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# TURKISH JOURNAL OF OPHTHALMOLOGY

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

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

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

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

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EDITORIAL

## 2021 Issue 3 at a Glance:

Dear colleagues,

This issue of our journal includes 6 original research articles, 1 review, and 5 case reports that we hope you will read with interest.

Hematopoietic stem cell transplantation (HSCT) is the main treatment for malignant and benign hematological diseases such as thalassemia major, aplastic anemia, leukemia, and metabolic diseases such as Hurler syndrome. Graft-versus-host disease (GVHD) is a clinical disease with multiple organ and system involvement that occurs due to donor-derived T-cells recognizing host antigens as foreign. Ocular involvement can occur as a clinical manifestation of GVHD and is known as ocular GVHD. Kızıltunç et al. retrospectively reviewed the medical records of 218 pediatric patients who underwent allogeneic HSCT and determined that 51 (23.4%) of these patients developed GVHD. Four of the patients died during follow-up. Of the 47 patients who continued follow-up, chronic ocular GVHD was detected in 63.8%, and 4 patients with a median follow-up of 12.1 months were treated with topical cyclosporine-A due to severe dry eye findings. Two patients showed significant improvement in severe dry eye findings, while treatment was discontinued in one patient due to drug side effects. The authors emphasized that chronic ocular GVHD is a common finding of post-HSCT GVHD in children; therefore, patients should be examined periodically for dry eye. (See pages 134-138)

Subaşı et al. conducted a study investigating the effects and safety of cataract surgery combined with ab interno gelatin microstent (XEN 45 Gel Stent; Aquesys Inc, Aliso Viejo, CA, USA) implantation to reduce intraocular pressure (IOP) in open-angle glaucoma (OAG). They retrospectively evaluated data pertaining to 30 eyes of 25 patients who underwent this procedure performed by the same surgeon. Preoperative IOP decreased from 20.37±4.80 mmHg using a mean of 3.07±1.04 drugs to 14.83±1.91 mmHg using a mean of 0.94±1.11 drugs at 24 months (p=0.001 and p<0.001, respectively). At 24 months, 55.6% of the patients had IOP ≤18 mmHg without medication, 94.4% had IOP ≤18 mmHg with or without medication, and 61.1% had ≥20% IOP reduction from baseline. The authors concluded that XEN 45 implantation provided a significant reduction in IOP and drug use and improved visual acuity with high success and low complication rates during follow-up. (See pages 139-145)

In a study aiming to determine the causes of blindness among patients applying to the health board of a hospital serving the Southeastern Anatolia region of Turkey, Karahan and Demirtaş retrospectively analyzed the records of 340 individuals with bilateral vision loss among 3,234 patients who applied to the health board. Among these patients, 166 (48.8%) were female, 174 (51.2%) were male, and the mean age was 64.3±25.4 years. The most common causes of vision loss were cataract in 158 patients (23.2%), corneal opacity in 114 patients (16.98%), retinal dystrophy in 92 patients (13.5%), optic atrophy in 73 patients (10.7%), glaucoma in 65 patients (9.6%), and phthisis bulbi in 59 patients (8.7%). When evaluated according to age group, the most common causes of blindness were retinal dystrophy in patients aged <15 years (n=9, 4.5%) and 15-40 years (n=21, 40.4%), and cataract in those aged >40 years (n=72, 27.1%). Cataract (27.1%) and corneal opacities (18.4%) were most common in the >40 age group. (See pages 146-150)

Clinical assessment of fixation behavior can be used to predict visual performance in children. In preverbal children with strabismus, evaluation of binocular fixation pattern is a good option for determining fixation preference. Şekeroğlu et al. conducted a study investigating the relationship between fixation preference and macular function on pattern electroretinogram (pERG) in children with strabismus. The study included 11 children with strabismus who underwent ophthalmological examination including binocular fixation pattern test, best corrected visual acuity (BCVA), and pERG. Correlations were observed between BCVA and P50 and N95 amplitudes in the non-preferred eyes (p=0.023 and p=0.014) and between interocular differences in BCVA and P50 amplitude (r=0.688, p=0.019). This result highlights the need for further and larger studies to evaluate the relationship between fixation preference and the electrophysiological function of the macula. (See pages 151-155)

Bilgeç et al. analyzed the ophthalmological, neurootological, audiological, and vestibular data of 16 individuals with pseudoexfoliation syndrome (PES) (study group) and 17 healthy individuals (control group) and found that PES patients had elevated pure-tone thresholds and reduced superior and inferior vestibular nerve function. The authors concluded that among the systems involved in balance, both the visual and vestibular systems are affected in patients with PES. (See pages 156-160)

Kıyat et al. conducted a prospective cross-sectional study to determine the functional and anatomical results obtained with intravitreal aflibercept (IVA) therapy in eyes with newly diagnosed, untreated neovascular age-related macular degeneration (nvAMD) and to investigate the effect of initial lesion characteristics on treatment outcomes. Of the

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139 eyes of 133 patients included in the study, all 139 eyes received 3 doses of IVA (group 1) and 62 of the eyes received 6 doses of IVA (group 2). Both groups had a statistically significant increase in mean BCVA with treatment ($p<0.001$ for both) and the proportion of eyes that showed complete response to treatment was 54.6% in group 1 and 58.0% in group 2. In addition to the successful functional and anatomical responses with 3 and 6 doses of IVA treatment in eyes with newly diagnosed and untreated nvAMD, it was noted that the presence of PED and especially serous PED were initial lesion characteristics that negatively affected treatment success. (See pages 161-168)

Fundus autofluorescence (FAF) is a noninvasive imaging method based on the principle of stimulating fluorophores with specific wavelengths and measuring the light they emit through barrier filters, and it has been embraced as a useful imaging method for explaining the pathophysiological mechanisms of retinal diseases, evaluating the risk of progression, and monitoring treatment outcomes. In this issue's review, Keşkek and Şermet provide basic information about FAF imaging and convey to the readers the importance of its use in dry age-related macular degeneration (AMD) and in identifying eyes with a high risk of progression. (See pages 169-176)

Endogenous bacterial endophthalmitis (EBE) accounts for less than 10% of all cases of endophthalmitis. It occurs as a result of hematogenous microbial spread that infiltrates the eye by crossing the blood-ocular barrier. Corredores et al. describes the case of a young athlete with a history of recurrent skin and soft tissue infections (SSTI) who presented with secondary disseminated infection and bilateral methicillin-resistant Staphylococcus aureus (MRSA)-EE as a complication of a suture abscess in the pelvic region. The authors point out that rapid initiation of ophthalmological and systemic treatment provided early infection control and prevented irreversible consequences. (See pages 177-180)

Yazıcı et al. report a 75-year-old diabetic man who presented with a black wound on his left eyelids and severe periorbital pain after falling and hitting the left side of his face 4 days earlier. He had black, necrotic crust over the left upper and lower eyelids and partially necrotic oval lesions in the temporal and malar areas surrounded by erythematous skin that was firm and tender to the touch. In addition, the patient had proptosis, diffuse ophthalmoplegia, and central retinal artery occlusion suggesting deep orbital involvement. Computed tomography showed soft tissue abnormalities in the anterior orbit. The patient was successfully treated with subcutaneous debridement, antibiotic therapy, and metabolic support. The authors emphasized that periorbital necrotizing fasciitis should be differentiated from true bacterial invasion of the posterior orbit, which may require more aggressive treatments such as exenteration. (See pages 181-183)

Macular hole is characterized by a full-thickness defect in the retinal layers at the foveal center, and is an important cause of central vision loss. Although most macular holes are idiopathic, it is also a common complication in eyes with high myopia. Myopic macular holes are more difficult to repair with vitreoretinal surgery than idiopathic forms. Spontaneous closure is less common. Yüksel et al. report spontaneous macular hole closure by bridge formation after 66 months in a 51-year-old woman with degenerative myopia who was diagnosed with macular hole but refused surgical intervention. (See pages 184-187)

Menteş and Barış detected bilateral asymptomatic and quiescent type 1 neovascularizations (NV) on optical coherence tomography angiography (OCTA) in a 38-year-old man who presented with low vision in both eyes and had been diagnosed with Best vitelliform macular dystrophy (BVMD) 10 years earlier. They emphasized that OCTA is a noninvasive, easy, rapid, and reliable imaging method and is superior to other imaging methods in detecting NV lesions that occur secondary to BVMD, even if quiescent and asymptomatic. (See pages 188-191)

We hope that the articles featured in the third issue of this year will be of interest to you and will guide your medical practice.

**Respectfully on behalf of the Editorial Board,**

**Özlem Yıldırım, MD**

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Original Article

# Ocular Findings of Pediatric Dry Eye Related to Graft-Versus-Host Disease

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## Abstract

**Objectives:** To evaluate the frequency and findings of dry eye associated with ocular graft-versus-host disease (GVHD) in pediatric hematopoietic stem cell transplantation (HSCT) patients.

**Materials and Methods:** Retrospectively the records of pediatric patients with ocular GVHD were evaluated and ophthalmologic examination findings as well as Schirmer test results, tear film break-up time, and corneal staining grades were recorded. In severe dry eye patients topical cyclosporine-A was prescribed and the results were evaluated.

**Results:** GVHD was detected in 51 (23.4%) of 218 HSCT patients, 4 of whom died during follow-up. Thirty (63.8%) of the remaining 47 patients had chronic ocular GVHD and 4 patients with severe dry eye were treated with topical cyclosporine-A with a median follow-up of 12.1 months. Severe dry eye symptoms and findings significantly improved in 2 patients. However, 1 patient had to stop treatment due to side effects.

**Conclusion:** In children, chronic ocular GVHD is a common finding of GVHD after HSCT. Therefore, these patients should be examined periodically for dry eye.

**Keywords:** Cyclosporine-A, dry eye, graft-versus-host disease, pediatric, Schirmer test

## Introduction

Hematopoietic stem cell transplantation (HSCT) is the mainstay therapy for malignant and benign hematological diseases like thalassemia major, aplastic anemia, leukemia, and metabolic diseases like Hurler syndrome.[1,2,3] Graft-versus-host disease (GVHD) is a clinical disease with multiple organ and system involvement due to the donor-derived T cells recognizing host antigens as foreign, and is the main cause of morbidity and mortality after HSCT.[4] Ocular involvement can occur as a manifestation of GVHD and is referred to as ocular GVHD. Although ocular involvement is more common in chronic GVHD, it can also be seen in acute GVHD.[5] Ocular findings of chronic ocular GVHD include generalized ocular surface inflammation, dry eye syndrome, superficial punctate keratitis, persistent epithelial defects, symblepharon formation, sterile and infectious stromal ulceration, lacrimal gland and meibomian gland dysfunction due to cicatricial conjunctivitis, cataracts, uveitis, retinal vasculitis, retinal hemorrhage, and optic neuropathy.

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The aim of this study was to determine the frequency of dry eye associated with chronic ocular GVHD in pediatric HSCT patients and to explore the findings of dry eye associated with chronic ocular GVHD.

## Materials and Methods

In this retrospective study, we evaluated the medical records of 218 pediatric patients who underwent allogenic HSCT between 1996 and 2015. We noted patient characteristics including gender, age, primary hematologic diseases, and follow-up period.

In our clinic we routinely perform a detailed ophthalmologic examination to all patients with HSCT before and after transplantation. Hence we could evaluate the results of ophthalmological examinations in 51 patients with GVHD every 3 months, as well as the monthly examination results of patients with severe dry eye findings.

We recorded patient complaints such as decrease in vision, dryness, photophobia, foreign body sensation, irritation, redness, burning, itching, or any other ocular discomfort. Besides full ophthalmic examination, tear stability by tear film break-up time (TFBUT) using fluorescein impregnated paper strips (ERC Fluorescein strip, ERC Medical Products, Ankara, Turkey) were classified into 4 groups based on severity (>10 s, 6-10 s, ≤5 s).[6] We assessed corneal fluorescein staining under cobalt blue illumination to enhance staining details and graded according to the Oxford scale (grade 0-5).[7] We estimated tear production by the 5-minute Schirmer test (without anesthetics) with sterile strips placed in the inferior fornix. We classified Schirmer test results into 4 groups based on severity (>10 mm, 10-6 mm, ≤5 mm).[6]

We diagnosed ocular GVHD based on the National Institutes of Health Consensus criteria (a low Schirmer test value [≤5 mm/5 min]) or new keratoconjunctivitis sicca by slit lamp examination with moderate Schirmer test value (6-10 mm/5 min) in the presence of another affected organ system.[8] We graded dry eye according to Dry Eye Workshop Criteria.[6] Severe dry eye criteria were tear production less than 5 mm/5 min with Schirmer test, TFBUT less than 5 seconds, marked central corneal staining, and presence of filamentary keratitis. We recorded pre-treatment and post-treatment ophthalmological examination findings of patients who were treated with cyclosporine-A due to severe dry eye symptoms.

The local ethics committee approved this study (report number: 08-496-18, date: 07 May 2018), which was conducted adhering to the Declaration of Helsinki.

## Results

Of all the included HSCT patients (n=218), 51 patients (23.4%) had chronic systemic GVHD. Four patients died during the follow-up period; therefore, the records of 47 patients with chronic GVHD were included. Twenty-four patients (51%) were female and 23 (49%) were male. The mean age was 11.8±2.9 (range: 3-18) years and median follow-up period was 22.3 (9-72) months. The primary hematologic diseases of patients for allogenic HSCT are shown in Table 1.

In the follow-up period, chronic ocular GVHD developed in 30 of 47 patients (63.8%). Apart from dry eye syndrome, there were no associated anterior and posterior segment findings of GVHD. The most common complaints of dry eye syndrome were burning, stinging, foreign body sensation, and photophobia and were detected in 44% of the patients. The results of examination including Schirmer test, TFBUT, and corneal staining for dry eye are shown in Table 2.

Artificial tears without preservatives and ointments were prescribed as medical treatment to the patients with dry eye symptoms. Four patients (13.3%) with Schirmer test less than 5 mm/5 min were accepted as severe dry eye and topical cyclosporine-A was added to artificial tears and ointment.

Patients with severe dry eye used topical cyclosporine-A 0.05% (Restasis, Allergan, USA) twice daily and the mean

**Table 1. Primary hematologic diseases of hematopoietic stem cell transplantation patients**

| Primary hematologic disease | Number of patients, n (%) |
|---|---|
| Thalassemia major | 28 (59.6) |
| Fanconi aplastic anemia | 4 (8.5) |
| Acute lymphoblastic leukemia | 4 (8.5) |
| Acute myeloid leukemia | 3 (6.4) |
| Other | 8 (17) |
| Total | 47 (100) |

**Table 2. Dry eye examination findings**

| Schirmer test | | Tear film break-up time | | Corneal staining | |
|---|---|---|---|---|---|
| Value (mm/5 min) | Number of patients, n (%) | Value (s) | Number of patients, n (%) | Score | Number of patients, n (%) |
| >10 | 19 (40.4) | >10 | 18 (38.3) | Grade I | 15 (31.9) |
| 6-10 | 8 (17) | 6-10 | 9 (19.1) | Grade II | 15 (31.9) |
| ≤5 | 4 (8.5) | ≤5 | 4 (8.5) | Grade III | 3 (6.4) |
| No data | 16 (34.1) | No data | 16 (34.1) | Grade IV | 2 (4.2) |
| | | | | Grade V | 2 (4.2) |
| | | | | No data | 10 (21.4) |

duration of cyclosporine-A treatment was 13.25 (9-19) months. One patient (25%) stopped treatment because of side effects such as burning and irritation; a punctal plug was inserted in this patient. There were no other side effects in the remaining 3 patients (75%). Pre-treatment and post-treatment findings of the 4 patients with severe dry eye are seen in Table 3.

## Discussion

The frequency of ocular findings in GVHD patients was reported as 45-60% in different studies and dry eye syndrome is the most frequent ocular finding in ocular GVHD.[9,10] Severe complications such as corneal vascularization, keratitis, and corneal perforation can occur due to dry eye syndrome.

The prevalence of systemic GVHD in younger patients is lower than in adults. Different studies reported chronic GVHD in the pediatric population at rates of 22% to 29%.[11,12,13] In our series, we found the prevalence of chronic GVHD similar to the other studies (23.4%). The frequency of dry eye syndrome due to ocular GVHD is also different in the pediatric population. The prevalence of dry eye syndrome in adult patients after HSCT is up to 44%.[10,14] However, the prevalence of dry eye syndrome in children is difficult to extrapolate as they can report their symptoms less than adults and also all examination methods cannot be performed easily in children. De Marco et al.[15] investigated 33 children with HSCT and 24.4% of these patients had tear hyposecretion. Suh et al.[16] reported that ocular changes developed in 51% of pediatric patients after HSCT and the frequency of dry eye syndrome was 12.5% at a mean age of 8.4 years. Hoehn et al.[17] found the prevalence of dry eye syndrome in 14-year-olds as 41.4%. In our series, dry eye was detected in 30 (63.8%) of 47 patients with GVHD at a mean age of 11.8 years. This higher frequency in our study may be due to our routine evaluation of these patients before and after HSCT regardless to the presence of any complaints.

In children, the clinical features of dry eye syndrome are similar to those in adults, but they rarely complain of dry eye symptoms. Therefore, dry eye symptoms affect the quality of life, especially at younger ages. Ng et al.[18] found that 51.7% of pediatric patients with HSCT had tear abnormalities and one third of patients had corneal staining, but none of them had dry eye symptoms. The frequency of dry eye complaints such as foreign body sensation, red eyes, discharge, and photophobia in pediatric patients was 48% in Fahnehjelm's study.[19] However, corneal staining and a short TFBUT and/or pathological Schirmer was present in 62% of patients. In our study, 44% of patients had complaints related to dry eye. Although pediatric patients with HSCT do not have any complaints, they should be examined routinely for ocular GVHD.

Prevention of evaporation, maintenance of lubrication, tear preservation, and inflammation control are the mainstay of treatment of dry eye syndrome in ocular GVHD. In our study, all patients with dry eye were prescribed artificial tears without preservatives and ointments, and patients with severe dry eye additionally received topical cyclosporine-A.

T-cell related inflammatory processes, apoptosis, and fibrosis are the causes of ocular surface disease and dry eye in ocular GVHD. Westekemper et al.[20] showed the expression of Th1-associated chemokines in the conjunctiva of patients with chronic GVHD. Cyclosporine-A is an effective treatment modality in ocular GVHD. The main mechanism of cyclosporine-A in the treatment of ocular GVHD is related to T-cell activation and downregulation of inflammatory cytokines in the conjunctiva.[21] Cyclosporine-A also decreases epithelial cell turnover and increases conjunctival goblet cell density. The concentration of cyclosporine-A in the conjunctiva is higher after topical use compared with systemic use.[22] Furthermore, topical use eliminates the systemic side effects of the drug. Therefore, with its local immunosuppressive effect, topical cyclosporine-A may be more effective and safer than systemic immunosuppressive agents in the treatment of ocular GVHD. Topical cyclosporine-A both improves Schirmer test and TFBUT, and increases the conjunctival goblet cells and reduces punctate keratopathy.[23,24]

Previous studies evaluated the effect of different concentrations and dosage of topical cyclosporine-A.[25,26] A topical cyclosporine-A concentration of 0.05% was found to be safe and effective in the treatment of moderate to severe dry eye.[23,27] Clinical signs and symptoms can improve in 4 weeks, but sustained improvement was shown with decreased immune activation markers and inflammatory cytokines and increased conjunctival goblet cell number after 6 months of treatment.[23] Kiang et al.[25] found that

**Table 3. examination findings of patients with severe dry eye**

| | | Pre-treatment | | | Post-treatment | | | |
|---|---|---|---|---|---|---|---|---|
| Patient, diagnosis | Age (years) | TFBUT (s), OD/OS | Schirmer (mm/5 min), OD/OS | Corneal staining (grade),OD/OS | TFBUT (s), OD/OS | Schirmer (mm/5 min), OD/OS | Corneal staining (grade) OD/OS | Treatment duration (months) |
| 1, ALL | 16 | 5/7 | 4/2 | III/III | 5/6 | 3/2 | III/III | 19 |
| 2, TM | 10 | 6/8 | 4/4 | II/II | 10/>10 | >10/>10 | 0/I | 14 |
| 3, ALL | 3 | 4/4 | No data | I/I | 4/4 | No data | I/I | 9 |
| 4, ALL | 9 | 3/4 | 4/4 | II/II | >10/>10 | 10/>10 | 0/I | 11 |

ALL: Acute lymphoblastic leukemia, TM: Thalassemia major, TFBUT: Tear film break-up time, OD: Right eye, OS: Left eye

topical cyclosporine-A 1% used 6-8 times/day in the active or necrotizing stage of ocular GVHD helps to promote the healing process and decrease the immunological activity of the donor lymphocytes in adult patients. Malta et al.[26] evaluated the effect of topical cyclosporine-A 0.05% in the prophylaxis and treatment of ocular GVHD and found that adults and children who did not receive cyclosporine-A until at least 6 months after HSCT had significantly more severe dry eye symptoms than patients who received topical cyclosporine-A starting 1 month before HSCT. Use of topical cyclosporine-A 0.05% improved corneal fluorescein staining in all eyes and dry eye symptoms in 62.5% of patients in a study by Lelli et al.[28] Studies about the use of topical cyclosporine-A in pediatric GVHD patients are rare. Fahnehjelm et al.[19] reported that corneal findings improved in 2 pediatric patients who used topical cyclosporine-A with a concentration of 0.1% for 1 year. In our study, the concentration of topical cyclosporine-A was 0.05%, dosing was twice daily, and the mean duration of treatment was 13.25 (9-19) months. This concentration improved dry eye findings, with improved Schirmer test and TFBUT results and reduced corneal staining, in 2 patients (50%). One patient (25%) had to stop treatment because of side effects, mainly burning, redness, and irritation.

When we considered the limitations of our study, we only gave topical cyclosporine-A to severe dry eye patients. Therefore, this group was small. In addition, we only evaluated the effect of topical cyclosporine-A at a concentration of 0.05%. Further studies with large study populations and different concentrations may be more helpful to establish the effect of topical cyclosporine-A in pediatric patients with GVHD-associated dry eye syndrome.

## Conclusion

In conclusion, dry eye is an important and common finding of GVHD in children. Therefore, all patients with HSCT should be examined, even if patients do not have complaints.

### Ethics

**Ethics Committee Approval:** Ankara University, School of Medicine (report number: 08-496-49 18, date: 07 May 2018).

**Informed Consent:** The study is retrospective.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: P.B.K., T.Ç.B., H.A., F.N.Y., Concept: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Design: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Data Collection or Processing: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Analysis or Interpretation: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Literature Search: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Writing: P.B.K., T.Ç.B., H.A., E.İ.

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Original Article

# A Retrospective Analysis of Safety and Efficacy of XEN 45 Microstent Combined Cataract Surgery in Open-Angle Glaucoma over 24 Months

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## Abstract

**Objectives:** To evaluate the effect on intraocular pressure (IOP) reduction and safety of ab interno gelatin microstent (XEN 45 Gel Stent; Aquesys, Inc, Aliso Viejo, CA, USA) microincisional glaucoma/cataract surgery in open-angle glaucoma (OAG).

**Materials and Methods:** In this retrospective study, 30 eyes of 25 patients with OAG which underwent XEN 45 implantation combined with simultaneous phacoemulsification were clinically evaluated. Clinical outcomes analyzed included IOP, percent of IOP reduction, medication use, complications, best corrected visual acuity, and surgical outcomes at 24-month follow-up.

**Results:** After the XEN 45 combined cataract surgery procedure, IOP dropped from 20.37±4.80 mmHg with a mean of 3.07±1.04 medication classes preoperatively to 14.83±1.91 mmHg with a mean of 0.94±1.11 medication classes at 24 months (p=0.001 for both). At 24 months, 55.6% of patients had IOP ≤18 mmHg without medication, 94.4% of patients had IOP ≤18 mmHg with or without medication, and 61.1% of patients reached ≥20% IOP reduction from baseline.

**Conclusion:** XEN 45 is an effective minimally invasive surgical treatment for OAG with significant reduction in IOP and glaucoma medications and minimal complications in long-term follow-up.

**Keywords:** Cataract surgery, microincisional glaucoma surgery, open-angle glaucoma, XEN 45 Gel Stent

## Introduction

Glaucoma is an important cause of blindness and affects 3.54% of people worldwide.[1] The purpose of treatment is to reduce intraocular pressure (IOP) via various treatment strategies in order to halt optic nerve injury.[2] The most common surgeries are traditional incisional surgeries which provide the drainage of aqueous fluid to the subconjunctival space with an ab externo approach.[3] Although these methods have been successful in reducing IOP, both trabeculectomy and aqueous tube shunts come with a range of short- and long-term complications like hypotony, leakage, scarring, foreign body sensation associated with blebs, astigmatism, secondary cataracts, blebitis, endophthalmitis, and choroidal hemorrhage.[3,4,5,6]

Minimally invasive glaucoma surgery (MIGS) is less invasive than traditional incisional surgeries and offers more modest results with the benefit of a safe risk profile in patients with mild to moderate glaucoma.[7] The four main approaches to IOP reduction include increasing trabecular outflow, increasing

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uveoscleral outflow via suprachoroidal pathways, reducing aqueous production from the ciliary body, and creating a subconjunctival drainage pathway via an ab interno incision.[7]

The XEN 45 Gel Stent (Aquesys, Inc., Aliso Viejo, CA, USA) is a hydrophilic tube composed of gelatin crosslinked with glutaraldehyde, with the smallest model having an inner diameter of 45 µm and a length of 6 mm, which creates subconjunctival drainage like traditional incisional glaucoma surgeries with an ab interno microincisional approach.[8,9] It was created with adequate length, tube rigidity, and lumen diameter to limit flow and avoid hypotony by using the Hagen-Poiseuille equation.[8,10]

This retrospective analysis aimed to assess the results of combined glaucoma/cataract surgery using the smallest diameter XEN 45 Gel Stent in regard to IOP-lowering effect, visual acuity, and postoperative complications in open-angle glaucoma (OAG) patients.

## Materials and Methods

### Patients and Assessments

We retrospectively analyzed 30 eyes of 25 patients who were treated with XEN 45 implantation with mitomycin C (MMC) combined with cataract surgery by the same surgeon at the Kocaeli University Department of Ophthalmology between January 2016 and January 2018. The Local Ethics Committee of the Kocaeli University approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria for the Diagnostic Innovations in Glaucoma Study of primary OAG (POAG) were glaucomatous optic neuropathy in clinical examination including thinning of neuroretinal rim with retinal nerve fiber layer loss, visual field (VF) defect, and open angle confirmed with gonioscopy.[11] The diagnosis of pseudoexfoliation glaucoma (PXG) was based on clinically visible criteria on slit-lamp examination (accumulated extracellular material in the anterior segment of the eye) with the parameters mentioned above.[12] This study included eyes with primary and secondary (pseudoexfoliation) OAG and previously diagnosed cataract that had not reached target IOP or showed progressive VF loss with maximum medical therapy, as well as eyes of patients with medication intolerance or nonadherence.

Exclusion criteria were angle-closure, congenital, and neovascular glaucoma, prior uveitis or endophthalmitis, ocular surgery history (except glaucoma surgery), and aphakia. The patients who fulfilled these inclusion criteria and underwent combined cataract surgery and XEN 45 microstent implantation were evaluated in this retrospective case study.

Complete ophthalmic examination including visual acuity, gonioscopic evaluation, IOP measurement by Goldmann applanation tonometry, anterior and posterior segment evaluation, cup/disc ratio, central corneal thickness (CCT) with a fully automatic tonometer (Canon TX-20P, Tokyo, Japan), VF testing 30-2 strategies with a Humphrey Field Analyzer model 750I (Carl Zeiss Meditec, Dublin, CA, USA), and optical coherence tomography (SD-OCT, Heidelberg Engineering, Germany) were performed preoperatively (baseline) and at 1, 3, 6, 12, and 24 months postoperatively. Thirty eyes completed 12 months and 18 eyes completed 24 months of follow-up. None of the patients were excluded from analysis. Glaucoma staging was done according to mean deviation values (mild: >-6 dB, moderate: -6 to -12 dB, and severe: <-12 dB) as described in the European Glaucoma Society Guidelines.[13]

Primary outcome measures included IOP, mean IOP reduction, percentage of IOP reduction, the number of antiglaucoma medications used and their changes in repeated measures, IOP reduction ≥20%, the mean categorized IOP (8-12 mmHg, >12-15 mmHg, >15-18 mmHg, >18 mmHg), postoperative complications, logarithm of the minimal angle of resolution (LogMAR) best corrected visual acuity (BCVA), and vision changes (gain of ≥2 lines, stable, or loss of ≥2 lines; clinically significant change in BCVA was defined as 0.2 units of logMAR) during 24-month follow-up.[14]

Secondary efficacy outcomes were determined as the rate of needling and complete and qualified success rates. Complete success was defined as a postoperative IOP ≤18 mmHg but not <5 mmHg with ≥20% reduction in IOP without medication. Qualified success was defined as a postoperative IOP ≤18 mmHg but not <5 mmHg with ≥20% reduction in IOP with or without medication.[15]

### Surgical Technique

A single surgeon performed all surgical procedures under peribulbar anesthesia. After skin disinfection, the superior nasal conjunctiva was marked 3 mm from the limbus, then 0.1 mL of MMC (0.02%) was injected subconjunctivally using a 27-gauge needle and spread with a microsponge in the superior nasal quadrant. The surgeon performed cataract surgery using a 2.8-mm main incision at the 12 o'clock position and two 1.2-mm sideport incisions at the 10 and 2 o'clock positions. At the end of cataract surgery, the anterior chamber was filled with a cohesive viscoelastic device. A new incision was made for XEN implantation. The new clear corneal incision of 1.2 mm opposite the site (inferior temporal quadrant) of the desired XEN implant implantation (superior nasal quadrant) was performed using a metal keratome. The XEN handheld disposable injector was inserted through the opposite clear corneal incision. We used gonioscopy to verify correct placement and avoid iris insertion. The injector needle penetrated the angle and formed a tunnel through the sclera, emerging approximately 3.0 mm posterior to the limbus. The implant remained in position with further rotation of the dial. Having 2 mm of exposed implant in the subconjunctival space and 1 mm in the anterior chamber was accepted as ideal placement. The cohesive viscoelastic device was irrigated and the sideports and main incision were hydrated. The anterior chamber was pressurized. Bleb formation was readily visible.

All glaucoma medications were discontinued on the day of surgery, prednisolone acetate 1.0% drops (Pred Forte, Allergan) were used 6 times a day for 1 month and then tapered over 1 month. Moxifloxacin 0.5% drops (Vigamox, Alcon) were used

4 times a day for 15 days. Postoperatively, additional glaucoma medications were used as necessary.

If postoperative IOP was higher than target and flat or cystic bleb formation was observed, needling with MMC was performed. A 27-gauge angled needle was advanced subconjunctivally to the tip of the stent and the fibrous tissue around it. Using the tip of the needle, adhesions around the stent were disintegrated and the tip of the implant was released in flat blebs. In cystic blebs, the cyst was opened with the tip of the needle and all its walls were lysed. Then 0.1 ml of MMC (0.02%) was injected subconjunctivally in all needlings (Figure 1A-D).

### Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess the assumption of normality. Numerical variables were expressed as mean ± standard deviation, and categorical variables were summarized as count (percentage). Preoperative values were defined as baseline values. The changes in variables between time periods were analyzed by paired t test and Wilcoxon Signed Rank Test for normally and non-normally distributed variables, respectively. A two-sided p-value less than 0.05 was considered statistically significant.

## Results

### Baseline Parameters

Thirty eyes of 25 patients were included in our retrospective study. Seventeen patients (56.7%) were male and 13 patients (43.3%) were female. The mean age of the patients was 66.1±8.1 (49-81) years. Nineteen eyes (63.3%) had POAG and 11 eyes (36.7%) had PXG. In 4 patients, both eyes were included in the study and bilateral surgery was performed. Mean CCT was 562±21.71 µm and the mean cup/disk ratio was 0.52±0.24. The mean preoperative IOP was 20.37±4.80 mmHg with a mean of 3.07±1.04 medications. There was no statistically significant difference in preoperative IOP and medication use between POAG and PXG groups. Eleven patients (36.7%) had mild, 9 patients (30%) had moderate, and 10 patients (33.3%) had severe glaucoma. There was no statistically significant difference between POAG and PXG groups in terms of cup/disk ratio (p=0.611) and glaucoma stage (p=0.226). There were no major complications during implantation surgery and all cataract surgeries were uneventful. All patients completed the 12-month examination and 18 of them completed the 24-month follow-up. The mean follow-up time was 22.90 ± 8.22 months. All demographic and clinical baseline parameters are shown in Table 1.

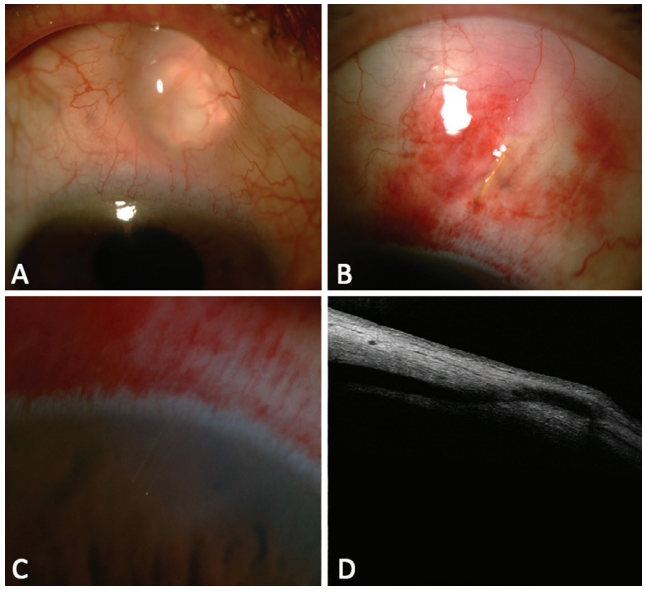


**Figure 1.** Color photograph showing cystic bleb formation requiring needling (A), the placement of the device subconjunctivally after needling (B), scanning of the suitable placement of the apparatus in the angle and anterior chamber (C). Anterior segment optic coherence tomography image showing the presence of XEN implant through the sclera (D)

### IOP and Medication Use

At 12 and 24 months, mean IOP decreased significantly to 15.0±1.91 mmHg and 14.83±1.91 mmHg (p<0.001 for both) with a mean of 0.87±1.13 and 0.94±1.11 medication classes (p<0.001 for both). None of the patients was using more medications compared to preoperative medication count. The mean number of medications used at 12 months was 1.05±1.22 and 0.55±0.93 in the POAG and PXG groups, respectively (p=0.350). At 24 months, there was a statistically significant difference in terms of medication use between POAG and PXG groups (1.63±1.06, 0.40±0.84, respectively) (p=0.043). IOP was reduced by a mean of 23.3% and 27.2% at 12 and 24 months of follow-up, respectively (Figure 2a-c). There was no statistically significant difference between PXG and POAG patients according to postoperative IOP or mean IOP reduction at 12 and 24 months. At 12 and 24 months, mean IOP reduction from baseline was -6.16±0.92 mmHg (95% confidence interval [CI]: -4.22, -8.11) and -6.44±1.19 mmHg (95% CI: -3.91, -8.96), respectively.

### Surgical Success

The distribution of patients according to the surgical success parameters is shown in Table 2. At 12 and 24 months, 96.7% and 94.4% of patients had IOP ≤18 mmHg, and 70% and 61.1% of patients achieved ≥20% IOP reduction from baseline with or without medication, respectively. The qualified success rate of the procedure was 70% and 61.1% and the complete success rate was 40% and 33.3% at 12 and 24 months, respectively. There was no statistically significant difference in terms of complete and qualified success rates between the PXG and POAG groups.

### BCVA Results

The mean preoperative LogMAR BCVA was 0.38±0.52, which improved significantly to 0.21±0.46 and 0.31±0.56 at 12 and 24 months (p<0.001, p=0.004, respectively) (Figure 2d). At month 12, 46.7% of patients gained ≥2 lines of BCVA, 53.3% had stable BCVA, and none lost ≥2 lines of BCVA. At month 24, 44.4% of patients gained ≥2 lines of BCVA, 55.6% had stable

| Table 1. Evaluation of the baseline parameters and primary surgical outcomes | |
|---|---|
| **Demographic and clinical data** | |
| Age (years), mean ± SD | 66.17±8.19 |
| Male/female, n (%) | 17 (56.7)/13 (43.3) |
| Right/left eyes, n (%) | 16 (53.3)/14 (46.7) |
| Bilateral cases, n (%) | 4 (13.3) |
| Primary open angle, n (%) | 19 (63.3) |
| Pseudoexfoliation, n (%) | 11 (36.7) |
| Central corneal thickness (µm), mean ± SD | 562.0±21.71 |
| Baseline BCVA LogMAR (mean ± SD) | 0.38±0.52 |
| Baseline IOP (mmHg), mean ± SD ($25^{th}$-$75^{th}$ percentile) | 20.37±4.80 (17.0-23.0) |
| Baseline medications, mean ± SD | 3.07±1.04 |
| M12 BCVA (LogMAR), mean ± SD | 0.21±0.46 |
| M12 IOP (mmHg), mean ± SD ($25^{th}$-$75^{th}$ percentile) | 15.0±1.91 (14.0-16.0) |
| M12 medications, mean ± SD | 0.87±1.13 |
| M24 BCVA (LogMAR), mean ± SD | 0.31±0.56 |
| M24 IOP (mmHg), mean ± SD ($25^{th}$-$75^{th}$ percentile) | 15.17±3.31 (13.75-16.0) |
| M24 medications, mean ± SD | 0.94±1.11 |

SD: Standard deviation, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution; IOP: Intraocular pressure, M12: Postoperative month 12, M24: Postoperative month 24

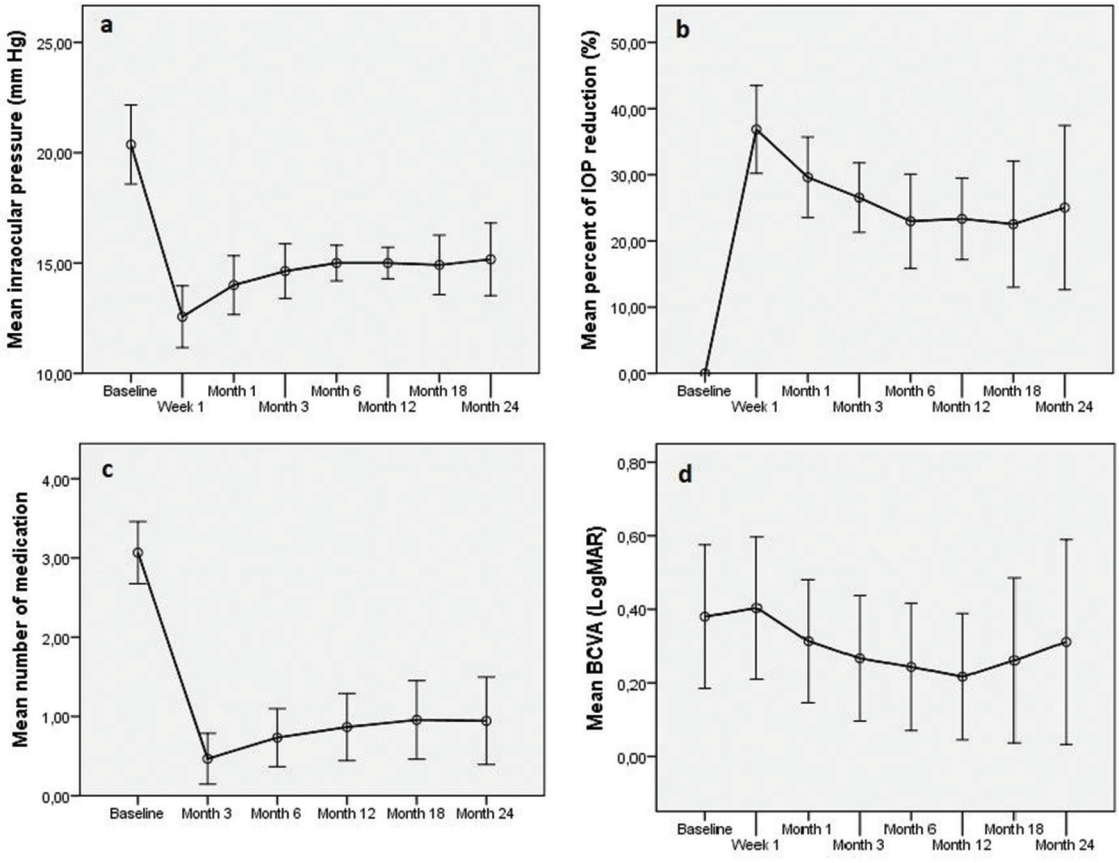


**Figure 2.** Mean IOP (a), mean percentage of IOP reduction (b), mean number of IOP lowering medication (c) and the change of mean BCVA LogMAR (d) over 24 months after XEN 45 Gel Stent implantation with cataract surgery. Error bars represent two standard deviations
*IOP: Intraocular pressure, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimal angle of resolution*

BCVA, and none lost ≥2 lines of BCVA. The change in BCVA values was similar in PXG and POAG patients, and there was no significant difference between them according to BCVA values at 12 and 24 months (p=0.497, p=0.068, respectively).

**Needling Intervention**

Thirteen patients (43.3%) required needling during follow-up. Needling was needed in the first week in 1 patient (7.7%), between 1 week and 3 months in 11 patients (84.6%), and after 3 months in 1 patient (7.7%). Seven patients required needling procedure twice and 1 patient required it 4 times. The patient requiring needling 4 times needed additional glaucoma surgery due to stent insufficiency. This patient had trabeculectomy history and the etiology of glaucoma was POAG. The mean IOP was 25.9±5.3 mmHg pre-needling and was 18.2±5.3 mmHg after needling (p<0.001). No patient had hypotony or anterior chamber shallowing after needling. The rate of needling intervention was 47.4% in PXG and 36.4% in POAG patients. There was no statistically significant difference in needling requirement between PXG and POAG patients (p=0.708).

**Surgical Complications**

There were no cases of endophthalmitis, wound leak, device exposure or migration, macular edema, choroidal effusion or hemorrhage, iritis, or retinal detachment over 24 months. One patient had hyphema on postoperative day 1 that resolved completely by 1 week with topical steroid and cycloplegic eye drops. One patient had additional glaucoma surgery (aqueous tube shunt) at postoperative 3 months because of stent insufficiency. This patient had trabeculectomy history and the etiology of glaucoma was POAG. In terms of complications, there was no statistically significant difference between the POAG and PXG groups (p=1.000).

**Discussion**

Although cataract surgery provides a decrease in IOP, additional glaucoma surgery is required in some glaucoma patients.[16,17,18] Combined procedures with traditional surgery methods had additional risks related to the surgery type.[4,19] Because of this, new MIGS techniques were adopted. The XEN 45 Gel Stent is an apparatus that shunts aqueous to the subconjunctival space via a minimally invasive ab interno approach. This type of subconjunctival drainage avoids the risk of outshow obstruction while lowering IOP, and the XEN Gel Stent is the only filtering MIGS device that works in this way. The ab interno installation of the device provides safety with a low rate of long-term complications. Although some complications have been reported as case reports, rates of serious complications are lower than in traditional surgery.[20]

In a prospective clinical study with XEN 45 Gel Stent combined cataract surgery, 80.4% of patients had IOP ≤18 mmHg at 12 months.[21] In a multicenter open-label study, 75.4% of patients had ≥20% IOP lowering from baseline on the same or fewer medications at 12 months, while this rate was 70.0% in our study.[22] Similar to the literature, 61.1% of patients reached ≥20% IOP reduction from baseline and 94.4% of patients had IOP ≤18 mmHg at 24 months in our study. The percentage of IOP reduction could differ according to baseline IOP and the indication (medication intolerance or nonadherence). Moreover, almost all patients had IOP ≤18 mmHg with a lower number of medications at 12 months and this benefit continued over 24 months.

IOP reduction of 36.4% and 30% was reported in clinical studies with XEN 140 without MMC and with XEN 140 and XEN 63 combined with cataract surgery without MMC, respectively.[23,24] In a prospective study of the XEN 45 microimplant with MMC, 29.4% reduction in IOP was reported.[25] Our IOP reductions were 23.3% and 27.2% at months 12 and 24, respectively. Different degrees of IOP reduction could be related to the proportion of patients with well-controlled IOP in study populations and the distribution of patients with different types of OAG. The results vary depending on many factors such as the type of XEN stent used, whether glaucoma surgery is applied in conjunction with cataract surgery, and the use of MMC, but sufficient IOP lowering and decreased

**Table 2. Surgical success parameters**

| | **Preoperative (n=30), % (n)** | **Month 12 (n=30), % (n)** | **Month 24 (n=18), % (n)** |
|---|---|---|---|
| **IOP category** | | | |
| 8-12 mmHg | 0.0 (0) | 0.0 (0) | 0.0 (0) |
| >12-15 mmHg | 16.6 (5) | 63.3 (19) | 66.7 (12) |
| >15-18 mmHg | 23.3 (7) | 33.3 (10) | 27.8 (5) |
| >18 mmHg | 60.0 (18) | 3.3 (1) | 5.6 (1) |
| **≥20% IOP Reduction** | | | |
| Without medication | | 40.0 (12) | 33.3 (6) |
| With or without medication | | 70.0 (21) | 61.1 (11) |
| **≤18 mmHg the mean of IOP** | | | |
| Without medication | | 60.0 (18) | 55.6 (10) |
| With or without medication | | 96.7 (29) | 94.4 (17) |
| Qualified success | | 70.0 (21) | 61.1 (11) |
| Complete success | | 40.0 (12) | 33.3 (6) |

medication use are reported in all studies. Ozal et al.[26] reported that the patients who underwent cataract surgery with XEN implantation and those who underwent only XEN implantation were similar in terms of IOP reduction. In our study, combined cataract surgery with XEN implantation was applied to all patients because they had cataracts and glaucoma. Therefore, no comparison was made in terms of these conditions in our study. When evaluated in the light of the literature data, as XEN implantation is an ab interno surgery that does not cause conjunctival damage, it is thought that inflammation induced by cataract surgery will not affect surgical success as much as trabeculectomy. Combined surgery also decreases the burden of multiple surgeries.

At 12 and 24 months, the qualified success rates of our procedure were 70% and 61.1%, and complete success was achieved in 40% and 33.3%, respectively. Using the same criteria for complete and qualified success, Gillmann et al.[27] reported complete success rates of 24.5% and 36.4% and qualified success rates of 30.6% and 38.6% at 24 months in their POAG and PXG groups, respectively. Many factors can determine surgical success, including low baseline and postoperative IOP and higher number of baseline medications, because the success rate calculations are based on both postoperative IOP 5-18 mmHg and ≥20% IOP reduction.[27]

The rate of needling was 43.3% in our study, 47% in a study by Sheybani et al.[23] in which MMC was not used, 30.7% in a study by Galal et al.[25], 27% in a study by Hengerer et al.[25] in which MMC was used during implantation, and 43.0% in the study by Gillmann et al.[27] in which MMC was used. We thought that the difference between percentages could be related to MMC use and the profile of the study groups (PXG, POAG, and pigmentary glaucoma). According to our results, PXG patients required more needling interventions than POAG patients, but this difference was not statistically significant. Average needling times were reported as 4.5 months by Mansouri et al.[28] and between 1 week and 3 months by Hengerer et al.[24] In our study, the mean time to needling was between 1 week and 3 months in 84.6% of patients.

## Conclusion

This study has limitations such as the small sample size and noncomparative design. Nevertheless, we provided valuable data for clinicians when choosing the procedure for their patients. This retrospective study demonstrated that XEN 45 implantation in patients with inadequately controlled IOP despite maximum medical therapy or in patients with medication intolerance or nonadherence provided significant reductions in IOP and medication use and improved visual acuity with high success rates and low complication rates during follow-up.

### Ethics

**Ethics Committee Approval:** The Local Ethics Committee of the Kocaeli University approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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

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Original Article

# Causes of Blindness in Adults in Southern Turkey According to Health Committee Reports

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## Abstract

**Objectives:** To reveal the causes of blindness in patients who applied to the medical board of a hospital serving the Southeastern Anatolian region of Turkey.

**Materials and Methods:** We retrospectively reviewed the records of 340 bilaterally blind patients who were among 3,234 patients referred to our hospital's medical board between March 2016 and November 2018 for disability evaluation and rating report.

**Results:** One-hundred sixty (48.8%) were female, 174 (51.2%) were male, and the mean patient age was 64.3±25.4 years. The most common cause of blindness was cataract in 158 eyes (23.2%), followed by corneal opacities in 114 eyes (16.8%), retinal dystrophy in 92 eyes (13.5%), optic atrophy in 73 eyes (10.7%), glaucoma in 65 eyes (9.6%), and phthisis bulbi in 59 eyes (8.7%).

**Conclusion:** Avoidable causes of blindness such as cataract and corneal opacity (secondary to trachoma) were detected at high rates. Therefore, we believe that more awareness and effort might be required in our region to reduce avoidable blindness due to these causes.

**Keywords:** Visual impairment, epidemiology of visual impairment, blindness, low vision

## Introduction

Visual impairment is one of the greatest public health problems worldwide, especially in developing countries. The World Health Organization (WHO) World Report on Vision, prepared in 2019, states that at least 2.2 billion people have vision impairment globally.[1] Among the 1 billion of these individuals with an impairment that could have been prevented or has yet to be addressed, uncorrected presbyopia tops the list, affecting 826 million people. Next highest is unaddressed refractive error (123.7 million), followed by cataract (65.2 million), glaucoma (6.9 million), corneal opacities (4.2 million), diabetic retinopathy (3 million), and trachoma (2 million). The WHO report notes that 1 billion is almost certainly an underestimation, as potentially preventable cases of age-related macular degeneration (AMD) are unknown and data on childhood visual impairment is hard to come by. The report does estimate a visually impaired AMD population of 10.4 million among the 2.2 billion overall cases. Cataract, uncorrected refractive error, and AMD are the major causes of visual impairment.[2] However, the prevalence and etiology of blindness may differ between different geographical regions and ethnic groups.[3,4,5,6] The WHO report also points out that the burden of eye conditions and vision impairment is often far greater in people living in rural areas, those with low incomes, women, older people, people with disabilities, ethnic minorities, and indigenous populations.[1]

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Visual impairment does not only concern health and rehabilitation services but is also a concern in the areas of education, employment, and social security. Ophthalmologists play an important role in the application of most suitable rehabilitation methods for people with visual loss and helping them to receive the social security benefits they deserve. The single most important way to achieve these goals is to determine the clinical features of visual impairment. Epidemiological evaluation of visual impairment helps improve preventive and therapeutic health services.

A disability report is a document issued by hospital medical boards that describes and measures disability and health. It allows persons with disabilities to exercise their social rights and also serves as a medical certificate for employment. Turkish law defines "blind eye" as functionally blind eye (BCVA ≤0.02) or anatomically blind eye (no eyeball). A bilaterally blind patient's visual system impairment rating is calculated as 100%, which means the patient has a whole-body impairment rating of 90%.[7]

The aim of this study was to determine the underlying ocular diseases in people who had a disability report with 90% whole-body impairment rating due to their visual system impairment rating.

## Materials and Methods

In this retrospective study, the medical records of 3,234 patients who had appealed to the hospital medical board for evaluation of their disability status between March 2016 to November 2018 were evaluated. Institutional review board approval was obtained from the local ethics committee and the study was conducted in accordance with the Declaration of Helsinki. No informed consent was obtained since this was a retrospective study. Patient information that is available through the hospital information system and the health board reports were reviewed.

Patients who appealed to the medical board for disability reports were included in this study. Other health report applications for gun license, medication, medical certificate, invalidity retirement, and special education were excluded from the study. All cases were evaluated by the medical board based on the "Regulation on Disability Criteria, Classification, and Medical Board Reports for Disabled People" published in Official Gazette number 28603, dated 30.03.2013.[8] According to this regulation, an individual's rated disability (loss of whole body function) is expressed as a percentage (0-100%). As described above, blindness was defined as functional (BCVA ≤0.02) or anatomical (no eyeball). Bilaterally blindness (whether functional or anatomical) is rated as 100% visual impairment and results in a whole-body impairment rating of 90%. Patients who had a disability report with 90% whole-body impairment due to a visual impairment rating of 100% were included.

In the previous disability regulation (2013), a disabled person, congenital or acquired, refers to a person who has difficulties in adapting to social life and meeting their daily needs and needs protection, care, or rehabilitation, counseling, and support services due to loss of their physical, mental, spiritual, sensory, and social abilities to various degrees. Severely disabled persons, those whose disability rate is determined to be 50% or higher, are those who have been evaluated by the health committee as unable to perform their daily life activities without the help of others. In the current disability regulation (2019), individuals who are judged to be unable to perform their daily living activities on their own despite receiving help are defined as "fully dependent disabled individuals" based on the evaluation of reasoning ability in connection with disability due to tissue, organ and/or function loss and/or psychiatry diagnosis. People who have a corrected visual acuity of 20/200 or less in the better-seeing eye and field of view of 20 degrees or less in the better-seeing eye are called legally blind. In the regulation text, the fully dependent disabled person is described on the basis of body functions in necessary daily activities. According to this regulation, a legally blind person may not be defined as a fully dependent disabled person if otherwise healthy. This study included subjects defined as severely disability according to the previous regulation.

The patients' age, gender, best corrected visual acuity (BCVA), and anterior and posterior segment examination records were obtained.

### Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (IBM Corp, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages.

## Results

Of the total 340 patients, 166 (48.8%) patients were female and 174 (51.2%) patients were male. The mean patient age was 64.3±25.4 years. When both eyes of the 340 patients were reviewed, the most common cause of blindness was cataract in 158 eyes (23.2%). This was followed by corneal opacities in 114 eyes (16.8%), retinal dystrophy in 92 eyes (13.5%), optic atrophy in 73 eyes (10.7%), glaucoma in 65 eyes (9.6%), phthisis bulbi in 59 eyes (8.7%), proliferative diabetic retinopathy in 32 eyes (4.7%), AMD in 22 eyes (3.2%) eyes, bullous keratopathy 18 eyes (2.6%), retinal detachment in 18 eyes (2.6%), degenerative myopia in 13 eyes (1.9%), microphthalmus in 6 eyes (0.9%), anophthalmus in 3 eyes (0.4%), corneal dystrophy in 2 eyes (0.3%), nystagmus in 2 eyes (0.3%), uveitis in 2 eyes (0.3%), and aphakia in 1 eye (0.1%). Table 1 shows the causes of blindness in right and left eyes.

Cataract (24.7%) was the most common cause of vision loss in female patients. Corneal opacity (19.9%) and retinal dystrophy (12%) were other common causes. Similarly, in males the most common cause was cataract (19.5%), followed by optic atrophy (16.1%) and retinal dystrophy (14.9%) (Table 2). The male group was younger than the female group (60.1±24.1 years and 68.6±24.1 years, respectively). The difference in mean age between the two groups was statistically significant (p=0.002).

When evaluated by age group, the most common causes of blindness were retinal dystrophy in patients aged <15 years (n=9, 4.5%) and 15-40 years (n=21, 40.4%), and cataract (n=72, 27.1%) in patients aged >40 years. The highest rates of cataract (27.1%) and corneal opacity (18.4%) were observed in patients aged >40 years (Table 3).

## Discussion

Even though access to health services has increased for all socioeconomic groups in Turkey recently, the high incidence of cataracts, which can be corrected by surgery, and traumatic causes of blindness such as phthisis bulbi and corneal opacities indicate that health consciousness remains low.

**Table 1. The causes of blindness in patients**

| Ocular pathologies | Right eyes n (%) | Left eyes n (%) |
|---|---|---|
| Cataract | 75 (22.1) | 83 (24.4) |
| Corneal opacity | 54 (15.9) | 60 (17.6) |
| Retinal dystrophy | 46 (13.5) | 46 (13.5) |
| Optic atrophy | 37 (10.9) | 36 (10.6) |
| Glaucoma | 34 (10.0) | 31 (9.1) |
| Phthisis bulbi | 33 (9.7) | 26 (7.6) |
| PDR | 16 (4.7) | 16 (4.7) |
| AMD | 11 (3.2) | 11 (3.2) |
| Bullous KP | 10 (2.9) | 8 (2.4) |
| RD | 10 (2.9) | 8 (2.4) |
| Degenerative myopia | 6 (1.8) | 7 (2.1) |
| Microphthalmus | 3 (0.9) | 3 (0.9) |
| Other diseases | 5 (1.5) | 5 (1.5) |

PDR: Proliferative diabetic retinopathy, AMD: Age-related macular degeneration, KP: Keratopathy, RD: Retinal detachment

Cataract, followed by glaucoma, AMD, childhood blindness, corneal opacities, uncorrected refractive errors, trauma, and diabetic retinopathy were reported as the main causes of visual impairment by the WHO.[9] Negrel et al.[4] determined cataract (50.0%), corneal diseases (15.0%), glaucoma (12.0%), phthisis bulbi (6.0%), and optic atrophy (6.0%) as common causes of blindness in southern Turkey. Apart from our findings that are consistent with these results, we also found that retinal dystrophy was reported in 92 (13.5%) eyes. This difference in outcomes might be due to differences in study design, since our study included subjects applying to a medical board for a disability report. In a study designed similarly to ours, the most frequent causes of visual impairment were reported as

**Table 2. The causes of blindness in patients according to gender**

| Ocular pathologies | Female n (%) | Male n (%) |
|---|---|---|
| Cataract | 41 (24.7) | 34 (19.5) |
| Corneal opacity | 33 (19.9) | 21 (12.1) |
| Retinal dystrophy | 20 (12) | 26 (14.9) |
| Optic atrophy | 9 (5.4) | 28 (16.1) |
| Glaucoma | 15 (9) | 19 (10.9) |
| Phthisis | 13 (7.8) | 20 (11.5) |
| PDR | 14 (8.4) | 2 (1.1) |
| AMD | 6 (3.6) | 5 (2.9) |
| Bullous KP | 4 (2.4) | 6 (3.4) |
| RD | 5 (3) | 5 (2.9) |
| Degenerative myopia | 3 (1.8) | 3 (1.7) |
| Other diseases | 3 (1.8) | 5 (2.9) |

PDR: Proliferative diabetic retinopathy, AMD: Age-related macular degeneration, KP: Keratopathy, RD: Retinal detachment

**Table 3. The causes of blindness according to age groups**

| | Age (years) | | |
|---|---|---|---|
| **Ocular pathologies** | **<15 (n=22)** | **15-40 (n=52), n (%)** | **>40 (n=266), n (%)** |
| Cataract | 1 (4.5) | 2 (3.8) | 72 (27.1) |
| Corneal opacity | 1 (4.5) | 4 (7.7) | 49 (18.4) |
| Retinal dystrophy | 9 (4.5) | 21 (40.4) | 16 (6.0) |
| Optic atrophy | 5 (22.7) | 10 (19.2) | 22 (8.3) |
| Glaucoma | 1 (4.5) | 4 (7.7) | 29 (10.9) |
| Phthisis bulbi | 0 | 6 (11.5) | 27 (10.2) |
| PDR | 1 (4.5) | 0 | 15 (5.6) |
| AMD | 0 | 0 | 11 (4.1) |
| Bullous KP | 0 | 0 | 10 (3.8) |
| RD | 2 (9.1) | 1 (1.9) | 7 (2.6) |
| Degenerative myopia | 0 | 0 | 6 (2.3) |
| Other diseases | 2 (9.1) | 4 (7.7) | 2 (0.8) |

PDR: Proliferative diabetic retinopathy, AMD: Age-related macular degeneration, KP: Keratopathy, RD: Retinal detachment

macular diseases, evisceration and phthisis bulbi, amblyopia, optic nerve diseases, degenerative myopia, and acquired corneal and hereditary retinal diseases.[10] Kıvanç et. al.[11] also selected their study population from medical board records and studied subjects aged 64 years or over. They found that cataract, glaucoma, and AMD were the common ocular diseases causing severe disabilities in older patients. Another important point is that demographic features influence the result. For example, another study conducted in a relatively more developed socioeconomically region in Turkey revealed AMD, Stargart's disease, and myopic degeneration as the most common causes of visual impairment.[12] In our study, cataract, corneal opacity, and retinal dystrophy were detected at high rates among people with blindness. Low sociocultural development may be the reason for this outcome. In addition, the high frequency of retinal dystrophy can be explained by the high incidence of consanguineous marriages in the region. A study evaluating parental consanguineous marriage among patients with visual impairments in Turkey found choroidal and retinal diseases as the main underlying cause of visual impairment (62.7%), followed by nystagmus (23.7%), optic tract and nerve diseases (11.0%), congenital cataracts (0.8%), and glaucoma (1.7%). The authors also reported parental consanguinity in 26.3% of the patients, which was significantly more common in the 15- to 30-year age group (50%) compared to the other age groups.[13]

Uncorrected refractive errors are another important cause of visual impairment worldwide.[14,15] However, the medical board does not take visual impairments that can be corrected by refraction into account; therefore, our study does not provide any information about frequency of refractive errors.

A large cohort study conducted by Buch et al.[16] found that unilateral blindness is caused by AMD (57.0%), glaucoma (14.0%), and degenerative myopia (14.0%) in patients younger than 64 years, whereas optic nerve diseases (29.0%), retinitis pigmentosa (29.0%), and glaucoma (14.0%) were the most common causes in patients aged over 64 years. In this study, all of the subjects were bilaterally blind. When we evaluated right and left eyes separately, the results were very similar. The most common causes of blindness were cataract, corneal opacity, and retinal dystrophy in both eyes with approximately equal percentages. That means if a patient becomes blind in one eye, it will not be surprising the other eye also may become blind due to the same ocular disease. Since taking care of a disabled individual requires extra expenditure from both families and the community, taking preventive measures to protect the healthy eye is very important.

### Study Limitations

Another fact is that blindness and visual impairment are not only age-related but also related to gender and socioeconomic level.[17] Our study has shown that cataract was the most common cause of blindness for both sexes, whereas the second most common reason was corneal opacity for women and optic atrophy for men. This finding should be questioned because this is a retrospective study and the etiology of optic atrophy is unknown. This an important limitation of this study. Another limitation is that we do not have the socioeconomic data of the patients and their families. To our knowledge, socioeconomic level is generally low in the region and our comments are based on this assumption.

## Conclusion

In conclusion, this study found that retinal dystrophy and optic atrophy were the most common causes of blindness in the whole sample after cataract and corneal opacities. We speculate that this might be due to increased consanguineous marriage rate in southern Turkey. We would like to emphasize that since this study only included patients who appealed to a medical board in a specific geographic region, these results may not be a projection of the entire population of patients with blindness in Turkey. Still, this study contributes to efforts to identify the causes of blindness in Turkey. We believe these results are useful for the development of screening programs and vision rehabilitation services.

### Ethics

**Ethics Committee Approval:** University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (number: 269).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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

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Original Article

# Is Fixation Preference a Potential Indicator of Macular Function in Children?

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## Abstract

**Objectives:** Fixation preference testing is widely used to detect amblyopia, particularly in preverbal children. Pattern electroretinogram (pERG) is an electrophysiological test which is a sensitive indicator of macular function. The aim of this study was to investigate the relationship between fixation preference and macular function on pERG in children with strabismus.

**Materials and Methods:** The study included 11 children with strabismus. All underwent ophthalmological examination including fixation preference by binocular fixation pattern test, best corrected visual acuity (BCVA) assessment, and pERG.

**Results:** The mean age of the patients was 10.09±1.18 years. All patients had unilateral fixation. The mean BCVA was 0.85±0.17 in preferred and 0.48±0.19 in non-preferred eyes (p=0.003). The mean p50 amplitude was 6.07±2.06 µV in preferred and 5.29±2.20 µV in non-preferred eyes (p=0.203), and the mean N95 amplitude was 8.27±2.86 µV and 8.03±3.24 µV respectively (p=0.594). BCVA was correlated with p50 and N95 amplitudes in the non-preferred eyes (p=0.023 and p=0.014). Interocular BCVA difference was correlated with interocular P50 amplitude difference (r=0.688, p=0.019).

**Conclusion:** Although amblyopia is typically considered a cortical phenomenon, future larger studies are needed to investigate the relationship between fixation preference and macular electrophysiological function.

**Keywords:** ERG, fixation, macular function, pattern ERG, strabismus

## Introduction

Visual acuity is a precise and established indicator of macular function. However, subjective evaluation of visual function is almost impossible in preverbal children. Vision can only be assessed qualitatively in this age group by fixation testing and tracking eye movements. Amblyopia, which can be considered a pediatric ophthalmological emergency, is defined as an interocular difference in visual acuity of 2 or more Snellen or logMAR lines.[1] Visual acuity measurement is imperative in amblyopia for diagnosis, follow-up, and assessment of treatment results. Thus, a valid evaluation of monocular visual acuity is always necessary in children.

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Clinical evaluation of fixation behavior can be used to estimate visual performance in children. The induced tropia test and binocular fixation pattern test have been introduced to assess equality of vision in preverbal children. Binocular fixation pattern assessment is a better option to estimate fixation preference in preverbal children with strabismus, whereas the induced tropia test with prisms can be used in children with a deviation of ≤10 prism diopters (PD) or without strabismus.[2,3,4] Fixation preference tests provide a qualitative measurement of vision. It is believed that children prefer to fixate with the healthy eye and there is no fixation preference in the absence of amblyopia.

Pattern electroretinogram (pERG) is a non-invasive clinical electrophysiological test which is mostly derived from macular ganglion cells.[5] The signal is very sensitive and can be affected by poor refraction or ocular surface and media problems that reduce the optical quality of the stimulus and retinal image.[5] P50 and N95 are the major components of pERG that reflect macular function.[5] pERG may also be combined with full-field ERG to differentiate macular and generalized retinal dysfunction, and with visual evoked potentials to differentiate macular and optic nerve dysfunction.[5]

The hypothesis of the present study was that fixation preference in a strabismic child may be associated with better ipsilateral macular function, thus suggesting a possible correlation between fixation preference and pERG signals, especially P50 amplitude. The purpose of the present study was to electrophysiologically evaluate macular function in children with strabismus and investigate its correlation with fixation preference.

## Materials and Methods

A total of 11 children with horizontal strabismus were recruited for the study. The study was conducted in full accordance with the tenets of the Declaration of Helsinki and was carried out upon approval of the Institutional Ethics Committee (GO 17/561-23). Informed consent was obtained from the parents. All children under 15 years old who had heterotropia of more than 10 PD, were able to undergo monocular visual acuity assessment, and had reliable pERG recordings were included. Patients with other ocular morbidities and systemic diseases were excluded.

All children underwent a complete ophthalmological and orthoptic work-up including best corrected visual acuity (BCVA) in decimal at distance and fixation preference. The same experienced pediatric ophthalmologist (H.T.S.) tested the fixation preference in all children with binocular fixation pattern test. The evaluation of fixation was performed with appropriate spectacles on according to full cycloplegic refraction by having the patient fixate with both eyes open at the same time. An accommodative fixation target was shown. Then, the non-deviating eye is occluded to allow the deviating eye to fixate. After the removal of the occluder, if the non-preferred eye cannot hold the fixation, a fixation preference is suggested and noted as right or left. If there is spontaneous alternation between both eyes during fixation or each eye can hold the fixation through blinking or smooth pursuit, the fixation preference is categorized as free alternation. The fixation characteristic was noted as unilateral or free alternation. The grade of the fixation was not included in the analysis. Fusion was evaluated with Worth 4-Dot test and stereopsis with Titmus test.

All patients underwent pERG recorded with DTL electrodes placed in the fornix of the lower eyelid (Roland Consult, Germany). The pERG protocol incorporated the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV).[6] Recordings were obtained from non-dilated eyes with appropriate refractive correction in place. According to the ISCEV guideline, the large positive component at 50 ms was defined as P50 and the following large negative component at 95 ms as N95.[6] Because external factors affecting optic quality may interfere with pERG recording, the best effort was made to position the electrodes appropriately to obtain stable and reliable pERG signals. Monocular stimulation was used during recording because of ocular misalignment.

### Statistical Analysis

All statistical analyses were performed by using IBM SPSS Statistics 23.0 software (IBM Corp, Armonk, NY, USA). Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for quantitative data according to the assumption of normal distribution, and frequency (percentages) for qualitative data. The Wilcoxon signed-rank test was used to compare two related samples. Relationships between variables were evaluated using Spearman's rank correlation coefficient. A p value less than 0.05 was accepted as statistically significant.

## Results

A total of 11 patients met the inclusion criteria. The mean age of the patients was 10.09±1.18 (9-12) years. In all patients, fixation was unilateral.

The mean BCVA was 0.85±0.17 in the preferred eye and 0.48±0.19 in the non-preferred eye (p=0.003). The mean amount of horizontal deviation (1 exo-deviations and 10 eso-deviations) was 21.36±9.51 (16-46) PD. The spherical equivalent refractive error was +3.07±2.09 (0.25-7.62) D for the preferred eyes and +4.09±2.18 (1.37-8.75) D for the non-preferred eyes (p=0.003).

The mean p50 amplitude was 6.07±2.06 μV in preferred and 5.29±2.20 μV in the non-preferred eyes (p=0.203), and the mean p50 implicit time was 48.36±1.05 ms and 48.63±4.59 ms, respectively (p=0.790). The mean N95 amplitude was 8.27±2.86 μV in the preferred and 8.03±3.24 μV in the non-preferred eyes (p=0.594), while the mean N95 implicit times were 86.92±7.69 and 90.78±10.13, respectively (p=0.328). For the preferred eyes, there was no correlation between BCVA

and N95 and P50 amplitudes or implicit times, whereas BCVA was correlated with p50 and N95 amplitudes in the non-preferred eyes (p=0.023, r=0.6734 and p=0.014, r=0.711, respectively). Moreover, interocular difference in BCVA was found to be correlated with interocular difference in P50 amplitude (r=0.688, p=0.019).

## Discussion

With an estimated prevalence of 1-5%, amblyopia is the most common cause of preventable and treatable monocular vision loss in children.[1] Thus, assessment of visual acuity is particularly essential for the detection and follow-up of children with strabismus and amblyopia. However, this may not be possible with uncooperative or disabled children. Assessment of fixing and following, consistent objection to occlusion, preferential looking techniques, and fixation preference tests are mainly used to evaluate visual performance in children. However, only preferential looking tests can quantify visual acuity, and evaluation of fixing and following may underestimate particularly severe amblyopia.[7]

The binocular fixation pattern test was first described by Knapp and Moore.[8] Fixation preference testing is widely used to roughly evaluate and compare the vision of both eyes. This is imperative when subjective and quantitative assessment of visual acuity is not applicable. The absence of a fixation preference is considered to be indicative for equal vision, whereas its presence is considered a sign of amblyopia in the non-preferred eye. Binocular fixation pattern evaluation is especially used in patients with a deviation of 10 PD or higher.[9] In contrast, induced tropia tests with various prism strengths are preferred to detect amblyopia as an alternative to binocular fixation pattern testing in patients without strabismus or with a deviation smaller than 10 PD.[10] The fixation preference test was found to be sensitive in patients with esotropia and those with an interocular visual acuity difference of more than 3 lines.[11] However, studies investigating the sensitivity, specificity, and positive and negative predictive values of the fixation preference test had inconsistent results and mainly suggest that this test should be used with caution and confirmed by other tests. Its reliability has been questioned many times in the literature.[2,4,10,11,12,13]

The fixation preference test was found to show a high level of interexaminer agreement in different types of strabismus cases despite having low reliability in detecting interocular differences in visual acuity.[14] Furthermore, in some studies the clinical value of the fixation pattern test was found to be poor in the identification of children with amblyopia.[13,15]

Procianoy and Procianoy[15] suggested that the binocular fixation preference test is particularly useful in cases with either strong fixation preference or free alternation but may have limited reliability at intermediate grades.

Şener et al.[12] compared standard fixation preference grades with interocular logMAR acuity difference found a correlation in amblyopic patients with large-angle strabismus and demonstrated that this test is fairly accurate to determine interocular vision difference.

Alharkan and Khan[16] investigated the reasons for misinterpretation of binocular fixation pattern testing and found that contralateral ocular dominance may interfere with the test results and cause a false prediction of amblyopia. Ocular dominance was not identified in the present study.

Electrophysiological tests complement ophthalmological examination, particularly when the etiology of the visual impairment is undetermined. Tests that reflect the function of particular retinal areas may be valuable tools to detect retinal dysfunction in the absence of or even prior to clinical signs. pERG is an electrophysiological test evoked by a pattern stimulus and requires central fixation.[6] It reflects mainly the function of the retinal ganglion cells, but for a normal response the integrity of photoreceptors, bipolar, horizontal and amacrine cells and Müller cells is needed.[17] However, electrophysiological function of the macula can be abnormal even if there is no evident anatomical change. The pERG signal is very sensitive and prone to noise caused by ocular surface irregularities, refractive errors, and stimulus/electrode-related problems.

pERG has been used to assess and monitor macular function in the literature. Machalińska et al.[18] investigated pERG data in patients with asymptomatic unilateral internal carotid artery stenosis along with full-field ERG, pattern visual evoked potentials, and optical coherence tomography (OCT) and found that both P50 and N95 amplitudes were significantly smaller compared to healthy controls.

Okada et al.[19] investigated structure-function correlation in patients with macular telengiectasia type 2 and found subnormal P50 amplitudes. Nowacka et al.[20] evaluated the structure and function of the macula in patients with diabetic macular edema with pERG in addition to other tests and did not find any significant change during follow-up after treatment. Mastropasqua et al.[21] compared pERG signal as a macular function parameter in patients with Stargardt disease with healthy controls and showed that both P50 and N95 amplitudes were significantly reduced and implicit times were significantly delayed in patients with Stargardt disease.

Lubiński et al.[22] investigated the value of pERG in the prediction of postoperative visual acuity in patients with epiretinal membrane and demonstrated improvement of pERG parameters postoperatively along with an increase in visual acuity and decrease in macular thickness on OCT. They suggested that pERG seems to be valuable to predict postoperative visual acuity.[22]

Parisi et al.[23] compared pERG values in anisometropic amblyopic patients with normal controls and found no significant difference.

de Souza Lima et al.[24] showed no difference in pERG between hypermetropic anisometropic amblyopic and strabismic amblyopic patients but found significant differences in P50 and N95 latencies between strabismic amblyopic and control

subjects. There were no patients with anisometropia in the present study.

Hamurcu et al.[25] demonstrated that P50 and N95 amplitudes were significantly lower in eyes with anisometropic amblyopia.

Multifocal ERG has also been studied in amblyopia. Al-Haddad et al.[26] investigated multifocal ERG in patients with anisometropic and strabismic amblyopia and found lower amplitude in the central ring in amblyopic eyes that was also correlated with the severity of amblyopia.

### Study Limitations

It is worth noting that the number of patients enrolled in the study was very limited, thus an inference regarding the relationship between electrophysiological macular function and fixation preference cannot be made. Furthermore, the significant difference in spherical equivalent values between preferred and non-preferred eyes might have influenced pERG values. The patient numbers in the fixation preference groups were too small to draw any other meaningful conclusion. However, the results of this study can be considered preliminary.

## Conclusion

The results of this study provide a comprehensive assessment of macular function in children with strabismus and demonstrate a potential correlation between interocular differences in electrophysiological parameters and visual acuity. Therefore, further larger studies are needed to emphasize the relationship between fixation preference and electrophysiological and clinical macular function.

### Ethics

**Ethics Committee Approval:** The study was conducted in full accordance with the tenets of the Declaration of Helsinki and was carried out upon approval of the Institutional Ethics Committee (GO 17/561-23).

**Informed Consent:** Obtained.

**Peer-review:** Externally and internally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: H.T.Ş., A.A.B., Concept: H.T.Ş., A.A.B., Design: H.T.Ş., Data Collection or Processing: H.T.Ş., A.A.B., J.K., Analysis or Interpretation: H.T.Ş., J.K., Literature Search: H.T.Ş., Writing: H.T.Ş.

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Original Article

# Evaluation of the Vestibulocochlear System in Patients with Pseudoexfoliation Syndrome

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## Abstract

**Objectives:** Patients with pseudoexfoliation syndrome (PES) can also have sensorineural hearing loss as well as balance problems. Our aim was to evaluate vestibulocochlear system involvement in PES patients.

**Materials and Methods:** The study included 16 subjects with PES (study group) with a mean age of 66.12±5.64 years and 17 healthy subjects (control group) with a mean age of 61.70±8.46 years. Both groups underwent ophthalmological, neuro-otological, audiological, and vestibular evaluation. Pure-tone audiometry and tympanometry were performed as audiological tests and bithermal caloric test and vestibular-evoked myogenic potential (VEMP) testing were used as vestibular tests. The Romberg, tandem Romberg, and Unterberger tests were also performed.

**Results:** In the PES group, bithermal caloric tests revealed right canal paresis in 6 patients, left canal paresis in 3 patients, and bilateral stimulation loss in 2 patients, despite no clinical evidence of balance loss. Paresis was not detected in any of the control subjects. Unilateral VEMP responses could not be obtained in 3 patients in the PES group. The ocular PES patients whose VEMP waves were obtained differed significantly from the control group ($p<0.05$). In office tests for vestibular evaluation, pathologic findings were found in 7 of 16 patients in the study group and only 4 subjects in the control group. Audiological evaluation with pure-tone thresholds revealed sensorineural decline at 4000 and 8000 Hertz in the PES patients. A statistically significant difference was found between the study group and the control group ($p<0.05$).

**Conclusion:** Patients with PES showed elevation in pure-tone thresholds and a decrease in superior and inferior vestibular nerve function, demonstrating that the vestibular system as well as the auditory system are affected in PES.

**Keywords:** Pseudoexfoliation syndrome, vestibular diseases, vestibular function tests, vestibular evoked myogenic potentials

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## Introduction

Pseudoexfoliation syndrome (PES), first described by Lindberg[1] in 1917, is a systemic disorder characterized by excessive synthesis and accumulation of fibrillary material in the ocular and extraocular tissues. This pseudoexfoliative material is believed to have many sources and occur secondary to abnormal basement membrane constituents produced by aging epithelial cells.[2]

Pseudoexfoliation fibrils can accumulate in the anterior segment structures of the eye such as the conjunctiva, corneal endothelium, anterior lens capsule, trabeculum, iris, zonules, and ciliary body, leading to glaucoma and subsequent progressive vision loss.[3] Light and electron microscopic analyses and immunohistochemical methods have also demonstrated the presence and accumulation of pseudoexfoliative material in the inner ear, as well as the extracellular matrices of systemic organs such as the skin, heart, lung, and liver.[4,5] In addition, the detection of material accumulation in the connective tissue layers of the skin and internal organs, the periphery of blood vessels, the smooth and striated muscle layers of the internal organs, and the cardiac muscle indicates that PES is a multisystemic disorder rather than just an ocular disease.[6,7] Its association with diseases that cause high mortality and morbidity, particularly cardiovascular and cerebrovascular diseases, further increases the importance of PES.[8]

The decline in hearing in PES patients at advanced ages has been attributed to the fibrillary material accumulated in the cochlea preventing the conversion of sound energy to electrical energy.[9,10,11] Several studies have shown that pseudoexfoliation fibrils accumulate in the basilar membrane, tectorial membrane, and stria vascularis of the inner ear. Embryologically, the ocular anterior segment and inner ear originate from the same germ layer.[12] However, there are few studies in the literature demonstrating the involvement of the vestibular apparatus, which constitutes another part of the inner ear.[13]

Balance is provided mainly by the visual, vestibular, and proprioceptive systems. The central nervous system integrates information from the relevant peripheral organs, then maintains balance via the necessary reflexes.[14]

In this study, we planned to investigate whether PES also affects the balance system to the same degree as the auditory system due to the likely accumulation of pseudoexfoliation fibrils.

## Materials and Methods

A prospective, case-controlled study was conducted. Approval was obtained from the Eskişehir Osmangazi University Ethics Committee. Informed consent forms were obtained from the patients.

Sixteen individuals with ocular PES (study group) and 17 healthy subjects (control group) were included.

Of the 16 patients in the study group, 10 were male and 6 were female. Of the 17 healthy volunteers in the control group, 12 were male and 5 were female. Ophthalmological, neurological, audiological, and vestibular evaluations were performed in both groups. Ophthalmological examination for all patients consisted of corrected visual acuity, biomicroscopy, intraocular pressure measurement, and fundus examination.

Vestibular evaluation was performed in both groups using vestibular-evoked myogenic potential (VEMP) testing, bithermal caloric test, and office vestibular tests; audiological evaluation was performed using pure-tone audiometry and tympanometric examination. The Romberg, tandem Romberg, Unterberger, and Dix-Hallpike tests were performed as office vestibular tests. Video electronystagmography, another vestibular test, was not used because it does not give reliable results in ocular pathologies.

### VEMP Test

The cervical VEMP test is based on measuring the electromyographic activity of the sternocleidomastoid muscle in response to high-intensity acoustic stimuli to the saccular macula. It is generally used to determine whether the saccule, inferior vestibular nerve, and central connections are working normally. The VEMP pathway is formed by the saccule, inferior vestibular nerve, lateral vestibular nucleus, medial vestibulospinal pathway, and sternocleidomastoid muscle after auditory stimulation of the saccule. VEMP tracings were recorded with a Medelec Synergy device. The first positive wave was taken as p13 and the first negative wave as n23. The p13 and n23 latencies and the amplitude between the two waves (p13-n23) were measured. The latency and amplitude values of the patient group were compared with normative data obtained from the control group.[15]

### Bithermal Caloric Test

Bitermal caloric test recordings were performed using a CHARTR water caloric stimulator, model NCI-480. Subjects were placed in supine position with the head at 30° anteroflexion during the test. The test was performed by administering water at two temperatures, 7°C above and below body temperature (30/44°C), to the external auditory canal. Activation is measured in the lateral semicircular canal, which is the most superficial and easiest to reach. This test can also provide information about the superior vestibular nerve. The test results were evaluated in terms of canal paresis and directional superiority. A 25% difference in the durations of nystagmus occurring with hot and cold stimuli in both canals was regarded as canal paresis.[16]

### Romberg Test

While standing with feet together, head upright, and arms at their sides, the subject was asked to close their eyes. After thus eliminating the auxiliary role of vision in balance, the subject's balance is observed and any vestibular system disorders are revealed. Movement in small circles suggested a central origin, while tilting backward or to the side was considered more suggestive of a cerebellar disorder.[16]

### Unterberger Test

Subjects were asked to take 40-50 steps in place with their hands outstretched in front of them. Rotational deviation

to either side that did not disappear with repeated tests was interpreted as indicating vestibular pathology on that side.[16]

**Dix-Hallpike Test**

In this test, the subject is quickly placed in supine position with the head facing one side and slightly extended. Rotary nystagmus associated with dizziness after a latency of 4-5 seconds after supine positioning was considered pathological.[16]

**Audiological Evaluation**

**Tympanometry**

Tympanometry was performed using a 256 Hz probe tone.[17]

**Odiometry**

Pure-tone threshold audiometry was performed using an InterCoustics AC-40 Audiometer and the results were recorded. In pure-tone audiometry, the average bone-conduction pathway thresholds at 500, 1000, 2000, and 4000 Hz and the air-conduction thresholds at 500-8000 Hz were included in the evaluation. Thresholds of 0-20 decibels were evaluated as normal hearing, 21-40 decibels as mild hearing loss, 41-60 decibels as moderate hearing loss, 61-80 decibels as moderate to severe hearing loss, and 81-100 decibels as severe hearing loss.[16]

Exclusion criteria for both groups were conductive hearing loss, family history of hearing loss, problems in the neck muscles, high noise exposure, acute or chronic ear infection, tympanic membrane perforation, otologic surgery, head trauma, active upper respiratory tract infection, history of drugs and systemic diseases that affect balance, and diagnosed or suspected glaucoma. Inclusion criteria were age over 40 years for both groups and for the study group, biomicroscopy findings of pseudoexfoliation not associated with glaucoma.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 15.0 software (SPSS Inc, Chicago, IL). Comparisons of measured variables between the groups were performed using Student's t-test for independent samples. Comparisons of categorical variables between the groups were performed with chi-square ($\chi^2$) analysis. P value <0.05 was accepted as significant.

## Results

The study included 16 ocular PES patients with a mean age of 66.12±5.64 years (study group) and 17 healthy individuals with a mean age of 61.70±8.46 years (control group). All 66 ears of the total 33 subjects were included in the evaluation.

In audiological evaluation, the PES patients were found to have sensorineural hearing loss at 4000 and 8000 Hz compared to controls in pure-tone threshold testing. The difference between the two groups was statistically significant ($p<0.05$). Tympanometric peak values were lower in the patient group than the control group.

Bithermal caloric testing in the PES group showed right canal paresis in 6 patients, left canal paresis in 3 patients, and bilateral low signal in 2 patients. Paresis was not detected on caloric tests in the control group.

VEMP testing was performed in all 16 PES patients, but unilateral VEMP waves could not be obtained in 3 patients. The p13, n23, and amplitude values of the 29 ears with VEMP waves from the patient group were compared with those of the 34 ears with VEMP waves in the control group. Comparison of the control subjects and PES patients with VEMP waves revealed significant differences in right amplitude, left p13, and left n23 values ($p<0.05$) but no significant differences in right p13, right n23, and left amplitude ($p>0.05$) (Table 1).

In the vestibular office tests, pathological findings were detected in 7 of 16 patients in the study group (positive Romberg test in 2 patients and positive Unterberger test in 5 patients) and only 4 subjects in the control group (Unterberger test).

## Discussion

In many embryological studies conducted to date, it has been reported that the inner ear and ocular anterior segment originate from the same germ layer.[12] In patients with PES, it is known that the accumulation of pseudoexfoliation material in the ocular anterior segment causes glaucoma and that accumulation of the same material in the cochlea leads to sensorineural hearing loss.[9,10,11,12]

Detorakis et al.[18] reported that PES patients had lower tympanometric peak values and suggested that this was caused by fibrillar deposits in the middle ear impairing middle ear elasticity. We observed similar findings on the tympanograms obtained in our study. The tympanometric peaks were also low in our study, although the decrease in these values may also be due to age-related loss of middle ear elasticity. However, Stenklev et al.[19] found no significant difference in tympanometric peaks with age.

Numerous other studies have also indicated that the cochlea is affected in patients with ocular PES and that these patients have significant sensorineural decline compared to age-matched control groups. Samarai et al.[11] attributed this to impairment of the mechanism by which hair cells convert sound to electrical energy as a result of the accumulation of pseudoexfoliation fibrils in both the tectorial and basement membranes. Yazdani et al.[9] supported this view in their study of 166 patients and 83 controls with the same findings and the same mechanism.

Many studies have shown that PES is associated with vascular disease and that fibrillary material accumulates in various organs and tissues.[10,11,12] This study was planned considering that the accumulation of fibrillary deposits in the vessel walls may affect the end arteries feeding the cochlea and vestibular apparatus, which may result in ischemia and the development of high-frequency hearing loss and balance problems. In our study, significant sensorineural hearing loss was observed at 4000 and 8000 Hz in the study group compared to the control group. In addition, although we observed pathological findings in VEMP and bitermal caloric tests, patients did not have balance problems.

Significant degeneration occurs in all structures of the vestibular system with age. Different studies have indicated

| Table 1. Visual-evoked myogenic potential (VEMP) values in the patient and control groups | | | |
|---|---|---|---|
| | **Patients** | **Control mean ± SD** | **P value** |
| Right p13 | 13.22±1.18 | 13.10±1.22 | 0.781 |
| Right n23 | 20.18±5.39 | 22.01±1.81 | 0.200 |
| Right amplitude | 118.64±66.98 | 181.40±43.39 | 0.004 |
| Left p13 | 14.68±1.99 | 12.67±1.32 | 0.002 |
| Left n23 | 23.05±1.33 | 21.65±1.43 | 0.008 |
| Left amplitude | 153.58±72.82 | 191.65±46.63 | 0.085 |
| Age (years) | 66.12±5.64 | 61.70±8.46 | 0.090 |
| SD: Standard deviation, *: Student's t test | | | |

different ages for the onset of this degeneration.[20,21,22] Each decade, an average of 3% of the vestibular hair cells are lost.[20,21,22] Despite histological changes, these individuals generally do not have a problem with balance in their daily lives. This has been attributed to strong central compensation. There are studies showing no significant age-related differences in vestibular assessment tests.[23]

Turgut et al.[13] included vestibular assessment in the tests performed on patients with PES. The study group consisted of 34 patients and the control group consisted of 40 individuals. Vestibular function was assessed using the Romberg test, gait test, Dix-Hallpike test, and bitermal caloric test. Although impairment was detected in the vestibular tests of the patients in the study group, they had no complaints of balance problems. To explain this, they stated that balance is supported by the vestibular apparatus as well as the visual system and the proprioceptive system. They observed that even if vestibular functions were impaired, central compensation occurred over time and patients did not develop problems such as loss of balance.[13]

In our study, significant differences in VEMP parameters were detected between the study and control groups ($p<0.05$). In addition, responses were low unilaterally in 9 patients and bilaterally in 2 patients. Despite these vestibular system findings and the significant visual system involvement in patients with PES, they did not report significant difficulty in daily life. Although the number of patients is small, this finding is due to central vestibular system activation to offset the gradual deterioration caused by pseudoexfoliative material accumulation in the vestibular system, and the individual adaptating to their new state. As we age, however, aging of the vestibular system is inevitable, and the proprioceptive system is also affected. As a result, balance disorders and associated falls and injuries are important in aging societies. In a study conducted in our country with 1078 people over 50 years of age, 3.4% of the individuals reported a fall in the last 6 months. In that study, dizziness was identified as a risk factor in 25.1% of those under 65 years of age and 26.2% of those over 65 years of age.[24,25] Therefore, it would be beneficial to inform patients with PES about balance problems, to perform vestibular tests, and to make home and environmental modifications for patients whose vestibular system is affected and include them in appropriate rehabilitation programs.

### Study Limitations

Limitations of our study are the small size of the patient and control groups and the fact that we did not perform a comparison between PES patients with and without glaucoma.

## Conclusion

Our study showed that among the systems responsible for balance, both the visual and vestibular systems are affected in patients with PES. In the light of the literature, it is important that ophthalmologists who follow-up PES patients keep in mind that the cochlear and vestibular compartments of the inner ear may be affected and ensure that these patients are examined periodically by an otorhinolaryngologist.

### Ethics

**Ethics Committee Approval:** Approval was obtained from the Eskişehir Osmangazi University Ethics Committee.

**Informed Consent:** Informed consent forms were obtained from the patients.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.D.B., N.E.K., L.B., A.İ., N.Y., Concept: M.D.B., N.E.K., L.B., A.İ., N.Y., Design: M.D.B., N.E.K., L.B., A.İ., N.Y., Data Collection or Processing: M.D.B., N.E.K., L.B., A.İ., N.Y., M.D.B., N.E.K., L.B., A.İ., N.Y., Analysis or Interpretation: Literature Search: M.D.B., N.E.K., L.B., A.İ., N.Y., Writing: M.D.B., N.E.K., L.B., A.İ., N.Y.,

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Original Article

# Aflibercept Treatment Results and Association with Baseline Characteristics in Cases of Newly Diagnosed Neovascular Age-Related Macular Degeneration

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## Abstract

**Objectives:** To evaluate functional and anatomical responses to intravitreal aflibercept (IVA) treatment in newly diagnosed and untreated neovascular age-related macular degeneration (nvAMD) cases and to investigate the effect of baseline lesion characteristics on anatomical responses.

**Materials and Methods:** This prospective, cross-sectional study included a series of 139 eyes of 133 patients that were diagnosed with active nvAMD and had not been treated. All eyes were subjected to complete ophthalmological examination, spectral-domain optical coherence tomography and fluorescein angiography, and 42 eyes also underwent indocyanine green angiography. IVA treatment was performed using a "treat and extend" regimen after 3 injections at 4-6 weeks intervals. Anatomical and functional responses at 4 weeks after the last injection were evaluated in eyes that completed 3 injections and the subgroup of eyes that completed 6 IVA injections. The effect of baseline lesion characteristics on IVA treatment results was also investigated.

**Results:** All 139 eyes included in the study received 3 IVA injections (group 1) and 62 received 6 IVA injections. Both groups showed statistically significant improvement in best-corrected visual acuity ($p<0.001$ for both). The rate of complete response was 54.6% and 58.0% in groups 1 and 2, respectively. In group 1, the presence of pigment epithelial detachment (PED) and serous PED were identified as negative initial factors ($p=0.043$, $p=0.005$, respectively). However, none of the baseline characteristics were significantly associated with anatomical response in group 2.

**Conclusion:** In our study, it was determined that successful anatomical and functional results were achieved with 3 and 6 doses of IVA in eyes with newly-diagnosed and untreated nvAMD. Among baseline characteristics, the presence of PED and serous PED in particular were found to be factors affecting treatment response negatively.

**Keywords:** Aflibercept, anti-VEGF, neovascular age-related macular degeneration

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## Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) drug therapy has been accepted as a standard treatment method for neovascular age-related macular degeneration (nvAMD). In clinical trials, most eyes have been reported to respond well to anti-VEGF treatments, with improved or preserved visual acuity and anatomical improvement in retinal hemorrhage and/or exudative changes. However, despite these positive results, it is also known that a small proportion of eyes do not respond adequately to anti-VEGF drugs and develop severe vision loss.

Aflibercept, a 115 kDa anti-VEGF drug that first entered clinical use in 2011, is a recombinant fusion protein that both acts as a competitive VEGF inhibitor and binds placental growth factor 1 and 2, which have been shown to play a role in the pathogenesis of AMD.[1] In the VIEW 1 and VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration) studies to determine the efficacy and safety of intravitreal aflibercept (IVA) therapy in eyes with nvAMD, it was reported that a large proportion of eyes had improved and/or maintain visual acuity with 3 consecutive monthly injections followed by continued IVA therapy every 2 months.[2,3]

It is clear that determining the initial lesion characteristics of treatment-resistant and inadequately responsive eyes is important and necessary to facilitate the prediction of functional and anatomical outcomes and to rationalize expectations of IVA therapy in eyes with nvAMD. Making effective changes in treatment and follow-up strategies in clinical practice will only be possible with the guidance of such data.

Therefore, a clinical study was planned to determine the functional and anatomical outcomes obtained with IVA therapy in eyes with newly diagnosed and untreated nvAMD and to investigate the effect of baseline lesion characteristics on treatment outcomes.

## Materials and Methods

This clinical study included 139 eyes of 133 consecutive patients with treatment-naive active nvAMD diagnosed in the Retina Unit of the Ege University Faculty of Medicine Ophthalmology Department between February 2015 and April 2017. Patients who were younger than 50 years of age, had previously been treated for nvAMD, had any contraindication to anti-VEGF therapy or developed complications during treatment, and did not adhere to the follow-up and treatment protocol were excluded from the study.

An informed consent form was obtained from each patient and approval was obtained from the Ege University Clinical Research Ethics Committee (decision no: 17-8/11, 70198063-050.06.04). The study was conducted in adherence to the principles of the Declaration of Helsinki.

Before treatment, each patient's age, gender, and best corrected visual acuity (BCVA) values (in decimal) were recorded and all eyes underwent a complete ophthalmological examination as well as spectral-domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA) scans performed using a Heilderberg Spectralis HRA + OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) device. Indocyanine green angiography (ICGA) was also performed with the same device in patients for whom indocyanine dye could be obtained. According to SD-OCT findings, baseline lesion characteristics, presence and type of pigment epithelial detachment (PED), and nv type based on location (type 1, 2, 3) were recorded. On FA, nv type was determined based on staining properties and the presence of dye leakage in the late phases were recorded. Eyes in which nv type could not be determined due to extensive hemorrhage or scar formation were classified as "undetermined". For eyes with ICGA data, the presence of polypoidal choroidal vasculopathy (PCV) was investigated based on Everest 2 criteria.

Eyes exhibiting fresh hemorrhage on clinical examination or subretinal, intraretinal, and sub-retinal pigment epithelium (RPE) fluid on SD-OCT and leakage on FA were evaluated as having active nvAMD. These eyes were treated with IVA (Eylea; Bayer/Regeneron Pharmaceuticals, Inc., Tarrytown, NY) (2 mg/0.05 cc) injection under fully sterile operating room conditions.

Follow-up examinations were performed 4-6 weeks after treatment and included fundus examination as well as BCVA measurement and reassessment of SD-OCT findings. Eyes with ongoing signs of active disease in examination 1 month after 3 consecutive IVA injections continued treatment at the same intervals, while for those without signs of activation, treatment intervals were extended by adding 2 weeks to the previous interval at each follow-up examination, as per the "treat and extend" protocol. Thereafter, follow-up and treatment were continued at a maximum interval of 3 months between treatments. For eyes that showed signs of reactivation during this treatment protocol, treatment intervals were returned to 4-6 weeks.

Anatomical and functional responses at follow-up examination performed 1 month after the last injection were cross-sectionally analyzed in the eyes that received 3 consecutive IVA injections at 4-6 weeks intervals and those eyes that continued regular follow-up and treatment and completed 6 doses of IVA, and the relationship between treatment outcomes and baseline lesion characteristics was statistically investigated. Eyes with complete regression of signs of activation on SD-OCT were classified anatomically as completely responsive, those with some improvement were classified as partially responsive, and eyes that showed no improvement or worsening were classified as unresponsive/worsening.

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 17.0 package software. For statistical analyses, BCVA values were converted from decimal to LogMAR. Numerical variables were tested for normal distribution using Kolmogorov-Simirnov test. Two dependent median values were compared using Wilcoxon test.

Two dependent categorical variables were compared using McNemar test. Differences between independent median values were evaluated with Kruskal-Wallis test. Relationships between independent categorical variables were investigated using chi-square test. Logistic regression analysis was used as a multivariate analysis method. The study was conducted at a confidence level of 95% ($p<0.05$ was accepted as a statistically significant difference).

## Results

Of the 133 patients included in the study, 73 (54.9%) were men and 60 (45.1%) were women, 6 (4.5%) had bilateral disease, and the mean age was 71.1±9.5 (51-90) years. All 139 eyes in the study received 3 consecutive injections and were included in group 1, while the 62 eyes that continued regular follow-up and treatment and completed 6 consecutive injections were included in group 2. The demographic characteristics and lens status of the eyes in both groups are shown in Table 1. The eyes in group 2 received 6 IVA injections over a mean of 7.3±0.6 (6-8) months, with a maximum interval of 2.5 months between injections according to the treat and extend protocol.

The baseline SD-OCT, FA, and ICGA lesion features of the eyes in both groups are shown in Table 2. In group 1, according to SD-OCT findings, the most common type of nv was type 1 (59.0%), most eyes had PED (78.4%), and the most common type of PED was fibrovascular (Fv) PED (53.2%). According to the FA characteristics in this group, the most common nv type was occult (51.1%), while PCV was detected in 34 (81.0%) of the 42 eyes (30.2%) that underwent ICGA imaging. In group 2, SD-OCT showed that the most common nv type was type 1 (56.4%), PED was present in 79.0%, and Fv PED was most common (48.4%). FA findings also demonstrated that occult nv was most common in this group (56.5%) and the prevalence of PCV was 84.0% in the 25 eyes (40.3%) eyes that underwent ICGA.

In the cross-sectional evaluation of treatment responses at 1 month after the last injection in the 139 eyes in group 1 who received 3 doses of IVA, 76 eyes (54.6%) were classified as completely responsive, 50 eyes (36.0%) as partially responsive, and 13 eyes (9.4%) as unresponsive/worsening (Figure 1). Similarly, in the cross-sectional evaluation of the 62 eyes in group 2 at 1 month after the last of 6 IVA injections, 36 eyes

**Table 2. Baseline SD-OCT, FA, and ICGA lesion characteristics in groups 1 and 2**

| | Group 1 n (%) | Group 2 n (%) |
|---|---|---|
| SD-OCT: nv type | | |
| Type 1 | 82 (59.0) | 35 (56.4) |
| Type 2 | 37 (26.6) | 15 (24.2) |
| Type 3 | 20 (14.4) | 12 (19.4) |
| PED | | |
| PED (-) | 30 (21.6) | 13 (21.0) |
| PED (+) | 109 (78.4) | 49 (79.0) |
| Serous PED | 15 (10.8) | 8 (12.9) |
| Fv PED | 74 (53.2) | 30 (48.4) |
| Serous + Fv PED | 18 (13.0) | 11 (17.7) |
| Drusenoid PED | 2 (1.4) | 0 (0) |
| FA: nv type | | |
| Predominantly classic | 36 (25.9) | 15 (24.2) |
| Minimally classic | 28 (20.2) | 11 (17.7) |
| Occult | 71 (51.1) | 35 (56.5) |
| Undetermined | 4 (2.8) | 1 (1.6) |
| ICGA | | |
| Obtained | 42 (30.2) | 25 (40.3) |
| PCV (+) | 34 (81.0) | 21 (84.0) |
| PCV (-) | 8 (19.0) | 4 (16.0) |
| Not obtained | 97 (69.8) | 37 (59.7) |

FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: Neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

**Table 1. Demographic characteristics and lens status of groups 1 and 2**

| | Group 1 | Group 2 |
|---|---|---|
| Number of patients | 133 | 60 |
| Number of eyes | 139 | 62 |
| Age (years), mean ± SD (min-max) | 71.1±9.5 (51-90) | 70.6±9.1 (61-89) |
| Gender, n (%) | | |
| Male | 73 (54.9) | 31 (51.6) |
| Female | 60 (45.1) | 29 (48.4) |
| Lens status, n (%) | | |
| Phakic | 86 (61.9) | 38 (61.3) |
| Pseudophakic | 53 (38.1) | 24 (38.7) |

SD: Standard deviation, min: Minimum, max: Maximum

(58.0%) were classified as completely responsive, 16 (25.8%) as partially responsive, and 10 (16.2%) as unresponsive/worsening (Figure 2).

The mean pre- and post-treatment BCVA values in groups 1 and 2 are shown in Table 3. There were significant increases in mean post-treatment BCVA compared to pre-treatment values in both groups (p<0.001 for both).

The comparison of pre- and post-treatment BCVA and baseline lesion characteristics according to treatment response after 3 IVA injections in the 139 eyes in group 1 is shown in Table 4. There was no significant relationship between mean pre- and post-treatment BCVA values and treatment responses (p=0.786 and p=0.147). In addition, there was no significant relationship between the nv types detected by SD-OCT and FA at diagnosis and treatment responses (p=0.061 and p=0.229). However, the presence of PED at diagnosis was negatively associated with anatomic response (p=0.043) and serous PED had a more negative affect on anatomic response than other PED types (p=0.005). There was no statistically significant relationship between the presence of PCV and treatment response (p>0.999).

The comparison of pre- and post- treatment BCVA and baseline lesion characteristics according to treatment response after 6 IVA injections in the 62 eyes in group 2 is shown in Table 5. There was also no significant relationship between mean pre- and post-treatment BCVA values and treatment responses in this group (p=0.877 and p=0.144). Treatment response did not show a significant association with nv types detected by SD-OCT and FA at diagnosis (p=0.346, p=0.579) or with the presence of PED, PED types (serous, Fv, serous + Fv), and presence of PCV (p=0.734, p=0.579, p=0.666, p=0.538, p=0.801, respectively).

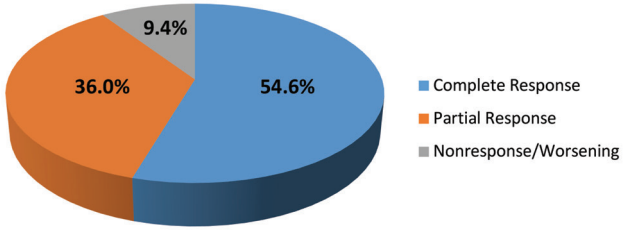


**Figure 1.** Treatment responses in group 1 after 3 intravitreal aflibercept injections

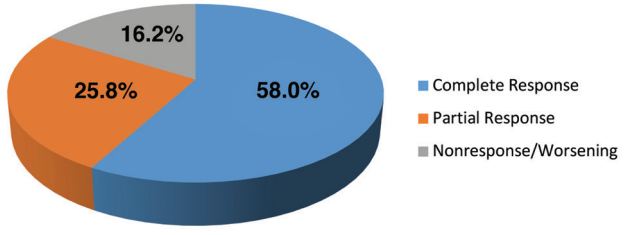


**Figure 2.** Treatment responses in group 2 after 6 intravitreal aflibercept injections

## Discussion

This study evaluated the functional and anatomical results obtained with IVA therapy in newly diagnosed and untreated eyes with nvAMD and investigated the association between these results and baseline lesion characteristics. The results showed that there were statistically significant increases in mean BCVA after treatment in both groups compared to pre-treatment, independent of anatomic treatment response. Our results regarding the increase in BCVA were similar to and consistent with visual acuity improvements in nearly all other clinical trials in eyes with treatment-naive nvAMD treated with aflibercept.[2,3,4,5,6]

In our study, we also evaluated regression of disease activity as another criterion of treatment outcome (i.e., anatomic results) and found that groups 1 and 2 had complete response rates of 54.6% and 58.0%, partial response rates of 36.0% and 25.8%, and nonresponse/worsening rates of 9.4% and 16.2%, respectively. The VIEW 1 and VIEW 2 studies were multicenter, randomized, controlled clinical trials to determine the efficacy and safety of aflibercept therapy and showed that most eyes achieved positive results in both anatomic and functional terms.[2,3] Barthelmes et al.[7] applied the treat-and-extend regimen in 136 eyes diagnosed with treatment-naive nvAMD and reported that inactivation was achieved in 68% of eyes with 3 or fewer injections, while this rate increased to 82% and 90% at the end of 1 and 2 years. In a series of 140 eyes with treatment-naive nvAMD, Kikushima et al.[8] administered 3 monthly aflibercept injections followed by a pro re nata regimen and reported that only 32.9% of the eyes did not require retreatment based on anatomic criteria after 3 months. Minami et al.[9] used an aflibercept regimen of 3 consecutive monthly injections followed by treatment at 2-month intervals in naive nvAMD eyes with good baseline visual acuity and reported a significant increase in visual acuity from month 2, as well as "dry macula" (no exudative findings on OCT) in 80% of eyes after the 3 loading doses and in 66% and 71% at months 6 and 12, respectively. In a similar study, Miyamoto et al.[10] reported anatomical success rates

**Table 3. Mean BCVA before and after treatment in groups 1 and 2**

| | Pre-treatment BCVA (LogMAR), mean ± SD (min-max) | Post-treatment BCVA (LogMAR), mean ± SD (min-max) | p |
|---|---|---|---|
| Group 1 | 0.80±0.56 (0-2.1) | 0.63±0.47 (0-1.8) | <0.001 |
| Group 2 | 0.68±0.49 (0-2.0) | 0.42±0.38 (0-1.3) | <0.001 |

SD: Standard deviation, min: Minimum, max: Maximum, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution

| Table 4. Distribution of BCVA and baseline lesion characteristics in group 1 according to treatment response | | | | |
|---|---|---|---|---|
| | **Complete response (n, %)** | **Partial response (n, %)** | **Nonresponse/worsening (n, %)** | **P** |
| **BCVA (LogMAR) mean ± SD (min-max)** | | | | |
| Pre-treatment | 0.76±0.53 (0-2.1) | 0.81±0.57 (0-1.8) | 0.83±0.54 (0.2-1.8) | 0.786 |
| Post-treatment | 0.57±0.44 (0-1.8) | 0.65±0.49 (0-1.8) | 0.78±0.39 (0.2-1.8) | 0.147 |
| SD-OCT: nv type | | | | |
| Type 1 | 41 (53.9) | 34 (68.0) | 6 (46.2) | |
| Type 2 | 23 (30.3) | 12 (24.0) | 2 (15.4) | 0.061 |
| Type 3 | 12 (15.8) | 4 (8.0) | 5 (38.4) | |
| PED | | | | |
| PED (-) | 22 (28.9) | 8 (16.0) | 0 (0) | |
| PED (+) | 54 (71.1) | 42 (84.0) | 13 (100.0) | **0.043**[b] |
| Serous PED | 4 (5.3) | 10 (20.0) | 4 (30.8) | **0.005**[b] |
| Fv PED | 44 (57.9) | 25 (50.0) | 5 (38.4) | 0.168 |
| Serous + Fv PED | 6 (7.9) | 7 (14.0) | 2 (15.4) | 0.126 |
| Drusenoid PED | 0 (0) | 0 (0) | 2 (15.4) | |
| FA: nv type | | | | |
| Predominantly classic | 22 (28.9) | 12 (24.0) | 2 (15.4) | |
| Minimally classic | 17 (22.4) | 7 (14.0) | 4 (30.8) | |
| Occult | 37 (48.7) | 28 (56.0) | 6 (46.2) | 0.229 |
| Undetermined | 0 (0) | 3 (6.0) | 1 (7.6) | |
| ICGA | | | | |
| Obtained | 18 (23.7) | 19 (38.0) | 6 (46.2) | |
| PCV (+) | 14 (77.8) | 15 (78.9) | 5 (83.3) | >0.999 |
| PCV (-) | 4 (22.2) | 4 (21.1) | 1 (16.7) | |
| Not obtained | 58 (76.3) | 31 (62.0) | 7 (53.8) | |

SD: Standard deviation, min: Minimum, max: Maximum, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

of 37%, 62%, and 81% at months 3, 6, and 12, respectively, in eyes with naive AMD given aflibercept at 2-month intervals following a 3-month loading dose. Looking at studies conducted in our country, Erden et al.[11] evaluated the anatomic and functional efficacy of aflibercept and ranibizumab in nvAMD and observed statistically significant positive changes at the end of 12 months with the pro re nata protocol in the aflibercept arm of the study. Similarly, Unsal et al.[12] investigated the effect of aflibercept therapy on naive eyes with AMD and reported anatomic improvement in 92.1% of the eyes at 12 months with the pro re nata protocol.

Most clinical studies of aflibercept in naive eyes with nvAMD have shown that exudative findings completely or partially regressed and favorable anatomical results were achieved in a large proportion of the eyes, as in our study.[13,14] However, the sizable differences in success rates reported in various studies are also noteworthy. We believe that this variance may be due to differences among the studies in the definition of anatomic success and activation criteria, as well as differences in the treatment regimens used, different baseline lesion characteristics of the eyes, the possibility that case series include different nvYBMD subgroups such as PCV, and that they are conducted in different ethnic populations.[15]

In our study, when the initial SD-OCT, FA, and ICGA lesion characteristics of the eyes in group 1 and group 2 were examined, it was found that based on SD-OCT, the most common type of nv in both groups was type 1 nv (59.0% and 56.4%), that nearly 80% of the eyes had PED, and that approximately 50% of these eyes had Fv PED. Similarly, occult nv accounted for the majority in both groups according to FA characteristics, and rates of PCV were high (81% and 84%) among the eyes that underwent ICGA. In terms of the frequency and distribution of baseline lesion features of the eyes in our study, they had similar characteristics and no differences from other studies, including the high prevalence of PCV.[4,16,17] When our study results were analyzed, it was observed that the

| Table 5. Distribution of BCVA and baseline lesion characteristics in group 2 according to treatment response | | | | |
|---|---|---|---|---|
| | **Complete response (n, %)** | **Partial response (n, %)** | **Nonresponse/worsening (n, %)** | **P** |
| **BCVA (LogMAR) mean ± SD (min-max)** | | | | |
| Pre-treatment | 0.68±0.51 (0-2.0) | 0.68±0.43 (0.1-1.3) | 0.66±0.46 (0.2-1.8) | 0.877 |
| Post-treatment | 0.38±0.36 (0-1.3) | 0.61±0.48 (0-1.3) | 0.54±0.35 (0-1.3) | 0.144 |
| SD-OCT: nv type | | | | |
| Type 1 | 20 (55.6) | 11 (68.7) | 4 (40.0) | |
| Type 2 | 9 (25.0) | 4 (25.0) | 2 (20.0) | 0.346 |
| Type 3 | 7 (19.4) | 1 (6.3) | 4 (40.0) | |
| PED | | | | |
| PED (-) | 8 (22.2) | 3 (18.8) | 2 (20.0) | |
| PED (+) | 28 (77.8) | 13 (81.2) | 8 (80.0) | 0.734 |
| Serous PED | 6 (16.7) | 3 (18.7) | 2 (20.0) | 0.579 |
| Fv PED | 19 (52.8) | 8 (50.0) | 3 (30.0) | 0.666 |
| Serous + Fv PED | 3 (8.3) | 2 (12.5) | 3 (30.0) | 0.538 |
| FA: nv type | | | | |
| Predominantly classic | 8 (22.2) | 5 (31.3) | 2 (20.0) | |
| Minimally classic | 8 (22.2) | 1 (6.2) | 2 (20.0) | 0.579 |
| Occult | 20 (55.6) | 9 (56.3) | 6 (60.0) | |
| Undetermined | 0 (0) | 1 (6.2) | 0 (0) | |
| ICGA | | | | |
| Obtained | 15 (41.7) | 6 (37.5) | 4 (40.0) | |
| PCV (+) | 12 (80.0) | 5 (83.3) | 4 (100.0) | |
| PCV (-) | 3 (20.0) | 1 (16.7) | 0 (0) | 0.801 |
| Not obtained | 21 (58.3) | 10 (62.5) | 6 (60.0) | |

SD: Standard deviation, min: Minimum, max: Maximum, IVA: Intravitreal aflibercept, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

presence of PCV at diagnosis was not associated with anatomic response to IVA treatment in group 1 or 2 (p>0.999, p=0.801, respectively). Miyamoto et al.[10] also reported that the presence of PCV did not affect anatomic response to IVA in their study of naive eyes with nvAMD, nearly half of which had PCV, while Ijiri and Sugiyama[18] reported an anatomic success rate of 97% in naive eyes with PCV after 3 consecutive IVA injections.

According to our study results, there was no significant relationship between nv types detected by SD-OCT and FA at diagnosis and treatment response in group 1 or group 2. Vaze et al.[19] did not detect any relationship between the initial FA patterns and anatomic treatment response, as in our study.

In group 1, anatomic responses were poorer in the presence of PED at diagnosis compared to the absence of PED and with serous PED compared to other PED types, whereas there was no significant association between the presence of PED or its subtypes and anatomic response in group 2. In their study, Miyamoto et al.[10] found that detection of PED at diagnosis was associated with inadequate response to IVA therapy, while Ying et al.[20] reported that patients with PED at diagnosis may have functional abnormalities in RPE activity that result in poorer anatomical response. Nagai et al.[21] investigated the reasons for nonresponse to IVA therapy and reported that the presence of serous PED at diagnosis negatively affected anatomic treatment response, similar to our results.

Another striking finding of our study was the similar anatomical response rates obtained in group 1 and group 2. The rate of complete response was 54.6% in group 1 and 58% in group 2. Framme et al.[22] reported that eyes showing complete response on OCT and a functional increase in vision after the first 3 injections continued this success at month 12 of treatment.

## Conclusion

Similarly, Nguyen et al.[23] reported that visual response after the fourth injection was the most important factor in predicting visual success at year 3 of treatment and that shorter time to lesion inactivation was associated with better visual outcomes at 3 years; therefore, they concluded that early response may be

useful in predicting long-term outcomes. In our study, the very similar anatomical response rates in groups 1 and 2 supported this view and may be a helpful factor in predicting treatment responses in the longer term.

In conclusion, in this study evaluating the functional and anatomical outcomes with IVA therapy and their association with baseline lesion characteristics in eyes with newly diagnosed, previously untreated nvAMD, we attempted to identify baseline lesion characteristics that will serve as a guide in the prediction of treatment responses in newly diagnosed eyes that will start receiving treatment.

### Ethics

**Ethics Committee Approval:** Ege University Clinical Research Ethics Committee (decision no: 17-8/11, 70198063-050.06.04).

**Informed Consent:** Obtained.

**Peer-review:** Externally and internally peer reviewed.

### Authorship Contributions

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

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Review

# The Use of Fundus Autofluorescence in Dry Age-Related Macular Degeneration

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**Abstract**

Fundus autofluorescence (FAF) has been a well-known imaging method for quite some time. However, with developing technologies and novel imaging devices, FAF is being used more often to diagnose and monitor retinal diseases. The density of lipofuscin (LF) and other fluorophores in the retina have a determining role in FAF images. In dry age-related macular degeneration (AMD), hyperautofluorescence is seen in cases of increasing LF in the retina pigment epithelium, whereas hypoautofluorescence is detected in decreasing LF resulting from geographic atrophy. In recent years, studies have shown that FAF images provide prognostic information in patients with AMD. This review aims to highlight the importance of FAF imaging in dry AMD.

**Keywords:** Age-related macular degeneration, fundus autofluorescence, geographic atrophy, lipofuscin, retina

## Introduction

Fundus autofluorescence (FAF) is a noninvasive imaging method based on the principle of stimulating fluorophores with specific wavelengths and measuring the light they emit through barrier filters.

The presence of autofluorescence in the fundus was first detected in images taken immediately before performing fundus fluorescein angiography (FA) and was called pseudofluorescence.[1] The introduction of confocal laser scanning ophthalmoscopy (cSLO) systems increased the quality of FAF images, and the method became widely used in the diagnosis and follow-up of retinal diseases.

FAF images demonstrate fluorophore density in the retina. Lipofuscin (LF), found in the retinal pigment epithelium (RPE), is one of the main fluorophores in the retina. An increase in the amount of LF leads to hyperautofluorescence and a decrease results in hypoautofluorescence.

FAF imaging has been embraced as a useful imaging method for explaining the pathophysiological mechanisms of retinal diseases, evaluating the risk of progression, and monitoring treatment outcomes.

The aim of our review is to provide basic information about FAF imaging and emphasize the importance of its use in dry age-related macular degeneration (AMD).

### The Retinal Pigment Epithelium and Lipofuscin

The RPE consists of a single layer of polygonal cells separating the choroid from the neurosensory retina. It has a critical role in normal retinal functioning, being responsible for

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phagocytosis and lysosomal destruction of photoreceptor outer segments.[2] Each RPE cell phagocytoses 3 billion outer segments during its lifetime.[2]

With aging, insufficient clearance of the photoreceptor outer segments leads to accumulation of LF in the RPE. LF is a macular fluorophore that absorbs blue light at a wavelength of 470 nm and emits yellow-green light at a wavelength of 600-610 nm.[3] It is a heterogeneous molecule consisting of vitamin A and byproducts of the visual cycle. The accumulation of LF in the RPE lysosomes increases with age, with LF and melanolipofuscin occupying a quarter of the RPE cytoplasm and after the age of 70 years.[4] However, excess LF accumulation is pathological and causes apoptosis in the RPE. The amount of LF is also known to increase in retinal degenerative diseases such as AMD and macular dystrophies such as Best and Stargardt disease.[5]

Although LF is composed of many different molecules, the most important is N-retinyl-N-retinylidene ethanolamine (A2E). A2E is formed in the outer segment of the photoreceptor by the combination of two vitamin A aldehyde (all-trans retinal) molecules with a phosphatidyl ethanolamine.[6] A2E is believed to accumulate in lysosomes because lysosomal enzymes are unable to recognize and degrade it. Another theory to explain the excess accumulation of LF is that the reactive A2E molecule inhibits the metabolism of lysosomal enzymes and inactivates proteolytic enzymes.[7] The accumulation of this substance in the lysosomal compartment of RPE cells is characteristic of the aging process.

Another component of LF, all-trans retinal, is a toxic aldehyde produced in the photoreceptor outer segments as a result of light exposure. As photoreceptors do not have cis-trans isomerase function, all-trans retinal cannot be converted to 11-cis-retinal.[8] All-trans retinal accumulates in the photoreceptor and forms bisretinoids. The oxidation of bisretinoids yields LF.[9] Light-induced photoreceptor loss is known to reduce the accumulation of LF.[10]

LF has other components besides A2E and all-trans retinal.[11] These molecules include A2E precursors, fragments of oxidized A2E molecules, and protein and lipid peroxidation products.[11]

The retinoid fluorophores that form LF are composed of long conjugated bonds. These structures allow retinoid fluorophores to absorb light and then emit fluorescence. Their autofluorescent properties allow LF granules in RPE cells to be detected by fluorescence microscopy.[12]

### Fundus Autofluorescence and the Working Principle

In fluorescent microscopy, ultraviolet light is used to detect LF in *in vitro* examinations. LF excitation can occur at a broad spectrum of wavelengths ranging from 300 nm to 600 nm. Although the emission spectrum is also wide (480-800 nm), its peak is between 600 and 640 nm.[13]

The definition of autofluorescence emerged with the use of fundus FA, while the quantitative evaluation of autofluorescence was performed using fluorometry in 1989 by Kitagawa et al.[14,15]

An important factor that prevents the acquisition of clear FAF images is autofluorescence from anatomical structures anterior to the retina, such as the lens. In recent years, improvements in camera systems and new, sophisticated imaging methods have produced clearer FAF images.

### Wide-Field Retinal Imaging: Wide-Angle Fundus Cameras

Fundus cameras for retinal imaging were first introduced by Carl Zeiss in 1926.[16] While the first device enabled imaging of a 20-degree area of the fundus, the field of view has expanded with developing technology. Today, many devices used in clinical practice provide 50-degree images. Fundus cameras with a field of view greater than 50 degrees are described as "wide-field". Devices that image even larger retinal areas, called "ultra-wide-field", have recently been introduced.[17] One of these devices, the Heidelberg Spectralis (Heidelberg Engineering, Inc., Heidelberg, Germany), can provide 102-degree retinal images. In addition, performing FAF, FA, and indocyanine green angiography examinations with the same device enables evaluation of the choroidal and retinal structures extending to the equator.

Another wide-field imaging system that became commercially available in 2000 is the Optos (Optos PLC, Dunfermline, UK), which includes a cSLO system and allows the retinal periphery to be examined in a single image without pupil dilation or a contact lens. Within the Optos system, an ellipsoid mirror is used to visualize the peripheral retina.[18] This design provides a wide-field image. If the patient is very cooperative and the pupil is well dilated, images up to the ora serrata can be obtained.

In addition to the conveniences it provides, the Optos system has some disadvantages. These include the inability to visualize the entire peripheral retina, the fact that image coloring differs from the actual appearance, and the low posterior pole resolution compared to standard fundus cameras and high-resolution confocal scanning laser systems such as the Spectralis.

Both the Optos and Spectralis systems can provide simultaneous FA and indocyanine green angiography images. Although the Spectralis does not produce clear FAF images with its ultra-wide-field lens system, the 30- and 55-degree FAF images have high resolution.

### Confocal Scanning Laser Ophthalmoscopy

The cSLO was developed by Webb et al. and introduced into clinical use by von Rückmann et al.[19] In this system, the retina is scanned with a low-power laser projected from a point source to produce retinal autofluorescence. The reflected light passes through a small aperture (confocal pinhole) located at the focal point of the lens in the device to prevent light scattering, thus providing clear fundus images. The cSLO obtains several images, an average of the sections is created, and the pixel values are normalized to yield a clear image.[20] Although the field of view is 30 degrees, a larger area can be imaged by changing the lens through the system.[20] The cSLO prevents autofluorescent structures anterior to the retina from blocking retinal autofluorescence.

At present, there are many cSLOs that provide FAF images, including the Zeiss SM 30 4024 (ZcSLO, Zeiss, Oberkochen, Germany), Rodenstock cSLO (RcSLO; Rodenstock, Weco,

Düsseldorf, Germany), Heidelberg Retinal Angiography System (HRA classic, HRA 2, Spectralis®, Heidelberg Engineering, Dossenheim, Germany), F-10 (Nidek, Aichi, Japan), and Optomap® Panoramic 200 Tx (Optomap; Optos, Scotland).

The excitation light of the HRA 2 is blue solid-state diode laser with a wavelength of 488 nm and acquires FAF images with a 500 nm barrier filter.[21] The Spectralis® (Spectralis SD-OCT, Heidelberg Engineering GMbH, Heidelberg, Germany) device synchronizes cSLO and optical coherence tomography (OCT) images, unlike the HRA 2.

The fluorophores in the retina emit fluorescence in a wide spectrum of wavelengths. Therefore, depending on the excitation wavelength, the fluorophores producing the autofluorescence change and the FAF image may vary. The most commonly used excitation light is blue light (488 nm) and is called blue autofluorescence (also known as short-wave autofluorescence, blue-AF, short wave-AF). In blue autofluorescence, excitation is at 488 nm (blue light) and emission is between 500 and 800 nm with a peak at 630 nm. A peak is observed at this wavelength because LF emits at 630 nm.[22]

Near-infrared autofluorescence (NIR-AF) uses a 787 nm excitation wavelength and 800 nm emission filter. The main fluorophore for NIR-AF is melanin. Fluorescence is more pronounced in the choroid and RPE due to the high density of melanin.[23] In NIR-AF imaging, RPE atrophy appears as a reduced signal, but a low-level signal may be detected due to melanin in the choroid.

Recently, the use of green light (504 nm and 532 nm) has been introduced and adapted to wide-field retinal imaging systems. Because green light is absorbed less by macular pigments than blue light, it can provide a better evaluation of the LF signal in the macula.[24] Therefore, green autofluorescence can reveal changes in fovea more clearly. The lower energy of the green excitation light also makes the patient more comfortable during imaging.[25]

**Fundus Autofluorescence Appearance of the Healthy Fundus**

1. Appearance of the healthy fundus on short-wave (blue) autofluorescence:

In the healthy fundus, diffuse autofluorescence is most intense between 5 and 15 degrees from the fovea. The optic nerve and retinal vessels are hypoautofluorescent because the optic nerve does not contain LF and blood blocks autofluorescence.

Xanthophylls (lutein and zeaxanthin) protect the photoreceptor and RPE cells in the fovea by filtering blue light, eliminating free radicals, and masking the natural autofluorescence of the subfoveal RPE cells.[26] The blue light used in short-wave autofluorescence is absorbed by xanthophylls.[27] These pigments are dense in the fovea, resulting in hypoautofluorescence in this area. In addition, the density of melanin in the fovea also causes light to be absorbed.[28]

2. Healthy fundus appearance with NIR-AF:

Due to the density of melanin, the fovea appears hyperautofluorescent. The RPE cells in the macula are more cylindrical and contain less LF and more melanin, unlike the periphery.[28] Similar to short-wave autofluorescence imaging, the optic disc and retinal vessels are also hypoautofluorescent on NIR-AF.

Less of the light used in NIR-AF is absorbed by media opacities due to its long wavelength. Geographic atrophy lesions appear brighter than non-atrophic areas and the lesion margins in the fovea are more clearly distinguishable. There is less contrast in short-wave autofluorescence imaging. **Figure 1** shows FAF images of a normal fundus.

**Clinical Use of Fundus Autofluorescence Images**

FAF images can be examined to obtain information about the RPE. Hypoautofluorescence indicates a decrease in RPE cells and/or low concentration of LF. RPE atrophy appears hypoautofluorescent.[29] In addition, the presence of fibrosis, intraretinal fluid, pigment, and blood are also factors that impede autofluorescence. Situations and conditions that cause hyper- and hypoautofluorescence are presented in **Table 1**.

Increased autofluorescence is observed in conditions with LF accumulation, such as Stargardt disease, Best disease, and adult vitelliform macular dystrophy. Hyperautofluorescence is also observed in the presence of drusen and macular edema.[26] In eyes with geographic atrophy, areas of hyperautofluorescence can be observed surrounding the atrophic area. Changes in autofluorescence have also been demonstrated in the peripheral fundus of eyes with AMD.[30]

**Use of Fundus Autofluorescence in Dry Age-Related Macular Degeneration**

According to the Beckman classification, AMD was classified as the early, intermediate, and late stage.[31] In this classification, the presence of small drusen (drupelet, <63 µm) is considered a normal age-related change. The presence of medium-sized drusen (≥63 to <125 µm) was defined as early AMD, while the intermediate stage is defined as the presence of large drusen (≥125 µm) or medium-sized drusen together with pigmentary changes.

**Imaging Pigmentary Changes with Fundus Autofluorescence**

Hyperpigmentation in AMD can cause typical focal, linear, and/or lace-like hyperautofluorescence in FAF images.[32] Changes in FAF are thought to be due to the presence of

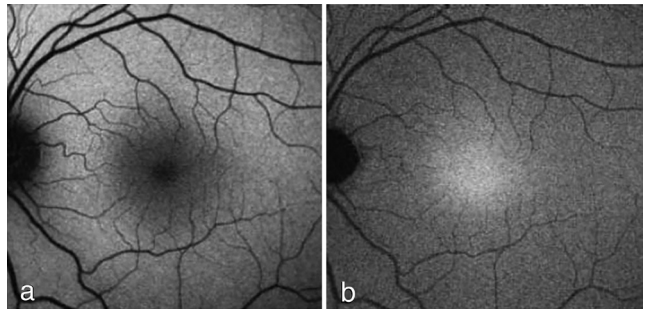


**Figure 1.** Short-wave (blue) (a) and near-infrared (b) fundus autofluorescence images of a normal fovea

melanolipofuscin.[32] Melanolipofuscin accumulation may not be uniform. Autofluorescence may vary depending on whether its melanin content is high or low.

Hypopigmented areas show hypoautofluorescence due to RPE degeneration or reduced LF.[33]

**Fundus Autofluorescence Imaging in Early and Intermediate AMD**

The imaging of drusen, which is an early finding of AMD, is important as it can provide clues regarding progression to the late stage. Drusen has subtypes such as soft, refractile, basal laminar, and cuticular drusen.[34] Reticular pseudodrusen (RPD) located under the retina is another subtype of drusen. Drusen can be differentiated using multimodal imaging methods including color fundus photography, fundus FA, near-infrared reflectance, FAF, and OCT.[34]

On FAF imaging, drusen can have different appearances.[33] A hyperautofluorescent appearance can be seen due to LF within the drusen or in the RPE overlying the drusen. A hypoautofluorescent appearance is caused by regressed drusen or degenerated RPE cells.

Small and medium-sized drusen can produce variable FAF images and may sometimes be overlooked.[33] Different appearances on FAF suggest that the drusen contents may also be different. Soft drusen appear as areas of hyperautofluorescence that is slightly more pronounced at the periphery than the center on FAF imaging. Cuticular drusen are punctate and hypoautofluorescent. Drusenoid pigment epithelium detachment shows a patchy pattern of hyper- and hypoautofluorescent areas.[35]

Reticular pseudodrusen, which differs from other drusen types by its subretinal location, is thought to be a risk factor for progression to late stage AMD. FAF imaging is known to be more sensitive than color fundus photography in demonstrating the presence of RPD.[36] Studies have shown that the presence of reticular drusen is an important risk factor for late stage AMD.[37,38] RPD appear as small, yellowish-white, round or oval lesions on fundus examination. On FAF imaging, they appear as multiple clusters of small (50-400 µm diameter, usually <200 µm), regularly arranged, homogeneous round or oval areas with low-contrast hypofluorescence.[33] They are located mostly in the superior part of the fovea, their prevalence increases with age, and they are more common in women.[33] In early AMD, the presence of RPD is called the "reticular pattern" due to its characteristic appearance in FAF imaging.[33] Although it is not clear why reticular drusen appear hypoautofluorescent, it is thought to be due to the accumulation of subretinal deposits that block the LF in the RPE.[39] **Figure 2** shows RPD imaged by cSLO.

**Table 1. Causes of hypo- and hyperautofluorescence**

| |
|---|
| **Hypoautofluorescence** |
| Reduction or absence of lipofuscin in the retinal pigment epithelium |
| Retinal pigment epithelium atrophy (geographic atrophy) |
| Hereditary retinal dystrophies |
| Increased melanin in the retinal pigment epithelium (retinal pigment epithelial hypertrophy) |
| Presence of fluid, cells, or extracellular material anterior to the retinal pigment epithelium |
| Intraretinal fluid (macular edema) |
| Presence of cells containing melanin |
| Presence of intraretinal and subretinal lipids |
| New intraretinal and subretinal hemorrhage |
| Fibrosis and scars |
| Retinal vessels |
| Luteal pigment (lutein and zeaxanthin) |
| Media opacities (vitreous, lens, anterior chamber, cornea) |
| **Hyperautofluorescence** |
| Increased LF accumulation in the retinal pigment epithelium |
| Lipofuscinopathies (Stargardt disease, Best disease, adult vitelliform macular dystrophy) |
| Age-related macular degeneration (hyperautofluorescent lesion at the geographic atrophy margin suggests the lesion may enlarge) |
| Fluorophores anterior or posterior to the retinal pigment epithelium |
| Intraretinal fluid (macular edema) |
| Subretinal fluid separating the retinal pigment epithelium and photoreceptors (due to insufficient outer segment turnover) |
| Conditions involving lipofuscin-containing macrophages in the subretinal space (choroidal tumors such as nevus and melanoma) |
| Drusen |
| Old intraretinal and subretinal hemorrhages |
| Choroidal vessels in eyes with retinal pigment epithelium and choriocapillaris atrophy |
| Conditions with a decrease in luteal pigment (idiopathic macular telangiectasia type 2) |
| Displacement of luteal pigment (cystoid macular edema) |
| Optic nerve drusen |
| Artifacts |

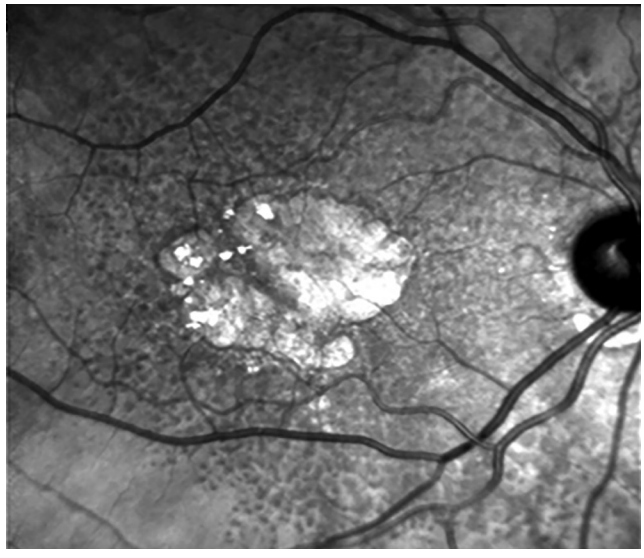

**Figure 2.** Confocal scanning laser ophthalmoscope image of reticular pseudodrusen

The frequency of RPD in eyes with geographic atrophy suggests that this finding is associated with the disease. However, the mechanism of RPD formation and its effect on disease progression have not been determined.

FAF changes in cases of early AMD were classified in an international study. The International Fundus Autofluorescence Classification Group (IFAG)[34] identified eight different autofluorescence patterns in these patients: normal, minimal change, focal increase, patchy, linear, lace-like, reticular, and speckled. Based on this study, it was predicted that in areas of abnormal autofluorescence, damage started at the RPE level. This classification of early AMD can provide clues about the prognosis of the disease.

The most common finding in intermediate AMD is areas with spots of increased autofluorescence (87.9%).[40] Punctate areas of decreased autofluorescence (26.7%) and linear areas of increased autofluorescence (19.8%) are also observed to a lesser extent.[40]

FAF findings have been reported to provide insight regarding neovascular transformation.[41] Analysis using FAF was reported to be the most sensitive method for identifying conversion to neovascularization compared to other imaging methods (color fundus photography, FA, indocyanine green angiography, and OCT.[41] Batioglu et al.[33] showed that the patchy, linear, and reticular FAF patterns were at high risk of transformation into choroidal neovascular membranes. FAF phenotypes identified in early and intermediate AMD provide information about disease prognosis and may be useful for informing the patient and determining follow-up intervals.

**Use of Fundus Autofluorescence in Geographic Atrophy**

The presence of geographic atrophy is a nonspecific finding of late AMD. In FAF imaging, geographic atrophy appears as well-defined areas of hypoautofluorescence. There may be a single or multiple hypoautofluorescent areas. In geographic atrophy, RPE loss results in LF loss, thus the hypofluorescent appearance. **Figure 3** shows a FAF image of geographic atrophy.

Geographic atrophy is frequently seen in the central or parafoveal macula, sometimes progressing to the peripapillary region.[42] Generally, patchy areas of geographic atrophy in the parafoveal area merge to form horseshoe or ring patterns, but over time may also affect the spared central zone. Geographic atrophy area is easier to measure with FAF than other imaging methods. This is because the lesion margins can be clearly determined. The contrast between the lesion and the normal retina in FAF imaging allows atrophic areas to be measured with advanced computer software. With these programs, enlargement of the atrophy area over time can be determined (**Figure 4**).

The presence or absence of foveal involvement can be determined by FAF imaging with 72-93% sensitivity and 59-88% specificity.[43] Both FAF methods should be compared when assessing whether geographic atrophy involves the fovea. Because the short wavelength used in blue autofluorescence is absorbed by pigments in the fovea, the boundaries of foveal involvement can be more clearly observed with the long wavelength used in NIR-AF. **Figure 5** shows blue and infrared FAF images of geographic atrophy.

FAF imaging can reveal hyperfluorescent areas around geographic atrophy. This suggests that cell death may occur in those areas.[42] The hyperautofluorescent areas may be punctate or large irregular areas.

FAF is a valuable imaging method in terms of geographic atrophy progression.[44] The extent of the hyperfluorescent areas

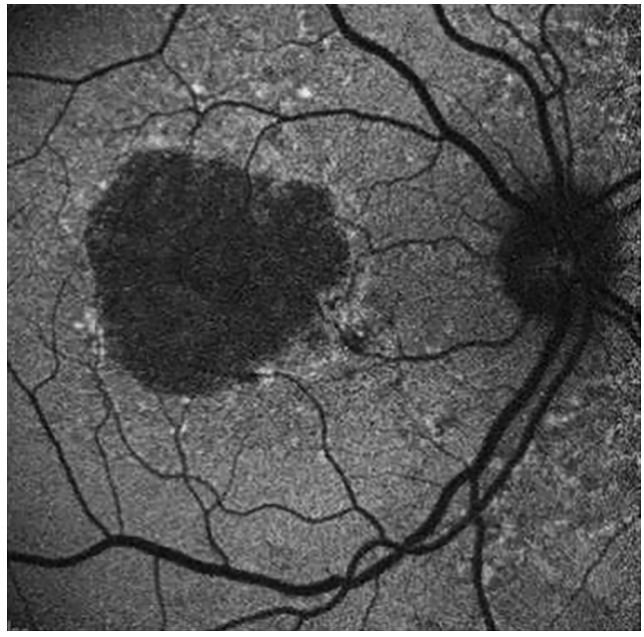

**Figure 3.** Blue autofluorescence image of geographic atrophy

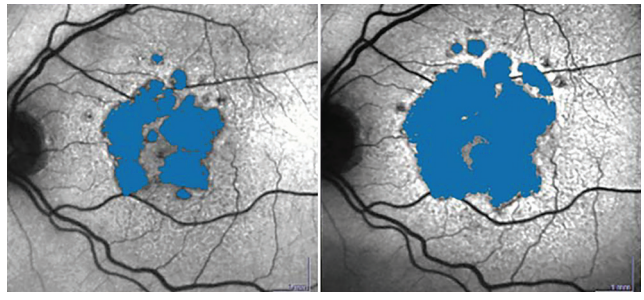

**Figure 4.** Area calculation from fundus autofluorescence images of geographic atrophy. Expansion of the geographic atrophy over time can be seen

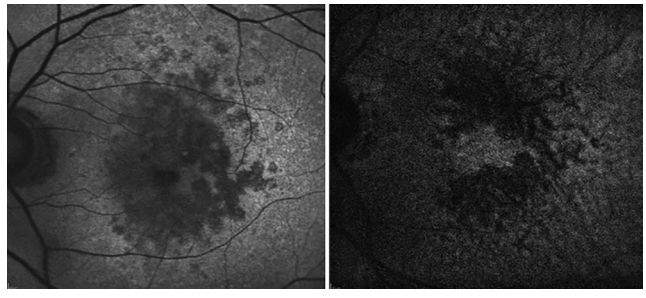

**Figure 5.** Blue (left) and near-infrared (right) fundus autofluorescence images of geographic atrophy

around the geographical atrophy was shown to be positively correlated with disease progression.[45] Schmitz-Valckenberg et al.[46] reported that retinal sensitivity was also reduced in these areas of hyperautofluorescence.

Different classifications have been described for FAF patterns surrounding geographic atrophy. Lois et al.[47] classified geographic atrophy as focal, increased, reticular, combined, and homogeneous. Subsequently, the FAM study group[30] developed a classification for FAF patterns around geographic atrophy. The researchers examined FAF patterns in four different groups: focal, band, patchy, and diffuse. The diffuse pattern describes a phenotype extending over a wider area than the geographic atrophy boundaries and is examined in five groups: granular, branching, trickling, reticular, and granular + peripheral punctate dots. Some of the described FAF patterns have been associated with a faster rate of progression. Holz et al.[48] showed that the enlargement rate was lowest in eyes with no hyperautofluorescence around the geographic atrophy and highest in those with the diffuse and band patterns. In addition, they reported that the "diffuse trickling" pattern, a subgroup of diffuse pattern, had the highest progression rate.[48] Similarly, Batıoğlu et al.[49] observed high rates of progression of the diffuse trickling and band patterns. **Figure 6** shows an example of the diffuse and band patterns.

There are different views about the cause of hyperfluorescence in the area surrounding geographic atrophy. RPE cell hypertrophy, RPE cell shedding into the subretinal space, phagocytosis of melanin and cellular debris, or a combination of all these events has been proposed.[50] Findings observed on FAF imaging are generally consistent with changes in the outer retinal layers on OCT.[50] Evaluating imaging methods together suggests a correlation between LF accumulation and geographic atrophy progression.

One of the current retinal imaging methods used to monitor the progression of geographic atrophy is fluorescence lifetime imaging ophthalmoscopy (FLIO), which measures FAF decay time. FAF times can be recorded *in vivo* with the Heidelberg Engineering ophthalmoscope (Heidelberg, Germany). The working principle is based on time-correlated single photon counting. With pulsed diode laser stimulation, the FAF lifetime and density can be examined in the 30-degree retinal area centered on the fovea. Several retinal diseases, including geographic atrophy, have been studied with FLIO.[51,52,53] Studies examining geographical atrophy with FLIO have shown that different phenotypes display different FLIO patterns.[54] Sauer et al.[55] reported that rapid FAF decay in the macular region was correlated with pigment in the macula. In atrophic areas, the low macular pigment density results in a long FAF lifetime. In addition, long FAF lifetime is seen in scar tissues containing collagen and elastin.[56]

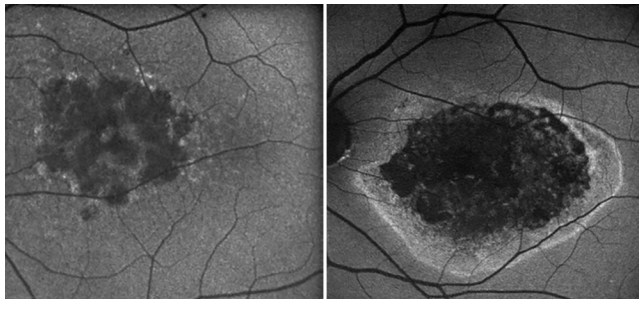

**Figure 6.** *Diffuse trickling* (left) and band (right) patterns

Sauer et al.[57] demonstrated in their study that eyes without hyperfluorescence surrounding the geographic atrophy had better visual acuity and shorter FAF lifetime than those with. The prolonged FAF lifetime in these regions may indicate the onset of change in the RPE cells. A slope of change in FAF lifetime between the unaffected and atrophic areas may be prognostic. All of these hypotheses can be investigated in future studies with large populations.

Deep learning, which is a type of machine learning algorithm, has recently attracted attention due to the ease of classification and diagnosis. There are studies in the ophthalmology literature on the use of fundus cameras and the suitability of the automatic diagnosis of retinal diseases.[58] Matsuba et al.[59] reported in their study that patients with AMD could be detected with high sensitivity using deep learning and Optos imaging, without ophthalmological examination.

In areas with insufficient numbers of medical personnel, wide-field fundus cameras will enable the diagnosis of patients with AMD. A telemedicine system based on imaging methods will be on the agenda in the future. Thus, it will be possible to diagnose AMD, plan treatment and follow-up, interpret FAF images to gain information about progression, and plan the use of new molecules that slow or treat progression in selected patients.

FAF imaging helps the clinician estimate the prognosis of AMD and is a valuable method that provides qualitative and quantitative information about the progression of geographic atrophy. Gaining a more detailed understanding of LF metabolism and identifying eyes at high risk of progression as detected by FAF will guide the use of new molecules in these patients.

**Ethics**

**Peer-review:** Externally peer reviewed.

**Author Contributions**

Concept: F.Ş., Design: F.Ş., N.Ş.K., Data Collection or Processing: N.Ş.K., Analysis or Interpretation: F.Ş., Literature Search: N.Ş.K., Writing: N.Ş.K.

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Case Report

# Bilateral Endogenous Methicillin-Resistant *Staphylococcus aureus* Endophthalmitis in a Young Athlete: A Story of Full Recovery

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**Abstract**

Endogenous endophthalmitis (EE) is an ophthalmological emergency. We report the long-term outcome of bilateral methicillin-resistant *Staphylococcus aureus* EE in a 23-year-old healthy immunocompetent athlete who presented with EE secondary to pelvic abscess and remained with excellent vision.

**Keywords:** Endophthalmitis, endogenous endophthalmitis, methicillin-resistant *Staphylococcus aureus*, vitrectomy

## Introduction

Endogenous bacterial endophthalmitis (EBE) is uncommon, accounting for less than 10% of all forms of endophthalmitis.[1] It develops after hematogenous microbial dissemination, infiltrating the eye through the blood-ocular barrier.

*Staphylococcus aureus* is a gram-positive bacterium known to most commonly cause skin and soft tissue infections (SSTIs), pneumonia, endocarditis, and sepsis.[2] Methicillin-resistant *S. aureus* (MRSA) strains are resistant to all kinds of penicillins and other ß-lactam antimicrobials and usually occur in hospitalized patients. MRSA has prompted a major public health issue since its emergence in the 1960s due to its aggressive course.

Community-acquired MRSA (CA-MRSA) usually affects young healthy patients, mostly manifesting as SSTIs.[2] Groups at risk for SSTIs by CA-MRSA include athletes, military personnel, and prisoners. Other groups at risk include household contacts of MRSA patients, veterinarians, and immunocompromised individuals. MRSA has been reported to be the causal agent of 18.2% of endophthalmitis.[3]

We describe the case of a young athlete with recurrent SSTIs who presented with bilateral MRSA-EE and disseminated infection secondary to a pelvic abscess complicating stitch abscess.

## Case Report

A healthy 23-year-old man presented because of an acute drop in right eye (RE) visual acuity (VA) for 1 day. He also had fever, myalgia, groin pain, and generalized weakness for 1 week. Vital signs showed fever of 39°C, blood pressure of 106/50 mmHg, and heart rate of 114 beats per minute. Distention of the right upper abdominal quadrant was noted with right groin lymphadenopathy, maculopapular skin rash of the upper

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limbs, and swelling and redness of the right forearm and right foot. Blood tests revealed leukocytosis of 14,300/μL, elevated C-reactive protein of 33.18 mg/mL (normal up to 0.5 mg/mL), and elevated liver enzymes with AST of 67 U/L (normal range 0-34 U/L) and alkaline phosphatase of 212 U/L (normal range 46-116 U/L).

Past medical history revealed MRSA-associated impetigo. He underwent repair of a right tibial fracture with closed reduction and stabilization with screws 1 year earlier. Three months before presentation, the screws were removed from his right leg. One week later, he developed MRSA-associated stitch abscess that was treated with one dose of intravenous (IV) cefazolin, followed by oral cephalexin for 5 days.

On presentation, RE VA was counting fingers at 1 meter and LE VA was 6/60. Intraocular pressures were normal in both eyes. Biomicroscopy revealed RE hypopyon and dense vitritis (binocular indirect ophthalmoscopy [BIO] score of 4) that prevented fundus visualization. In the LE, there was moderate non-granulomatous anterior uveitis, vitritis (BIO score of 3) and a peripheral inferior white fluffy retinal infiltrate (**Figure 1 A-B**). RE B-scan ultrasound showed a peripheral, temporally-located hypoechogenic round retinal lesion.

With a working diagnosis of EBE, the patient promptly underwent RE diagnostic and therapeutic vitrectomy with bilateral injection of intravitreal vancomycin (1 mg/0.1 cc), ceftazidime (2.25 mg/0.1 cc), and dexamethasone (0.4 mg/0.1 cc). Blood cultures grew MRSA and polymerase chain reaction was positive for Panton-Valentine leukocidin (PVL). Aqueous and vitreous samples were culture-negative. Topical moxifloxacin, prednisolone acetate 1%, and atropine drops were used. Intravitreal vancomycin was administered three times in total in the RE and twice in the LE. Treatment was initiated with IV vancomycin (1500 mg twice a day) for 6 weeks.

Total body computed tomography (CT) revealed the presence of a round, hyperreflective right pelvic lesion (**Figure 2**), hepatosplenomegaly, and bilateral pleural effusion. Fluorodeoxyglucose positron emission tomography-CT scan revealed a significantly enhancing round lesion in the right pelvic area (Figure 2), surrounded by similar but smaller lesions in the muscles, compatible with pelvic abscess and small muscle abscesses. The patient underwent ultrasound-guided surgical drainage twice. Samples from the pelvic abscesses grew MRSA and were positive for PVL. One month later, anterior and posterior segments were quiet with VA of 6/6 in each eye and scarred peripheral chorioretinal lesions (**Figure 1 C-D**).

Because of the known potential nephrotoxicity and other adverse effects such as neutropenia and thrombocytopenia (though infrequent), periodical evaluation of blood tests including complete blood count, kidney function tests, and serum antibiotic levels were monitored during his admission. Our patient did not develop any systemic toxicity or other adverse effects such as skin reactions or ototoxicity. One year later, the patient was well with quiet eyes and excellent vision.

## Discussion

EBE is an ophthalmological emergency because of its intrinsic sight-threatening potential. Its occurrence should prompt an urgent search for the underlying source, which could be life-threatening. The present case was of a young healthy athlete with recurrent SSTIs who developed stitch abscess following the removal of screws inserted at the time of tibial fracture repair. The stitch abscess was complicated by pelvic abscess 3 months later with consequent MRSA dissemination and endophthalmitis. EBE secondary to MRSA is relatively rare.[5]

A major review on 3,640 patients with MRSA infection identified that 70% had CA-MRSA. Only 1.3% had ophthalmic MRSA involvement. These patients tended to be younger than other MRSA patients. The most common manifestations

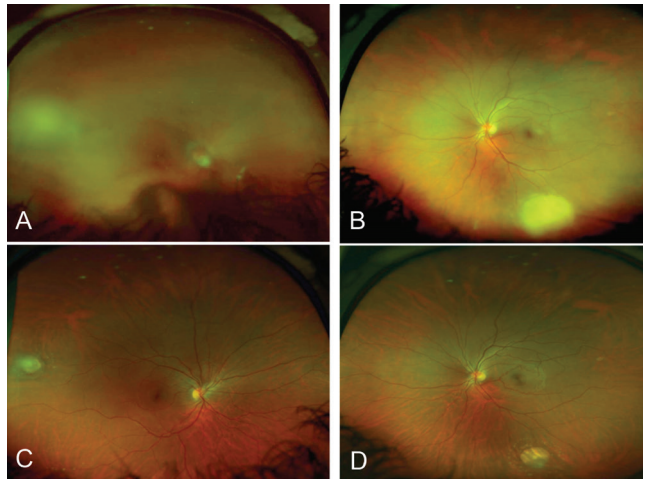


**Figure 1.** Wide-angle color fundus photographs on the first postoperative day show fluffy white retinal lesions in temporal periphery of the right eye (A) and inferiorly in the left eye (B). One month later (C, D), marked regression of the retinal lesions is noted with clearing of the vitreous opacities.

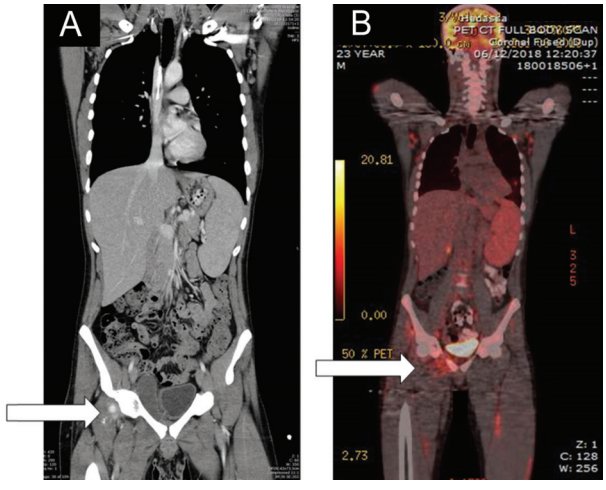


**Figure 2.** A) Total body computed tomography shows a hyperreflective right round pelvic lesion (arrow). B) Fluorodeoxyglucose positron emission tomography-computed tomography scan shows a significantly enhancing round lesion in the right pelvic area (arrow), surrounded by similar but smaller lesions in the muscles, compatible with pelvic abscess and small muscle abscesses

were preseptal cellulitis and/or lid abscess followed by conjunctivitis. Sight-threatening infections included corneal ulcers, endophthalmitis, orbital cellulitis, and blebitis.[5] Major et al.[6] evaluated 32 patients with culture-proven *S. aureus* endophthalmitis. There was no difference between methicillin-susceptible *S. aureus* and MRSA with regard to presenting or final VA. The only difference was the higher rate of vitrectomy in the MRSA group, possibly because of the more severe clinical presentation. Similarly, Yonekawa et al.[7] in a cohort of 13 patients with EBE (of whom 5 had MRSA infection) did not find an association between MRSA infection and visual outcome, although it was associated with mortality.

Ho et al.[8] reported a large series of 7 patients (mean age of 58 years, 8 eyes) with MRSA-EE. Five of the 8 eyes were treated with initial vitreous tap and injection of antibiotics. Final VA was 20/100 or worse in all except one eye. Six eyes developed retinal detachment and one eye was enucleated. Larson and Carrillo-Marquez[9] reported the first case of MRSA-EE in a healthy patient. The patient was a 13-year-old boy who fell on his right hip while playing basketball and developed a hip abscess that was surgically drained. Eight days later, he was diagnosed with LE choroidal abscess that resolved completely after intravitreal vancomycin. His VA improved to 6/7.5.

Vancomycin remains the gold-standard for severe systemic MRSA infections.[2,3] This is supported by the antibiotic sensitivity profile reported by Friedlin et al.[4], which suggested that vancomycin is the drug of choice for MRSA ocular infections. The PVL gene expressed by MRSA is associated with poor outcome, affects mostly patients in the community (CA-MRSA) such as healthy young individuals and children, and the majority of patients present with SSTIs followed by complications such as surgical site infections and pneumonia.[10]

Novel fifth-generation cephalosporins are promising drugs for the treatment of complicated SSTI and community-acquired pneumonia. Ceftaroline has been shown to be effective against MRSA and multidrug resistant bacteria including vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA, and vancomycin-resistant *S. aureus*. Ceftaroline was introduced to the market in 2011 after FDA approval and is the only fifth-generation cephalosporin available in the United States. Ceftobiprole, another fifth-generation cephalosporin, is available in some countries in Europe, but they are still not widely used and not readily available in hospitals.[11]

The most effective topical antibiotics for impetigo include mupirocin, fusidic acid, and retapamulin, with a resistance rate of <1%.[12] However, for mupirocin, the REDUCE-MRSA (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA) trial reported a higher resistance rate of 7.5% among 3173 MRSA isolates.[13] For MRSA-associated impetigo, systemic treatment is recommended. The available drugs are trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, fluoroquinolones, and tetracyclines. Linezolid has been shown to be effective, but its use is limited due to higher cost and toxicity. For complicated SSTIs, including abscesses, the guidelines recommend vancomycin or clindamycin, and similar effectiveness and safety has been reported for ceftaroline. In cases of suspected MRSA, TMP-SMX, daptomycin, and ceftaroline are equally effective and safe alternatives.[12,14]

Such patients often have a delayed diagnosis leading to delayed definitive treatment and poor prognosis. The promptness with which our patient received ophthalmic and systemic treatment enabled quick control of the infection and avoidance of irreversible consequences. Teamwork is the key to successful treatment of the infection and limitation of morbidity.

**Ethics**

**Peer-review:** Externally peer reviewed.

**Authorship Contributions**

Surgical and Medical Practices: R.A., M.H., J.C., O.C., Concept: R.A., Design: R.A., Data Collection or Processing: J.C., R.A., Analysis or Interpretation: R.A., Literature Search: R.A., J.C., Writing: R.A., J.C.

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Case Report

# Periocular Necrotizing Fasciitis Causing Posterior Orbitopathy and Vision Loss: How to Manage?

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**Abstract**

Necrotizing fasciitis (NF) is a rare, rapidly progressive bacterial infection. Periorbital NF may spread from the eyelid into the posterior orbit. Extent of the infection is critical in planning surgical debridement. A diabetic 70-year-old man presented with a black wound and severe pain in the left periorbital area following a mild trauma. Clinical findings were consistent with NF involving the eyelids, temporal and malar regions. In addition, he had proptosis, diffuse ophthalmoplegia, and central retinal artery occlusion, suggesting deep orbital involvement. Computed tomography showed soft tissue abnormalities in the anterior orbit. The patient was successfully treated with subcutaneous debridement, antibiotherapy, and metabolic support. Periorbital NF may be complicated with posterior orbital cellulitis-like symptoms and retinal vascular occlusions, possibly because of remote vascular thrombi induced by bacterial toxins. This clinical manifestation should be distinguished from true bacterial invasion of the posterior orbit, which may require more aggressive surgical treatments such as exenteration.

**Keywords:** Necrotizing fasciitis, central retinal artery occlusion, cellulitis, posterior orbitopathy, vision loss, treatment

## Introduction

Necrotizing fasciitis (NF) is a severe infection characterized by necrosis of the subcutaneous tissues spreading through the fascial planes. Although it rarely occurs in the periorbital region, the eyelid infection can rapidly spread into the posterior orbit and cervicofacial area and may result in blindness and death if untreated. The mainstay of treatment is early and complete surgical debridement of the infected tissues. Bacterial invasion of the posterior orbit, orbital cellulitis, can cause signs such as proptosis, ophthalmoplegia, and vision loss and requires treatment by orbital exenteration. However, in some cases, these symptoms may not be the result of true cellulitis. Such a case is presented herein, and this paradoxical condition, which may be critical for surgical planning, is discussed.

## Case Report

A 70-year-old man presented with a black wound involving the eyelids and severe periorbital pain on his left side. The patient had fallen and hit the left side of his face on the ground 4 days previously. He had a 5-year history of diabetes mellitus.

The patient was afebrile, fatigued, and in distress from the periorbital pain. Black, necrotic shells were noted on the left upper and lower eyelids. Two other oval, seminecrotic lesions were seen in the temporal and malar regions. The perilesional

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skin was erythematous, firm, and tender to palpation (**Figure 1A**). Lifting the upper eyelid with a Desmarres retractor revealed proptosis, restriction of eye movements in all directions, diffuse chemosis, and corneal edema. Visual acuity was 20/50 in the right eye and light perception in the left eye. A relative afferent pupillary defect (RAPD) was present in the left eye, and central retinal artery occlusion (CRAO) was detected on slit-lamp fundoscopic examination. Mild nonproliferative diabetic retinopathy was noted in the other eye.

Laboratory studies were significant for leukocytosis (19,800/mL), neutrophilia (85%) hyperglycemia (580 mg/dL), and high C-reactive protein (92 mg/L). Urine analysis was positive for glucose and negative for ketone bodies. Computed tomography (CT) showed diffuse soft tissue thickening, fascial plane blurring, and gas collection in the anterior periorbital regions (**Figure 1B**). Wound swabs were taken and empirical treatment with ampicillin-sulbactam (6 g/day, intravenous) and ciprofloxacin (1200 mg/day, intravenous) was initiated. The swab culture grew *Staphylococcus aureus, Streptococcus parasanguinis,* and *Enterobacter cloacae.*

At surgery, the necrotic shells were elevated with a sub-brow incision in the upper eyelid and a subciliary incision in the lower eyelid. All foul-smelling, necrotic tissues were excised up to the viable edges (**Figure 1C**). The operative field was copiously irrigated with povidone-iodine and 3% hydrogen peroxide solutions. The eyelid margins and ischemic (purplish) skin areas were not removed. After surgery, the patient experienced arterial hypotensive episodes that responded to fluid resuscitation in the intensive care unit. He was transferred to the ophthalmology ward 3 days later and received hyperbaric oxygen therapy (2.5 atmospheres absolute, 2 hours) in the following 10 days. Histologic findings were consistent with NF (Figure 1D).

Postoperatively, periorbital swelling and extraocular muscle motility improved gradually. Corneal scarring secondary to cicatricial lagophthalmos developed, and visual acuity remained at the level of hand motion. In the late period, upper and lower eyelid reconstructions were performed with skin grafts to correct cicatricial eyelid retractions (Figure 1E). During a follow-up of 11 months, no other complication occurred.

## Discussion

Suspected necrotizing infections are emergent conditions, and a delay in diagnosis and treatment is associated with worse results.[1] Most patients are taken to surgery based on clinical suspicion, and intraoperative findings play a critical role in making the diagnosis and determining the extent of surgical debridement.

Orbital exenteration surgery is indicated in some periorbital NF cases to overcome the infection, just as severe extremity NF requires amputation. In a review of 94 patients with periorbital NFs, rates of blindness, exenteration, and mortality were 13.8%, 7.4%, and 8.5%, respectively.[2] In two recent, large series, orbital exenteration rates were 2.5% (n=1/40) and 17.6% (n=3/17).[3,4] One of the prognostic factors for mortality is blindness, and the others are toxic shock, polymicrobial infection, and facial involvement.[2] In two studies, emergent orbital exenteration was performed to control the infection in 7 (58.3%) of a total of 12 patients with NF who had posterior orbitopathy signs (such as vision loss, proptosis, and ophthalmoplegia).[5,6] The etiology of vision loss was specified as central retinal or ophthalmic artery occlusion because of the spread of infection to the retrobulbar orbit in 5 patients.[5] Recently, there have been reports of other patients with periorbital NF who underwent exenteration without any signs of orbitopathy other than vision loss.[7,8]

In contrast, other periorbital NF cases were also described in the literature, which were successfully treated with only local/subcutaneous debridement, despite vision loss and other posterior orbitopathy signs.[5,6,9,10,11] Two well-described patients initially presented with CRAO and developed signs of orbital cellulitis within 12 to 24 hours.[9] In these cases, surgical debridement limited to subcutaneous and preaponeurotic fat tissues was sufficient for complete resolution of the NF. In a study of 40 eyes, orbital involvement presented as motility problems in 12 eyes, proptosis in 8 eyes, and RAPD in 9 eyes.[4] Although orbital involvement resulted in poor visual prognosis in 5 eyes, only 1 eye required exenteration surgery.

CT and magnetic resonance studies can help diagnose NF as well as indicate the extent of infection. Typical CT findings include thickening, fluid collections and, more specifically, gas bubbles in the soft tissues.[12,13] Of the 9 patients who

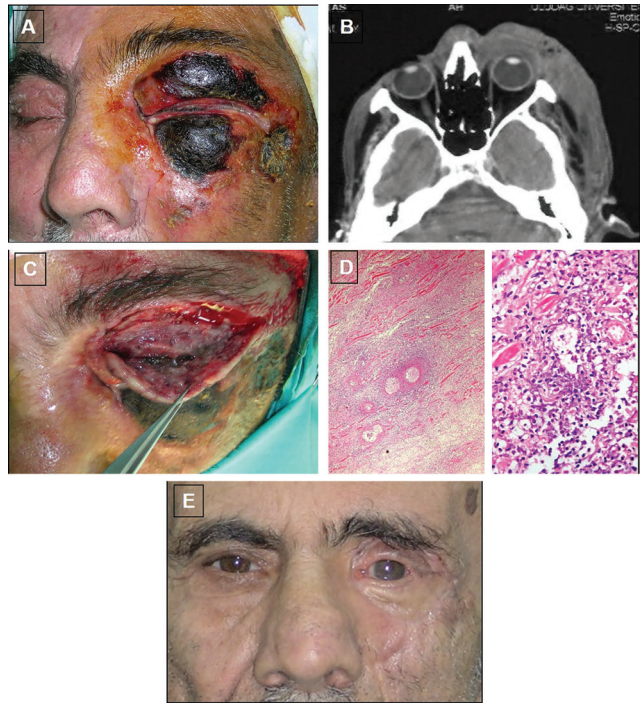


**Figure 1.** (A) Preoperative view of the patient with periorbital necrotizing fasciitis. (B) Computed tomographic scan shows gas collection in the preseptal area and soft tissue thickening in the periorbital and temporal regions. (C) Typical intraoperative appearance of the necrotic tissues. (D) Diffuse necrotic inflammation involving the subcutaneous muscle and fibroadipose tissue layers, and heavy, diffuse infiltration of neutrophils and macrophages into the subcutaneous tissues (hematoxylin-eosin, x40 and x200). (E) The patient's appearance after eyelid reconstruction

underwent exenteration due to periorbital NF in four different reports, only 2 had radiological images.[5,6,7,8] In these cases, CT images demonstrated soft tissue thickening in the anterior orbit and were no different from those in the present case and other non-exenterated periorbital NF cases.[9,10,11,12] No retrobulbar involvement was present in any CT images in the literature.[3,5,8,9,10,11,12] One recent report of an exenterated case does not include a radiologic image, but it states that orbital CT demonstrated preseptal cellulitis, without intra- or retro-orbital involvement.[7]

How can clinical signs indicating posterior orbitopathy (such as vision loss, proptosis, diffuse ophthalmoplegia, CRAO, and RAPD) be explained when only the anterior orbit is infected? It can be assumed that infection foci that are too small to be radiologically visible can reach the posterior orbit. If this were the case, subcutaneous debridement limited to the anterior orbit would likely be inadequate to control fasciitis, and exenteration would be required for definitive treatment in almost all cases with posterior orbitopathy. When treatment is only based on antimicrobial therapy and support, mortality approaches 100%.[1] Compartment syndrome associated with orbital edema or superinfection with vascular infiltration have been suggested to explain retinal arterial occlusions.[9,11]

Experimental NF models show that streptococcal toxin injection can trigger an immune-mediated platelet activation and thrombus formation.[14] Microthrombi develop at both the local site of infection and distant areas. Soft tissue blood flow decreases regionally within minutes, depending on the toxin dose. Toxin-induced arterial occlusion mediates the rapid ischemic destruction of tissue, continued expansion of the bacterial niche, and thwarting of the host immune response.[15] Vision loss, ophthalmoplegia, and CRAO may not be caused directly by bacterial invasion of the deep orbit, but by the vaso-occlusive effect of bacterial toxins released from the eyelid infection.

During surgery, it is possible to recognize the signs of NF and determine the infection margins macroscopically. Therefore, in the subgroup of patients with periorbital NF and posterior orbitopathy, when there is no retrobulbar involvement on radiologic studies, surgery can be initiated using subcutaneous debridement in the eyelid. If viable tissue is not reached in the aponeurotic fat and fasciitis signs persist into the posterior orbit, the surgery may be converted to an exenteration procedure. Thus, it may be possible to avoid unnecessary surgical morbidity in some cases.

### Ethics

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: B.Y., H.S., F.T., Concept: B.Y., H.S., F.T., Design: B.Y., H.S., Data Collection or Processing: B.Y., H.S., F.T., Analysis or Interpretation: B.Y., H.S., F.T., Literature Search: B.Y., H.S., Writing: B.Y., H.S., F.T.

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

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Case Report

# Spontaneous Closure of Large Full-Thickness Macular Hole in a Patient with Degenerative Myopia: Case Report

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**Abstract**

Macular hole is characterized by a full-thickness defect of the retinal layers in the center of the fovea and is an important cause of central vision loss. Spontaneous closure of a macular hole is rare, most often occurring in traumatic and idiopathic macular holes. In this case report, we present a 51-year-old woman with a myopic macular hole that closed spontaneously. The patient had degenerative myopia and a history of clear lens surgery and multiple laser retinopexy procedures due to retinal tear in both eyes. A macular hole was detected in her right eye, but she declined surgery and was followed up. At 66 months after presentation, bridge formation and spontaneous closure of the macular hole were observed. Spontaneous closure is extremely rare in cases of myopic macular hole, but may be seen in patients who are followed for a long time.

**Keywords:** Myopic macular hole, spontaneous closure, degenerative myopia

## Introduction

Macular hole is characterized by a full-thickness defect in the retinal layers at the foveal center and is an important cause of central vision loss. According to a series reported in 1982, 83% of cases are idiopathic and it frequently occurs in patients with vitreoretinal interface problems following posterior vitreous detachment.[1] The incidence of idiopathic macular hole in the general population is 0.33%.[2] The rate of macular hole closure has increased in recent years with pars plana vitrectomy (PPV), internal limiting membrane (ILM) peeling, gas tamponade, and supine positioning. Ch'ng et al.[3] reported anatomical success rates of 90% with this surgical procedure.

Although most macular holes are idiopathic, it is also a common complication in eyes with high myopia. In particular, eyes with an axial length greater than 26.5 mm and/or refraction greater than -6.00 diopter (D) were found to be at higher risk.[4,5] The prevalence of macular hole was reported as 8.4% in patients with high myopia.[6] While the pathology of myopic macular hole has not been fully elucidated, it has been emphasized that vitreoretinal changes such as axial elongation, posterior staphyloma, chorioretinal atrophy, and posterior vitreous detachment in myopic eyes induce anteroposterior traction on the retina.[7]

Myopic macular holes are more difficult to repair with vitreoretinal surgery than idiopathic forms. Spontaneous closure is a rare phenomenon. It is more common in traumatic holes, whereas the incidence of spontaneous closure of idiopathic macular holes has been reported at rates of 4% to 11.5%.[8] There are numerous publications and case reports in the literature on

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the spontaneous closure of idiopathic and traumatic macular holes, but only a few case reports of spontaneous closure of myopic macular holes.[9,10,11,12]

In this case report, we describe the spontaneous closure of a macular hole in a patient with degenerative myopia who was diagnosed with macular hole and followed up due to refusal of surgery.

## Case Report

A 51-year-old woman with no known comorbid disease underwent transparent bilateral clear lens extraction and intraocular lens implantation 12 years earlier at the center where she was followed up for degenerative myopia. The patient had amblyopia in her left eye and a history of multiple argon laser retinopexy procedures in both eyes due to retinal tears. She presented to the center where she was followed up with complaints of decreased vision in her right eye for 1 month and was diagnosed with macular hole and referred to our center. On initial examination, her best corrected visual acuity on Snellen chart was 0.4 bilaterally. Anterior segment examination revealed posterior chamber lenses in both eyes. Fundus examination revealed bilateral findings of degenerative myopia and posterior staphyloma, as well as a macular hole in the right eye (**Figure 1A, B, C**). Axial length was measured as 34.97 mm in the right eye and 34.68 mm in the left eye by optical biometry (Lensstar LS 900, Haag-Streit, USA). On optical coherence tomography (OCT), a full-thickness macular hole with a base diameter of 425 µm and minimum diameter of 403 µm was observed in the right eye (**Figure 1D**). When the patient refused the recommended surgical intervention, follow-up was advised. The patient had regular long-term follow-up at intervals of 3 months on average, during which her visual acuity and macular hole morphology remained stable. On follow-up examination in June 2020, 66 months after her initial admission, her visual acuity was still 0.4 on Snellen chart but OCT revealed that the macular hole had spontaneously closed by bridge formation (**Figure 2A**). At the patient's next follow-up 5 months later, it was observed that the macular hole was still closed and the bridge formation had progressed, with the neurosensory retina coming into contact with the retinal pigment epithelium (**Figure 2B**). After a total of 71 months of follow-up, there was closure of the macular hole to the level of the external limiting membrane and the fovea was attached, but there was no increase in vision (**Figure 3**).

## Discussion

In this case report, a macular hole was detected in a patient with an axial length of 34.97 mm and posterior staphyloma. Vitreomacular traction (VMT) was not observed on OCT, and the hole spontaneously closed after approximately 5.5 years. There was no change in the patient's visual acuity during this period and no complications such as retinal detachment or retinoschisis were observed. According to our study, this is the fifth spontaneous closure of myopic macular hole reported in the literature.

Our case was also noteworthy for having the highest axial length (34.97 mm) among the spontaneous closures reported to date. In 2014, Brue et al.[9] reported a 55-year-old woman with an axial length of 33.1 mm whose macular hole spontaneously closed after 4 years, with increased visual acuity and regression of metamorphopsia. Also in 2014, Yu et al.[10] reported the case of a 64-year-old woman with an axial length of 31.37 mm and a macular hole 66 µm in diameter accompanied by retinal detachment and VMT. At 54 months after her first admission, it was observed that the posterior hyaloid had detached, the hole had closed, and the retinal detachment had completely regressed. Li et al.[11] detected macular hole associated with retinoschisis, posterior retinal detachment, and VMT on OCT of a 76-year-old patient with refraction of -7.5 D and axial length of 27.8 mm. The patient was not able to undergo surgery due to poor general condition. On follow-up at 9 months, it was observed that although the VMT had not released, the macular hole was closed and retinal detachment had regressed slightly. In 2015, Golan and Barak[12] described a highly myopic 75-year-old woman

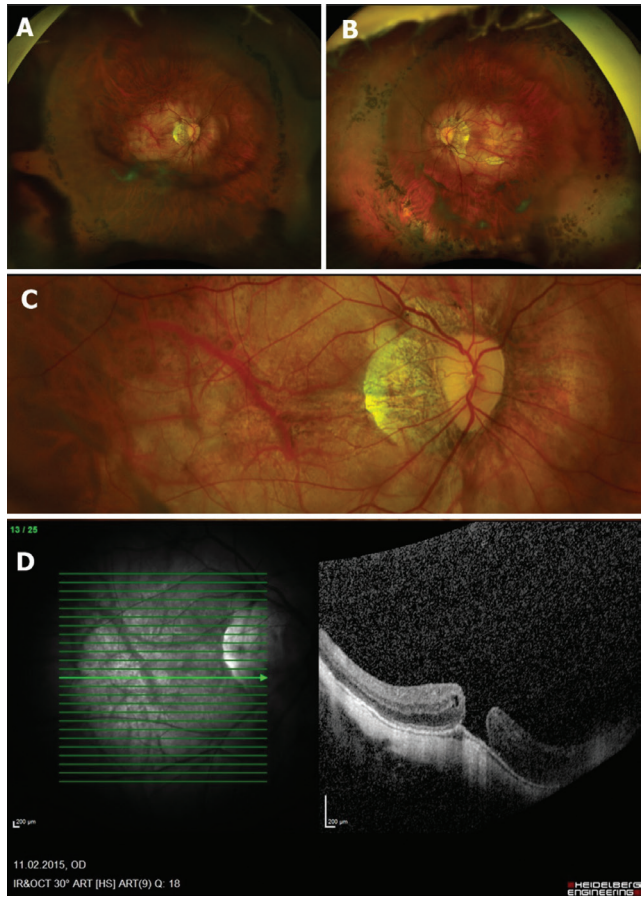


**Figure 1.** Fundus photograph and optical coherence tomography images of the patient taken at initial admission in 2015. A, B) Wide-angle fundus photographs of the right and left eye show myopic fundus and peripheral laser scars. C) A magnified fundus photograph of the right eye posterior pole shows macular hole with tilted disc, peripapillary atrophy, and severe chorioretinal atrophy. D) The optical coherence tomography section shows a full-thickness macular hole associated with dome-shaped maculopathy. At this presentation, the macular hole had a base diameter of 425 µm, minimum diameter of 403 µm, and hole height of 338 µm

whose macular hole recurred and spontaneously closed 3 times at intervals of several months.

Many stages related to the closure of idiopathic macular holes have been identified. Factors such as retinal tissue bridging, glial cell proliferation towards the opposite side of the hole, and the release of anteroposterior forces due to complete separation of the posterior hyaloid facilitate contraction of the hole and cell proliferation in the hole base.[13] Liang and Liu[8] reported that the chance of closure was higher in idiopathic macular holes that are smaller than 400 µm (especially smaller than 250 µm) and those with OCT findings such as VMT release, bridge-like connections, epiretinal membrane, and cystic structures at the edge of the hole. Mitamura et al.[14] found that young patient age, small hole diameter, and posterior vitreous detachment were associated with spontaneous closure of traumatic macular holes.

The mechanism of spontaneous macular hole closure has not been fully explained. Okubo et al.[15] described the OCT changes in a patient with a spontaneously closed idiopathic macular hole. They reported that Müller cells, which are found in all retinal layers, protruded at the external limiting membrane level, forming a bridge across the hole via centripetal extension. In our patient, we also observed that hole closure started with the external limiting membrane, upon which the outer nuclear and outer plexiform layers formed a bridge by centripetal extension (**Figure 2A**). Five months later, we saw that the bridge formation had settled on the retinal pigment epithelium and the fovea was flat (**Figure 2B**). The inner segment/outer segment junction layer of the photoreceptors was not fully restored, and the lack of visual improvement was attributed to this.

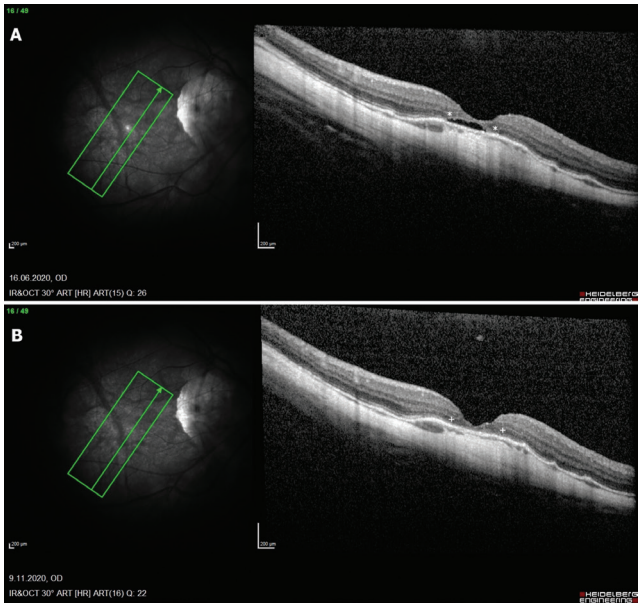


**Figure 2.** A) Optical coherence tomography images (OCT) of the patient showed that the macular hole had spontaneously closed due to formation of the external limiting membrane over the hole, over which the outer nuclear and outer plexiform layer formed a bridge (area indicated by white stars). B) Five months after initial closure, the neurosensory retina that formed in the closed hole had settled (area indicated by white pluses) and the hole remained closed

Macular hole is a well-known complication of high myopia. In highly myopic eyes, all anatomical structures such as the sclera, choroid, Bruch's membrane, RPE, neurosensory retina, and vitreous are affected, making the pathology of hole formation more complex.[9] Current theories regarding macular hole formation include the effects of anteroposterior and tangential forces at the vitreomacular interface. Perifoveal defects in these eyes are also thought to expand due to centrifugal forces around the axis of ocular rotation.[12] Therefore, the incidence of macular holes is higher in eyes with increased axial length.[5] The depth of posterior staphyloma, which is a scleral ectasia that causes axial elongation, also affects the strength of these potential traction forces. In patients with deep posterior staphyloma, limited flexibility due to the ILM and retinal vascular structures may lead to detachment of the neuroretinal tissues, causing foveoschisis. Foveoschisis can remain stable for years and later present with complications such as full-thickness macular hole and retinal detachment.[16] In shallower staphylomas, macular hole formation is similar to that in emmetropic eyes and the risk of retinal detachment is low.[16]

PPV is the preferred treatment for myopic macular holes. However, myopic macular holes have poorer anatomical and visual prognosis than nonmyopic eyes. PPV, ILM peeling, gas tamponade, and supine positioning provide anatomical closure rates higher than 90% in idiopathic macular holes, while closure

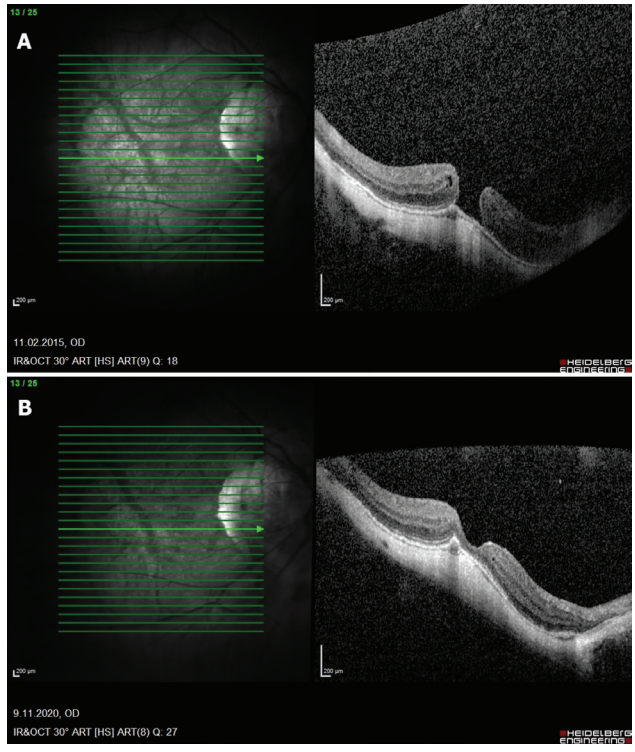


**Figure 3.** Optical coherence tomography (OCT) images at presentation to our center (A) and at final examination (B) demonstrate spontaneous closure of the macular hole in approximately 5.5 years of follow-up. Formation of the external limiting membrane and the overlying outer plexiform and outer nuclear layers was seen on OCT. The foveal contour appears to have formed on the dome-shaped macula

success in high myopic eyes ranges from 60% to 100% and may require multiple treatments.[17]

In conclusion, spontaneous closure is rare in patients with high myopia. Although vitreoretinal surgery is the most appropriate option for closure in these patients, spontaneous closure of small macular holes may be observed during follow-up, especially in patients who refuse or cannot tolerate surgery.

### Ethics

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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Case Report

# Multimodal Imaging Characteristics of Quiescent Type 1 Neovascularization in Best Vitelliform Macular Dystrophy

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**Abstract**

This case report of a 38-year-old man with bilateral Best vitelliform macular dystrophy (BVMD) presents bilateral quiescent type 1 neovascularizations (NV) detected by optical coherence angiography (OCTA) and their multimodal imaging characteristics. It was emphasized that this kind of quiescent and asymptomatic NV may be present in nearly every stage of BVMD and it was concluded that OCTA is a noninvasive, easy, and rapid method that is superior to other imaging methods in detecting them.

**Keywords:** Best vitelliform macular dystrophy, optical coherence tomography angiography, type 1 neovascularization

## Introduction

Best vitelliform macular dystrophy (BVMD), or Best disease, is a bilateral hereditary disease that has autosomal dominant inheritance and is characterized by a typical "egg-yolk" appearance in the macula. The disease emerges in childhood and young adulthood and has 5 stages based on clinical appearance.[1,2] It generally progresses slowly, with a decrease in visual acuity that is minimal and inconsistent with the fundus appearance in the early stages. There is often asymmetry in visual acuity between the eyes, and central scotomas and metamorphopsia appear at later stages.[3,4]

Reports indicate that sudden vision loss during the natural course of BVMD is caused by secondary neovascularization (NV) and is a relatively common occurrence.[3,4,5,6,7] Optical coherence tomography angiography (OCTA) is a fairly new, rapid, and noninvasive imaging method currently used to investigate the presence of all types of NV and polypoidal choroidal vasculopathy (PCV) in the retinal and choroidal layers. In addition, it has been reported in various studies that OCTA may be useful in various retinal diseases for the early detection of inactive and quiescent NV structures that do not yet show exudative symptoms.[8]

To the best of our knowledge, this article is the first to present asymptomatic and quiescent type 1 NV lesions detected by OCTA and their multimodal imaging features in both eyes of a patient diagnosed with bilateral BVMD.

### Case Report

A 38-year-old man presented to our clinic with complaints of low vision in both eyes. He reported that he had been diagnosed with BVMD 10 years earlier, his visual acuity had been stable for a long time, and his brother also had the same disease.

On examination, his best corrected visual acuity was 7/10 in the right and 5/10 in the left eye, intraocular pressures were

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12 mmHg bilaterally, and anterior segment examination was normal. Biomicroscopic fundus examination revealed bilateral round, well-defined lesions 2-3 disc diameters in size containing yellowish subretinal material. It was observed that the subretinal material in the right eye had descended to the inferior part of the lesion to form a pronounced level (pseudohypopyon, stage 3), while in the left eye most of the material had been resorbed and had a scrambled egg appearance (vitelliruptive, stage 4). In addition, the presence of a round, gray nodular formation surrounded by a dark halo just below the macular center was also noted in the left eye.

Color photographs (Topcon 3D-OCT 2000 Corporation, Tokyo, Japan) and infrared photographs were obtained, and fundus autofluorescence (FAF) images (Heidelberg Spectralis HRA + OCT, Heidelberg, Germany) revealed hyperautofluorescent subretinal fluid in both eyes (**Figure 1a-c and 2a-c**), while spectral domain optical coherence tomography (SD-OCT) images acquired with the same device also clearly demonstrated subretinal fluid under the macula in both eyes and the presence of vitelliform material forming a level that was less pronounced in the left eye. In addition to these findings, SD-OCT sections passing through the nodular structure in the left eye showed that this lesion appeared to be a slightly irregular, pointed, hyperreflective pigment epithelial detachment (PED) containing moderately reflective material (**Figures 1d-f and 2d-f**).

OCTA imaging (RTVue-XR Avanti OCT system, Optovue, Fremont, CA) revealed vascular networks originating from an NV structure at the choriocapillary level in both eyes (forming a ring in the left eye) and cross-sectional OCTA images clearly showed increased flow signals in these regions (**Figure 3a,b and 4a,b**). The patient underwent fluorescein angiography (FA) and indocyanine green angiography (ICGA) (Heidelberg Spectralis HRA + OCT, Heidelberg, Germany) to determine the activity of the NV lesions and investigate the possibility that the nodular lesion was PCV. Although FA examination demonstrated irregular hyperfluorescent staining patterns in both maculas, there was no dye leakage until the late phases (**Figure 3c,d and 4c,d**). On ICGA, there were hypercyanotic areas of punctate staining around the macula of both eyes starting in the early phases, although no hot-spot or plaque-style staining pattern was observed in the late phases. The nodular structure in the left eye was significantly hypocyanotic in the early phases of angiography, after which it showed a hypercyanotic character starting with mild staining at minute 13 and continuing to the end of angiography (**Figure 3e, f and 4e, f**).

## Discussion

In this article, we present asymptomatic and quiescent type 1 NV lesions detected only by OCTA in both eyes of a patient diagnosed with bilateral BVMD and their characteristics on multimodal imaging with OCTA as well as color and infrared photography, FAF, SD-OCT, FA, and ICGA. To the best of our knowledge, this article is the first to describe asymptomatic and quiescent type 1 NV and its multimodal imaging features in a patient with BVMD.

Several studies published in recent years have reported that quiescent NV lesions can be found in many retinal diseases, especially age-related macular degeneration, and that they may remain asymptomatic for years.[8,9] Histologically, NVs are divided into three types: type 1 NV, which is located under the retinal pigment epithelium (RPE) (angiographically occult); type 2, which originates from the choroid and passes through Bruch's membrane and RPE to extend into the subretinal space (angiographically classic); and type 3, which develops within the neurosensory retina (retinal angiomatous proliferation).[10] In our case, the NV lesion was seen at the choriocapillaris level on OCTA and was therefore classified as type 1. NV lesions in

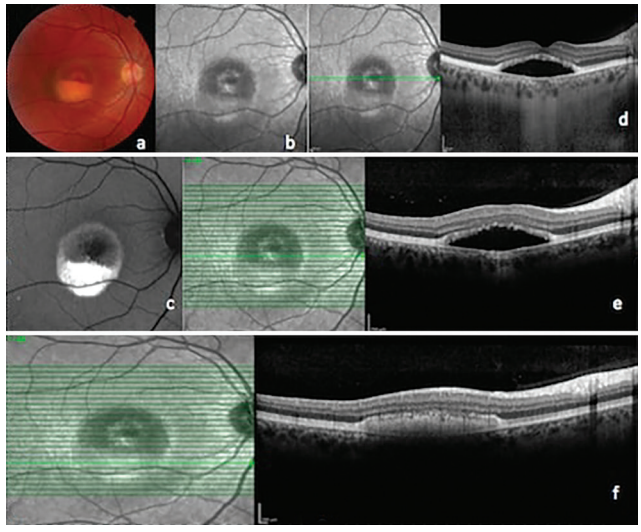


**Figure 1.** Right eye. a) Color fundus photograph, pseudohypopyon stage; b) Infrared photograph; c) Fundus autofluorescence image; d) Enhanced depth imaging optical coherence tomography (EDI-OCT); e, f) Spectral domain OCT

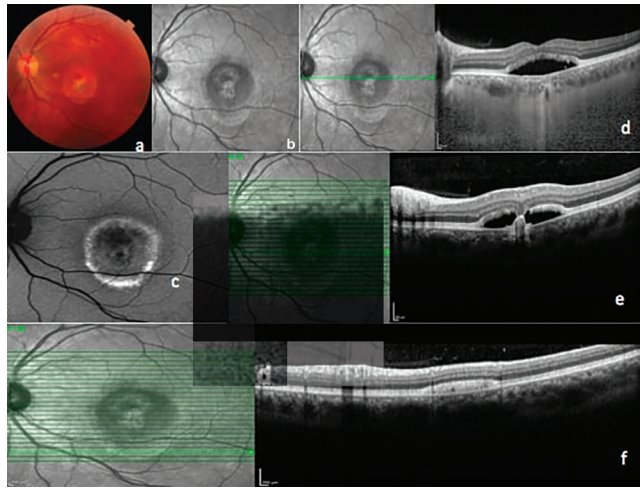


**Figure 2.** Left eye. a) Color fundus photography, vitelliruptive stage; b) Infrared photograph; c) Fundus autofluorescence image; d) Enhanced depth imaging optical coherence tomography (EDI-OCT); e, f) Spectral domain OCT

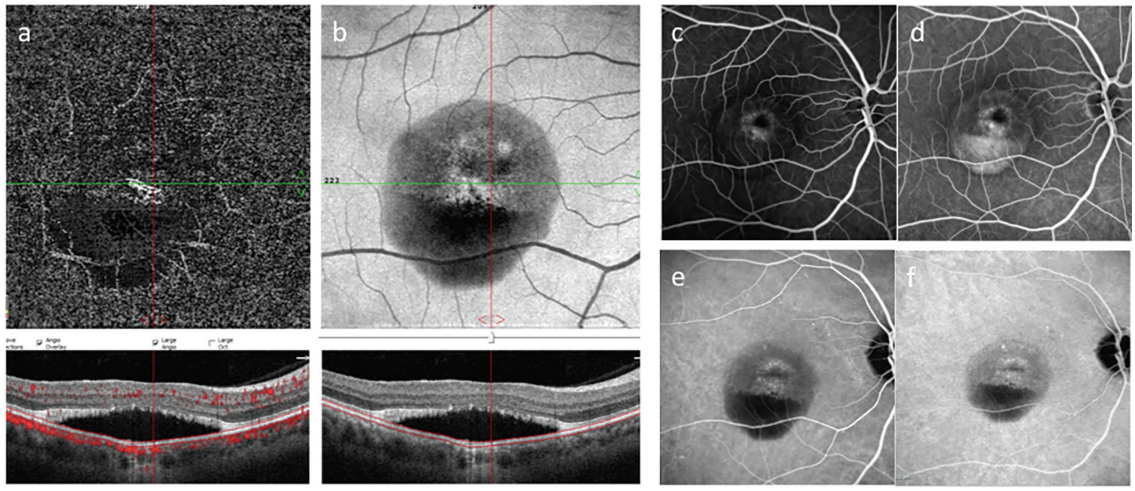


**Figure 3.** Right eye. a) En face optical coherence tomography angiography (OCTA); b) Structural OCTA; c, d) Fluorescein angiography early and late phase; e, f) Indocyanine green angiography, early and late phase

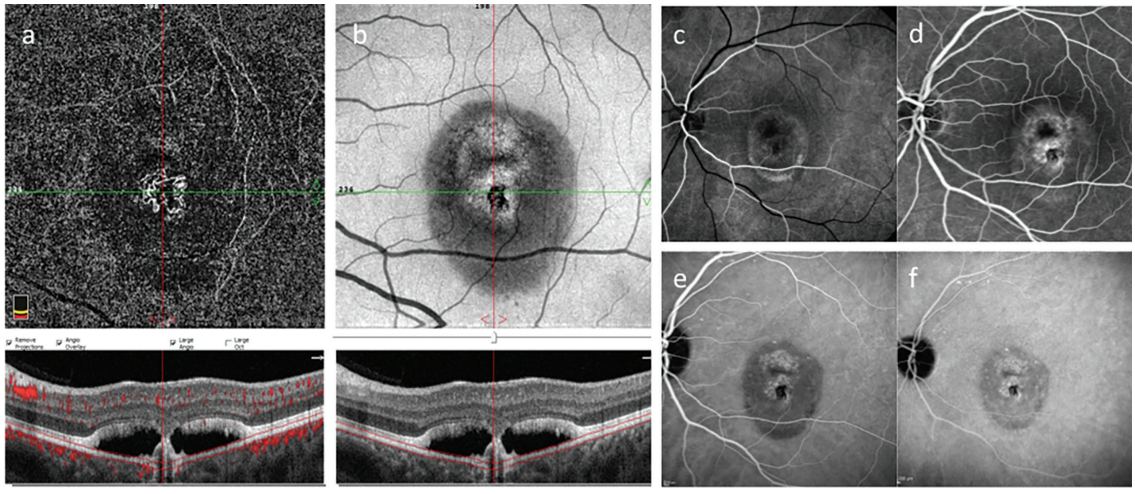


**Figure 4.** Left eye. a) En face optical coherence tomography angiography (OCTA); b) Structural OCTA; c, d) Fluorescein angiography early and late phase; e, f) Indocyanine green angiography, early and late phase

both eyes were considered inactive (quiescent) due to the absence of macular hemorrhage on clinical examination, no findings of subretinal, intraretinal, or sub-RPE fluid on SD-OCT, and no leakage in late FA.[11,12] The absence of fibrosis on clinical examination and imaging ruled out the possibility of scar tissue. The fact that the patient's eyes had very similar visual acuity, as well as being compatible with stage 3 and 4 BVMD and the patient having no complaints of a sudden decrease in vision also suggested that the NV was asymptomatic.

Using OCTA, Batıoğlu et al.[3] detected NV networks with associated polypoidal dilations at the choriocapillaris level in both eyes of a pregnant BVMD patient with complaints of reduced vision, and described the case as pachychoroid neovasculopathy. In our patient, a nodular formation was detected just below the macular center in the left eye and resembled a pointed PED on SD-OCT. We thought that it may be associated with a polypoidal structure and performed ICGA, but this diagnosis was discounted because its staining properties on ICGA were not typical for PCV.

There are many articles in the literature describing secondary NV lesions and their OCTA imaging features in eyes with BVMD. Patel et al.[5] used OCTA to examine eyes with 4 different retinal dystrophies and secondary NV development and emphasized that the morphological structure of the NV lesions could be clearly demonstrated on OCTA despite distortion of the retinal anatomy. Shahzad and Siddiqui[6] were able to visualize type 2 NV lesions secondary to BVMD with OCTA in one eye of a pediatric patient presenting with a sudden decline in vision. Guduru et al.[4] examined the vascular structure of the retina with OCTA and FA in 19 eyes with secondary NV. They reported that OCTA was superior to FA in measuring NV and that the ring-shaped NV pattern was rare. Stattin et al.[7] presented the features

of multimodal imaging using FAF, SD-OCT, FA, ICGA, and OCTA in a BVMD patient with metamorphopsia and sudden decline in vision in one eye. Researchers have detected NV lesions at the outer retinal and choriocapillary levels with OCTA while emphasizing that conventional angiography techniques such as FA and ICGA were inconclusive. In our case, we were only able to visualize the presence of a quiescent type 1 NV lesion at the choriocapillary level in both eyes with OCTA.

In summary, we concluded that OCTA is a noninvasive, easy, rapid, and reliable imaging method superior to other modalities for detecting secondary NV lesions in eyes with BVMD, even if quiescent and asymptomatic.

### Ethics

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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

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