoma due to insufficient tumor melanine and a thinned, degenerated RPE-Bruch's membrane complex.[1] While PDT provides short-term improvement in visual acuity, it has been demonstrated that retreatment may be necessary and final visual acuity may decline.[11] Surgical removal of subfoveal CNV membranes results in favorable anatomic outcomes, but researchers have reported the procedure unsuccessful in terms of visual acuity.[12]

Another method employed in the treatment of these patients is intravitreal anti-vascular endothelial growth factor (anti-VEGF). Bevacizumab and ranibizumab injections have been tested for this purpose, and positive outcomes were reported in both anatomy and visual acuity.[5,6] It is thought that in choroidal osteoma cases, normal tissues are also damaged during the process, and VEGF expression is increased as a result of choroidal and retinal ischemic stress and chronic inflammation. RPE damage together with thinning of Bruch's membrane and the choriocapillaris may contribute to the development of CNV. Thus, increased VEGF supports abnormal neovascularization. Therefore, anti-VEGF agents may be effective in treatment.[13]

The first trials of intravitreal bevacizumab in the literature were conducted for this purpose and yielded favorable results.[6,13] In a case reported by Ahmadieh and Vafi,[6] visual acuity

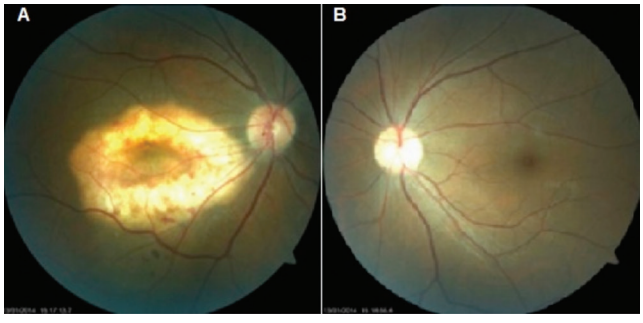


**Figure 1.** A) Hypopigmented choroidal osteoma in the right macula, B) The left fundus appears normal

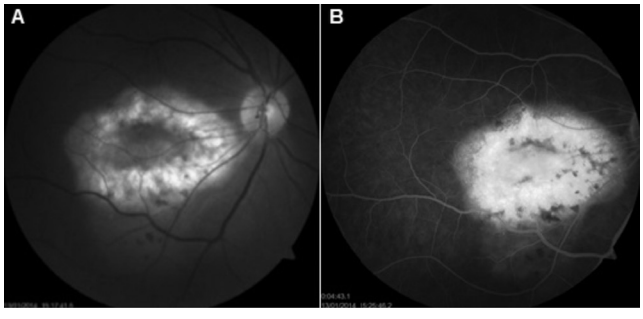


**Figure 2.** A) Fundus fluorescein angiography shows the osteoma area in the early phase, B) Increased active leakage in the late period in the area compatible with the osteoma

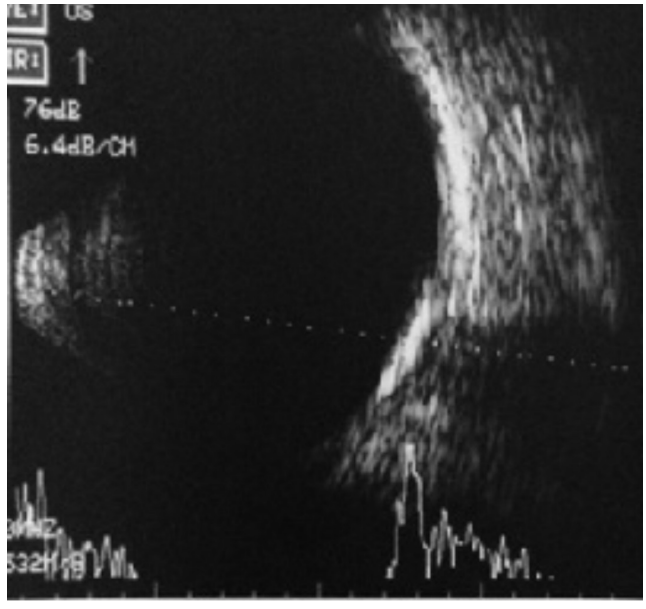


**Figure 3.** B-scan ultrasonography imaging of the right eye reveals a choroidal lesion causing acoustic shadowing

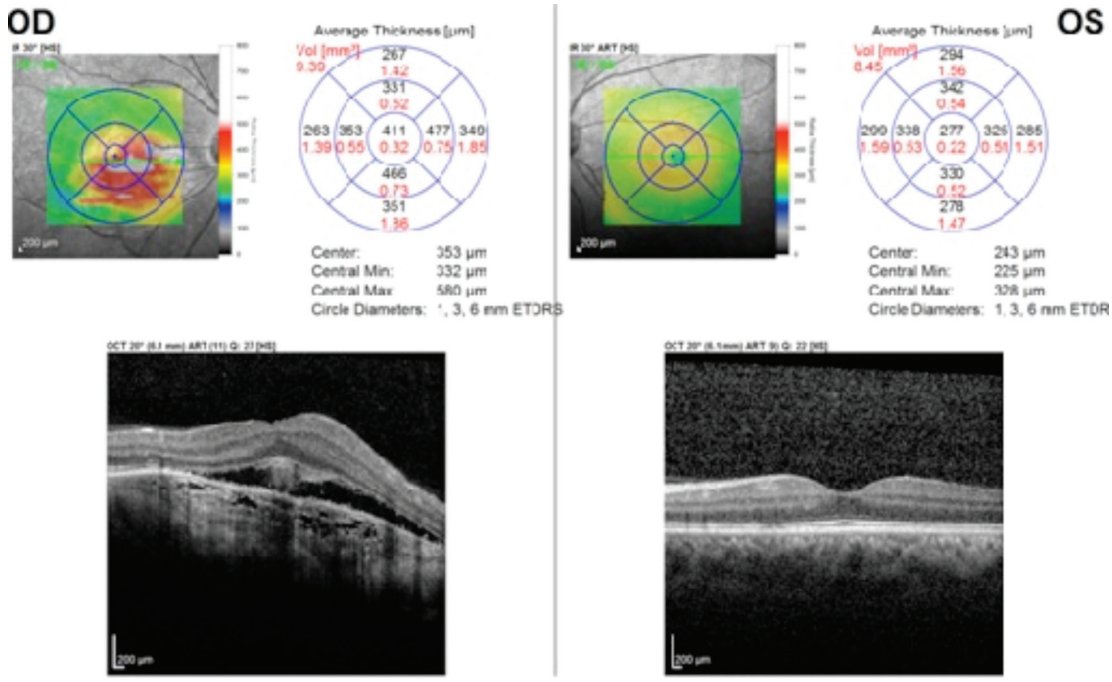


**Figure 4.** Pre-treatment optical coherence tomography imaging shows subretinal fluid and an area of choroidal neovascularization with a lesion situated in the cornea and optic shadowing behind it

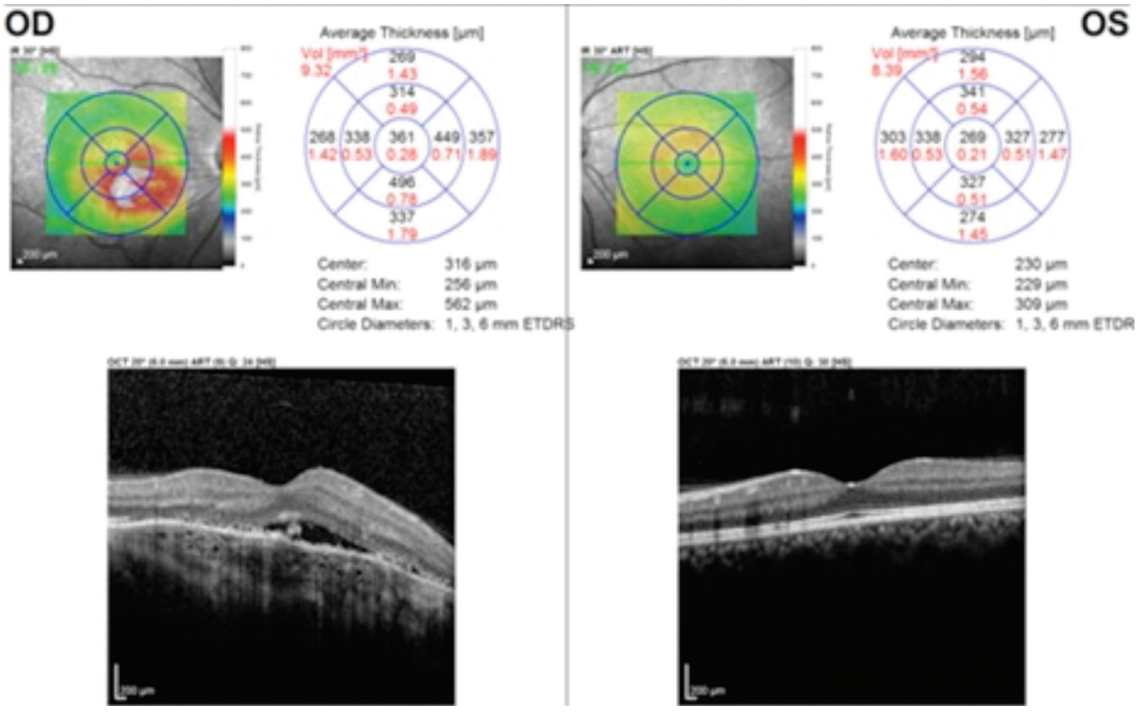


**Figure 5.** The subretinal fluid is reduced after intravitreal ranibizumab injection

improved from 20/200 to 20/20 after intravitreal bevacizumab injection and was preserved at this level throughout a 9-month follow-up period. In another case study from Kubota-Taniai et al.,[13] visual acuity improved to 0.7 from 0.2 after bevacizumab injection and was preserved over the course of 4 years of follow-up. The highly effective responses obtained with anti-VEGF injections were attributed to enhanced passage of the bevacizumab through the thinned and degenerated RPE and

Bruch's membrane to the subretinal area, thus increasing the drug's efficacy.[6]

The first reported use of intravitreal ranibizumab injection for CNV secondary to choroidal osteoma was by Song and Roh[5] in 2009; they found that CNV had regressed and visual acuity had improved from 20/200 to 20/100 at 6 months post-injection. In another case report, Gupta et al.[14] observed CNV regression after ranibizumab injection and no recurrence was detected in 30 months of follow-up. Wu et al.[15] reported a case in which visual acuity improved from 20/800 to 20/30 after 3 injection and no recurrence was observed during 1.2 years of follow-up. Mansour et al.[16] demonstrated in their series consisting of 26 cases that intravitreal ranibizumab and bevacizumab were effective. In our case, visual acuity improved from 0.16 to 0.9 after 3 monthly injections. However, a decrease in visual acuity 3 months after the final injection and CNV recurrence necessitated another ranibizumab injection.

In conclusion, although intravitreal ranibizumab injection is highly beneficial in the treatment of CNV secondary to choroidal osteoma in terms of visual acuity and anatomic recovery, recurrence may be observed, as our case also shows. Therefore, patients should be examined regular at monthly intervals, and treatment should be supported by repeated intravitreal anti-VEGF injections when required.

**Ethics**

Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Gürsel Yılmaz, Concept: Gürsel Yılmaz, Sezin Akça Bayar, Almila Sarıgül Sezenöz, Design: Gürsel Yılmaz, Sezin Akça Bayar, Almila Sarıgül Sezenöz, Data Collection or Processing: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Analysis or Interpretation: Gürsel Yılmaz, Sezin Akça Bayar, Almila Sarıgül Sezenöz, Literature Search: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Writing: Gürsel Yılmaz, Sezin Akça Bayar, Almila Sarıgül Sezenöz

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

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

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Letter to the Editor

# Pediatric Patients and Tonometers

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**DY Patil University Faculty of Medicine, Pune, India

**Dear Editor,**

The recent publication on "Pediatric Patients and Tonometers" is interesting.[1]

Eraslan et al.[1] concluded that "Because Tono-Pen (TP) measurements were lower than Goldmann applanation tonometer (GAT) measurements and non-contact tonometer measurements were higher than GAT measurements, patient follow-ups, treatment strategies, and surgery plans must be organized taking these differences into consideration". The results in this report are similar to a recent report by Galgauskas et al.[2] In fact, the use of different kinds of tonometer can result in different measures values and this has to be kept in mind by practitioners. The correlation study can be useful for checking the variability of the tool. Nevertheless, there are some concerns that should be addressed. First, the lack of a gold standard for the comparative study is a big issue for further discussion. At present, we can only perform the inter-tool agreement check but there is no gold standard for checking the accuracy of the measurement. Second, for each tool the within-day and between-day precision of the tool should also be checked. Finally, the calibration error of the tool should be regularly checked since it can contribute to incorrect measurement results.[3] In the present report by Eraslan et al.,[1] there is no error checking as well.

**Keywords:** Pediatric, Tonometer, measurement

**Ethics**

Peer-review: Internally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Sora Yasri, Viroj Wiwanitkit, Concept: Sora Yasri, Viroj Wiwanitkit, Design: Sora Yasri, Viroj Wiwanitkit, Data Collection or Processing: Sora Yasri, Viroj Wiwanitkit, Analysis or Interpretation: Sora Yasri, Viroj Wiwanitkit, Literature Search: Sora Yasri, Viroj Wiwanitkit, Writing: Sora Yasri, Viroj Wiwanitkit.

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## Reply to the Authors

**Dear Editor,**

We are grateful to Yasri and Wiwanitkit for their interest in our work and their valuable comments. The authors kindly reminded that the use of different kinds of tonometer can result in different measured values, which corresponds to the conclusion of our study. They mentioned the lack of a gold standard in intra ocular pressure measurements but as all we know, the Goldmann applanation tonometer (GAT) is defined as the gold standard measurement method in a large number of studies.[1] As they emphasized in their letter, the findings of our study are similar to a recent report of Galgauskas et al.[2] where GAT is defined as the gold standard. But as Garcia Feijoo et al.[3] mentioned in their study, despite GAT being the gold standard for determining intra ocular pressure since the last century, the substantial effects of several ocular variables such as axial length, curvature, rigidity, and corneal thickness are its obvious limitations. Yasri and Wiwanitkit also mentioned that we can only perform the inter-tool agreement and they recommended that a correlation study can be useful for checking the variability of the tool. However, to evaluate whether the differences between two measurements of the same variable are significant, previous studies recommend studying the differences, not the agreement.[4] The correlation shows the relationship between one variable and another, not the differences, and it is not the best technique for assessing the comparability between methods.[4] Bland-Altman (B-A) plots compare two clinical measurements that each provide some errors in their measure and these plots are extensively used to evaluate the agreement between two different instruments or two measurement techniques.[5] B-A plot analysis can also be used for assessing the comparability between a new measurement technique or method with a gold standard, as even a gold standard does not-and should not-imply it to be without error.[6] These analyses evaluate a bias between the mean differences and estimate an agreement interval, within which fall 95% of the differences of the second method compared to the first one. It is common to compute 95% limits of agreement for each comparison (average difference ±1.96 standard deviation (SD) of the difference). The compared methods can be used interchangeably unless the differences within mean ±1.96 SD are clinically important.[4]

In our study, Pearson's test was used to determine the presence of correlations. Differences of 1.96 SD from the mean were used when calculating the limits of agreement. Associations between differences and means were analyzed using B-A plots. This was mentioned in the third paragraph of the Materials and Methods section of our study.

Within-day and between-day precision was checked for each tool and because our GAT and Tonopen are older than 1 year, the calibration error of the tools is routinely checked on a daily basis and the non-contact tonometer was calibrated once a month as recommended by the manufacturers. These were also mentioned in the second paragraph of the Materials and Methods section of our study. This is consistent with the study of Choudhari et al.[7], which was mentioned by Yasri and Wiwanitkit in their letter; they concluded that GATs older than a year should be checked at least monthly. Therefore, we believe that all of the abovementioned limitations are important but it is unlikely that they affected our results significantly.

**Best Regards**

**Muhsin Eraslan, Eren Çerman, Sena Sümmen**

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## Distance Visual Acuity Measurements Equivalency Table

| | | | | | | Spatial Frequency |
|---|---|---|---|---|---|---|
| **ETDRS Standard Line Number** | **Qualitative Measurements** | **Decimal** | **Snellen** | **LogMAR** | **Angle of Resolution** | **Cycle per Degree** |
| -3 | | 2.00 | 20/10 | -0.30 | 0.5 | 60.00 |
| -2 | | 1.60 | 20/12.5 | -0.20 | 0.625 | 48.00 |
| -1 | | 1.25 | 20/16 | -0.10 | 0.8 | 37.50 |
| 0 | | 1.00 | 20/20 | 0.00 | 1 | 30.00 |
| | | 0.90 | | 0.05 | | 27.00 |
| 1 | | 0.80 | 20/25 | 0.10 | 1.25 | 24.00 |
| | | 0.70 | | 0.15 | | 21.00 |
| 2 | | 0.63 | 20/32 | 0.20 | 1.6 | 18.75 |
| | | 0.60 | | 0.22 | | 18.00 |
| 3 | | 0.50 | 20/40 | 0.30 | 2 | 15.00 |
| 4 | | 0.40 | 20/50 | 0.40 | 2.5 | 12.00 |
| | | 0.30 | | 0.52 | | 9.00 |
| 5 | | 0.32 | 20/63 | 0.50 | 3.15 | 9.52 |
| 6 | | 0.25 | 20/80 | 0.60 | 4 | 7.50 |
| 7 | | 0.20 | 20/100 | 0.70 | 5 | 6.00 |
| 8 | | 0.16 | 20/125 | 0.80 | 6.25 | 4.80 |
| 9 | | 0.13 | 20/160 | 0.90 | 8 | 3.75 |
| 10 | CF from 6 m | 0.10 | 20/200 | 1.00 | 10 | 3.00 |
| 11 | CF from 5 m | 0.08 | 20/250 | 1.10 | 12.5 | 2.40 |
| 12 | CF from 4 m | 0.06 | 20/320 | 1.20 | 16 | 1.88 |
| 13 | CF from 3 m | 0.05 | 20/400 | 1.30 | 20 | 1.50 |
| 14 | | 0.04 | 20/500 | 1.40 | 25 | 1.20 |
| 15 | CF from 2 m | 0.03 | 20/640 | 1.51 | 32 | 0.94 |
| 16 | | 0.025 | 20/800 | 1.60 | 40 | 0.75 |
| 17 | | 0.020 | 20/1000 | 1.70 | 50 | 0.60 |
| 18 | CF from 1 m | 0.016 | 20/1250 | 1.80 | 62.5 | 0.48 |
| 21 | CF from 50 cm | 0.008 | 20/2500 | 2.10 | 125 | 0.24 |
| 31 | HM from 50 cm | 0.0008 | 20/25000 | 3.10 | 1250 | 0.02 |

**Abbreviations:**
CF: Counting fingers, HM: Perception of hand motions, m= meter, cm= centimeter

**Equations of conversions for Microsoft Excel:**
- Log10 (Decimal Acuity)= LogMAR Equivalent
Power (10; -Logmar Equivalent)= Decimal Acuity (for English version of Microsoft Excel)
Kuvvet (10; -Logmar Equivalent)= Decimal Acutiy (for Turkish version of Microsoft Excel)

**Reference**
Eğrilmez S, Akkın C, Erakgün T, Yağcı A. Standardization in evaluation of visual acuity and a comprehensive table of equivalent. Turk J Ophthalmol. 2002;32:132-136.

| Near Visual Acuity Measurements Related Equivalency Table* | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Snellen** | **20/400** | **20/320** | **20/250** | **20/200** | **20/160** | **20/125** | **20/100** | **20/80** | **20/63** | **20/50** | **20/40** | **20/32** | **20/25** | **20/20** |
| Decimal | 0.05 | 0.063 | 0.08 | 0.10 | 0.125 | 0.16 | 0.20 | 0.25 | 0.32 | 0.40 | 0.50 | 0.63 | 0.80 | 1.00 |
| Jaeger | J19 | J18 | J17 | J16 | J15 | J14 | J13 | J11 | J9 | J7 | J5 | J3 | J2 | J1 |
| Times New Roman Point | 60 | 48 | 36 | 30 | 24 | 18 | 14 | 12 | 10 | 8 | 6 | 5 | 4 | 3 |
| LogMAR | 1.3 | 1.2 | 1.1 | 1.0 | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 | 0.0 |

*Adapted from Rabbets RB: Visual acuity and contrast sensitivity. In: Rabbets RB, editör. Clinical visual optics. Edinburgh: Butterworth-Heinemann, 1998:19-61.