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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

2018 Issue 5 at a Glance:

For this issue of our journal, we have selected six original articles, three of which concern the anterior segment and three concerning the posterior segment, five case reports, and a letter to the editor that we believe are valuable additions to the literature and that you will read with interest.

Pseudoexfoliation is an age-related systemic disorder characterized by the progressive accumulation of abnormal fibrillar extracellular material in the ocular and extraocular tissues. Pseudoexfoliation syndrome (XFS) is characterized by the presence of pseudoexfoliation material on anterior segment structures such as the anterior surfaces of the iris and the anterior lens capsule. XFS has been associated with increased risk of pseudoexfoliation glaucoma (XFG) and cataract. The *LOXL1* gene, which encodes an enzyme necessary for elastogenesis and collagen cross-linking, has been identified as a risk factor for developing XFS. Yaz et al. conducted a study evaluating three single nucleotide polymorphisms (SNPs) of *LOXL1* (rs3825942, rs1048661 and rs2165241) in individuals with XFS and XFG in the Turkish population. Their analysis of DNA obtained from 58 XFG patients, 48 XFS patients, and 171 healthy age- and sex-matched control subjects (277 people in total) showed that *LOXL1* gene polymorphism was a significant factor in XFS and XFG pathogenesis, and that the T allele of rs2165241 was the most important distinguishing risk factor in the study group (see pages 215-220).

Descemet membrane endothelial keratoplasty (DMEK) provides rapid and effective visual rehabilitation, but the graft preparation and unfolding stages of the procedure can be challenging. In their prospective, ex vivo, experimental study, Koçluk et al. evaluated whether various medium temperatures affected the unrolling times of DMEK grafts from donor corneas that could not be used due to positive serology, and determined that different BSS temperatures had no effect on the opening time of Descemet membrane rolls (see pages 221-226).

Aksoy et al. conducted a study comparing anterior segment parameters in pseudoexfoliative glaucoma (PEXG), primary closed-angle glaucoma (PCAG), and healthy eyes with dual Scheimpflug corneal topography. Forty-seven eyes of 38 patients with PEXG, 30 eyes of 15 patients with PCAG, and 66 eyes of 33 healthy participants were evaluated with a Galilei G4 Dual Scheimpflug Analyzer imaging device. The authors report that anterior chamber volume, anterior chamber depth, and mean anterior chamber angle were statistically significantly lower in the PCAG eyes than in the other groups, and emphasized that dual Scheimpflug corneal topography is a valuable diagnostic tool in the objective measurement of anterior segment parameters in glaucoma (see pages 227-231).

The Bosphorus Retinal Study Group, consisting of nine tertiary health care institutions, is conducting a multicenter retrospective study to evaluate the real-life outcomes of intravitreal anti-vascular endothelial growth factor (VEGF) therapy in patients with age-related macular degeneration (AMD). This initial report presenting 12-month results shows that the number of visits and injections achieved using a pro re nata (as needed) treatment regimen was suboptimal and insufficient (see pages 232-237).

In a cross-sectional study including 196 eyes of 98 AMD patients over 50 years of age, Gürbüz Yurtseven et al. investigated the relationships between AMD and refractive error and axial length, the sociodemographic characteristics that may influence it, and biochemical variables. They showed that hypermetropic refractive error and short axial length were associated with AMD independent of demographic and systemic findings, and essential hypertension was the most common comorbid systemic disease accompanying AMD (see pages 238-244).

Değirmenci et al. evaluated the effect of yellow micropulse laser (MPL) on best corrected visual acuity (BCVA) and retinal thickness in patients with non-center-involving parafoveal diabetic macular edema (DME). Nine eyes of 8 patients who underwent MPL therapy were examined retrospectively, changes in parameters between pre-treatment and 3-month

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post-treatment values were analyzed, and it was found that parafoveal retinal thickness was significantly reduced after MPL. The authors concluded that MPL can be used as an alternative to conventional argon laser in the management of non-center-involving DME (see pages 245-249)

Özdemir and Patel present their diagnosis, follow-up, and treatment of a preterm infant born at 24 weeks gestation and birth weight of 600 g who was screened for retinopathy of prematurity (ROP) using a noncontact wide-angle fundus imaging system. They emphasized the importance of using noncontact ultra-wide-angle fundus imaging together with indirect ophthalmoscopy in ROP screening (see pages 250-253).

Pregabalin is a gamma-aminobutyric acid (GABA) analogue with antiepileptic, analgesic, and anxiolytic effects. Tanyıldız et al. describe the case of a 24-year-old woman who presented with a 2-week history of blurred vision following a suicide attempt using pregabalin and was diagnosed with bilateral serous macular detachment. After 1 month of treatment with topical 0.1% nepafenac 3 times a day, her signs completely resolved and her visual acuity improved. The authors pointed out the necessity of detailed questioning of drug use history in patients with serous macular detachment or macular infarction (see pages 254-257).

Karaca et al. observed neuritis characterized by optic disc edema and star-shaped macular exudates in a 36-year-old male patient who presented with sudden and painless unilateral vision loss and had a history of consuming raw meat. Serological tests were positive for Toxocara. Combined treatment with steroid and albendazole resulted in increased visual acuity and complete regression of all clinical signs. In this case report, the authors emphasized that ocular toxocariasis can also be seen in adults, and raw meat consumption should be questioned when a patient presents with neuroretinitis (see pages 258-261).

Pachychoroid neovasculopathy (PNV) is a form of type 1 neovascularization characterized by dilated choroidal vessels in areas with increased choroidal thickness. Biçer et al. diagnosed PNV in a 50-year-old male patient with a 2-month history of blurred vision using fundus autofluorescence, fundus fluorescein angiography, indocyanine green angiography, spectral domain optical coherence tomography, and optical coherence tomography angiography, examined the findings obtained with these methods, and indicated the importance of multimodal imaging in the diagnosis of pachychoroid spectrum diseases (see pages 262-266).

The Harada-Ito (HI) procedure is a strabismus surgical technique developed to treat torsional diplopia caused by excyclotorsion associated with superior oblique muscle palsy. The main indication for the procedure is acquired trochlear nerve palsy following closed head injury, particularly from traffic accidents. Ayyıldız et al. reported that HI surgery in three patients with torsional diplopia due to acquired trochlear nerve paralysis successfully eliminated their torsional diplopia, but that patients should be adequately informed preoperatively about the outcomes of treatment. (See pages 267-273)

In a letter to the editor written in response to Aksoy et al.'s article entitled "Topography and Higher Order Corneal Aberrations of the Fellow Eye in Unilateral Keratoconus", Koç and Tekin share their views that the term 'unilateral keratoconus' is inaccurate, that it may be confused with 'subclinical keratoconus', and that posterior elevation and pachymetry data are more sensitive indexes for early diagnosis of keratoconus (see pages 274-275).

Respectfully on behalf of the Editorial Board,
Özlem Yıldırım, MD

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Turk J Ophthalmol 2018;48:215-220

Original Article

Three Single Nucleotide Polymorphisms of *LOXL1* in a Turkish Population with Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma

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Abstract

Objectives: To investigate the three single nucleotide polymorphisms (SNPs) (rs3825942, rs1048661, and rs2165241) of the *LOXL1* gene in pseudoexfoliation syndrome (XFS) and pseudoexfoliation glucoma (XFG) in the Turkish population.

Materials and Methods: DNA was obtained from blood samples of 48 XFS, 58 XFG, and 171 control subjects. Three *LOXL1* SNPs (rs3825942, rs1048661, rs2165241) were investigated with real time PCR, a probe-based genotyping method, and melting curve analysis.

Results: All three SNPs of *LOXL1* were significantly associated with XFS (rs3825942 $p=3.54x10^{-6}$, odds ratio [OR]=∞; rs1048661 p=0.008, OR=2.18; rs2165241 $p=8.69x10^{-9}$, OR=4.30) and XFG (rs3825942 $p=3.41x10^{-7}$, OR=∞; rs1048661 $p=1.75x10^{-5}$, OR=3.78; rs2165241 $p=3.85x10^{-11}$ OR=4.90). No significant differences were observed between the XFS and XFG groups for any of the SNPs. The GG genotype of rs3825942 was more valuable for distinguishing pseudoexfoliative cases from healthy individuals. The homozygous TT genotype of rs2165241 was associated with 6-fold increased XFS risk ($p=8.15x10^{-8}$, OR=6.32) and 7-fold increased XFG risk ($p=1.45x10^{-10}$ OR=7.95). The GGT haplotype consisting of all three risk alleles was associated with a 7.45-fold higher risk of XFS/XFG ($p=8.65x10^{-14}$, OR=7.45). Presence of T allele of rs2165241 conferred 3 times higher risk for men than women ($p=6.78x10^{-5}$, OR=3.202).

Conclusion: *LOXL1* SNPs are associated with increased risk for pseudoexfoliation in the Turkish population. T allele of rs2165241 was found to be the most important characterized risk factor for our cohort. All SNP distributions were similar to other European and American populations.

Keywords: Pseudoexfoliation syndrome, pseudoexfoliation glaucoma, *LOXL1* gene

Introduction

Pseudoexfoliation glaucoma (XFG) is the most common identifiable cause of secondary open-angle glaucoma worldwide.[1] Pseudoexfoliation is an age-related systemic disorder characterized by progressive accumulation of abnormal fibrillar extracellular material in ocular and extraocular tissues.[1,2] Pseudoexfoliation syndrome (XFS) is diagnosed based on the appearance of pseudoexfoliation material (PXM) on anterior segment structures like the pupillary border of the iris or the anterior lens capsule. XFS has been associated with increased risk of cataract and glaucoma[3,4] and predisposition to a broad range of intraocular complications during surgery.[1,2]

The structure and origin of PXM has not been determined. A recent genome-wide association (GWA) study identified the *LOXL1* gene, which encodes an enzyme necessary for elastogenesis and collagen cross-linking, as a major genetic risk factor for developing PXF.[5,6] Three single nucleotide polymorphisms

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(SNPs) have been associated with PXF: one intronic SNP, rs2165241 located in intron 1, and two nonsynonymous coding SNPs, rs3825942 (G153D) and rs1048661 (R141L) located in exon 1.[5] However, the frequency of risk alleles for both variants varies among different populations. Based on these studies, LOXL1 is necessary but not sufficient for PXM development.[5] Due to the relationship between PXM, the extracellular matrix, and basement membrane, the role of different genes were investigated in PXM formation. These genes were related to elastic fiber and extracellular matrix metabolism, such as MMP1, MMP3, FBN1, LTBP2, MFAP2, TGM2, TGF-β1, and CLU.[7,8,9] In addition, *LOXL1* promoter haplotypes, which influence gene expression and lead to reduced enzyme activity, are associated with XFS/XFG.[5]

The purpose of this study was to investigate variant SNPs (rs2165241, rs3825942 and rs1048661) of the *LOXL1* gene to determine the association of *LOXL1* polymorphism with XFG and XFS in the Turkish population.

Materials and Methods

Study Population

The study population comprised 277 individuals including 58 patients with XFG, 48 patients with XFS, and 171 healthy age- and sex-matched controls. Written informed consent was obtained from all participants. The study was approved by the ethics review board of the Eskişehir Osmangazi University Faculty of Medicine and adhered to the tenets of the Declaration of Helsinki.

All participants were questioned about systemic diseases (diabetes, hypertension, thyroid, and rheumatic diseases) and drug usage, then underwent a standardized detailed ophthalmic examination, which included refraction, visual acuity, intraocular pressure (IOP) (Goldmann applanation tonometry), anterior segment biomicroscopy examination, and fundus examination. XFG was defined as the presence of PXM on the anterior lens capsule or pupillary margin, elevated IOP (≥21 mmHg), glaucomatous optic disc changes (vertical cup-to-disc ratio [C/D] ≥0.5, C/D asymmetry ≥0.2), characterized visual field defects in computed perimetry (Zeiss Humphrey visual field analyzer white-to-white 30-2 threshold program). Patients with PXM on the anterior lens capsule and pupillary margin but whose IOP, optic disc, and visual field findings were within normal limits were defined as XFS. Individuals without clinical signs of XFS/XFG were recruited as a control group. Demographic and clinical characteristics of the groups are presented in Table 1.

DNA Extraction and Genotyping

Venous blood samples (5 mL) were collected from the antecubital region to investigate *LOXL1* gene polymorphism. The samples were collected in NaEDTA tubes and stored at -20 °C.

Roche Magna Pure Compact robotic DNA isolation system protocol was used for DNA extraction. Blood samples were put directly into the robotic DNA isolation system. Sample volume 200 µL, elution volume 100 µL and DNA isolation blood protocol were selected. The robotic system consists of proteinase K, irrigation solution, magnetic particles for DNA isolation, cartridge system for pipetting, tip trailer for pipette tips, and rack for sample and elution tubes. All of the steps were performed automatically except arranging the cartridge and tip trailer, and putting the samples and elution tubes into the robotic system. The procedure lasted approximately 25 minutes for each set of 8 samples. DNA samples were stored at -20 °C.

Amplification of isolated DNA samples with real-time PCR and melting analysis: After the replication of the SNPs to be investigated by Roche LightCycler 480 Real Time PCR, real-time PCR melting curve analysis was performed by using hybrid probe kits designed specifically for SNPs. Mutant types were determined with melting curve analysis by evaluating differences in melting temperature degrees of SNPs. Three hundred and eighty-four RXN Molbiol LightSNiP® kits which were designed for specific SNP regions were used for melting analysis according to the manufacturers' recommendations.

Reaction mixtures were prepared with LightCycler® FastStart DNA Master HybProbe, then put into plates and DNA was added. The recommended program was used in the real-time PCR device.

Fluorescence occurred at different temperatures for each allele. For rs3825942, signals detected at 62.21 °C were evaluated as G allele and those at 69.73 °C as A allele; for rs1048661, signals at 54.42 °C were evaluated as G allele and at 65.82 °C as T allele; for rs2165241, signals detected at 52.34 °C were evaluated as C allele and at 59.30 °C as T allele.

Statistical Analysis

The incidence was calculated as a percentage for each genotype. Allele and genotype frequencies in the patient and

Table 1. Demographic and clinical characteristics

		XFS (n=48)	XFG (n=58)	Controls (n=171)	p-value
Age median (25%-75%)		68 (66.5-70)	69 (68-73.25)	67 (64-70)	0.060*
Gender	Male (n/%)	21 (0.44)	38 (0.66)	69 (0.41)	0.004**
	Female (n/%)	27 (0.56)	20 (0.34)	101 (0.59)	
IOP (mmHg) median (25%-75%)		14 (12.5-16)	14 (12-17)	14 (13-16)	0.314*
C/D ratio median (25%-75%)		0.1 (0-0.2)	0.6 (0.4-0.8)	0.2 (0.2-0.325)	0.0001*

*The Kruskal-Wallis test was used. p-value of <0.05 was considered of statistical significance,**Pearson Chi-Square test was used. p-value of <0.05 was considered of statistical significance.
XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma, IOP: Intraocular pressure, C/D: Cup/Disk

control groups were compared with values predicted by Hardy-Weinberg equilibrium using the chi-square test. Kruskal-Wallis test was used for comparison of age, IOP, and C/D between the groups. Dunn's multiple comparison test was used for variables that showed differences among groups. Continuous variables were assessed using the Shapiro-Wilk test. Continuous variables were expressed as median (25%-75%) and categorical variables were shown as frequencies (percentages). Pearson and Yates correction chi-square tests were done for comparisons of allele and genotype variables between the groups. Odds ratios (OD) and 95% confidence interval (CI) were calculated. A p value of <0.05 was considered of statistical significance. The statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 277 individuals (58 XFG, 48 XFS, 171 controls) over 40 years old were recruited for this study in Eskişehir Osmangazi University Department of Glaucoma. The mean age was 68 (66.5-70) years for the XFS group, 69 (68-73.25) years for the XFG group, and 67 (64-70) years for control subjects.

The genotype distribution of all SNPs conformed to Hardy-Weinberg equilibrium. In both XFS and XFG, a strong association with the risk allele of each individual SNP (rs2165241T, rs1048661G, and rs3825942G) was observed (Table 2). The G allele of rs3825942 was present in all XFS and XFG patients, thus OR could not be calculated (OR=∞ $p=3.54x10^{-6}$, OR=∞, $p=3.41x10^{-7}$). In the control group, G allele for rs3825942 was more common than the A allele. For rs3825942, all patients in the XFS and XFG groups had the GG genotype, and again ORs could not be calculated (OR=∞ $p=1.57x10^{-6}$, OR=∞, $p=1.45x10^{-6}$). The G allele and GG genotype of rs1048661 were detected more frequently in all groups. The T allele of rs1048661 was underrepresented in patients with XFS (OR=2.18 95% CI=1.21-3.91, p=0.008) and XFG (OR=3.78 95% CI=1.99-7.18, $p=1.75x10^{-5}$) when compared to control subjects. No TT genotype of rs1048661 was detected in XFS (OR=1.93 95% CI=0.98-3.77, p=0.076) or XFG (OR=3.71 95% CI=1.83-7.47, $p=2.75x10^{-14}$) patients. In control subjects, the TT genotype of rs1048661 was detected more frequently when compared with XFS and XFG patients. However, the GG and GT genotype of rs1048661 were overrepresented in control subjects when compared to the TT genotype of rs1048661. For rs2165241, the T allele was more frequent than C allele in XFS (OR=4.30 95% CI=2.55-7.25 $p=8.69x10^{-9}$) and XFG (OR=4.90 95% CI=2.98-8.06 $p=3.85x10^{-11}$) patients, while in control subjects the C allele was more common. The genotype distribution of rs2165241 was different in XFS and XFG patients and control subjects. The TT genotype of rs2165241 was overrepresented and the CC genotype of rs2165241 was underrepresented in XFS (OR=6.32 95% CI=3.16-12.64, $p=8.15x10^{-8}$) and XFG (OR=7.95 95% CI=4.10-15.42, $p=1.45x10^{-10}$) patients when compared to control subjects. The CT genotype was the most frequent genotype in control subjects. For three SNPs the TT genotype of rs2165241 was detected more frequently in XFS (58%) and XFG (63%) when compared to control subjects (19%). Likewise, the homozygous TT genotype of rs2165241 was associated with 6.32-fold higher risk of XFS (95% CI=3.16-12.64) and 7.95-fold higher risk of XFG (95% CI=4.10-15.42).

For three SNPs, rs3825942, rs1048661, rs2165241, haplotype analysis of risk alleles was calculated to determine the combined effects on pseudoexfoliation patients (XFS+XFG) and control subjects (Table 3). The haplotypes consisting of risk alleles were overrepresented in pseudoexfoliation patients as compared to control subjects for each SNP ($p=8.65x10^{-14}$) and were associated with 7.45-fold increased risk of pseudoexfoliation (95% CI=4.22-12.99).

According to previous studies, females are affected by XFS more often than males, whereas XFG is more severe in males than females.[2] In our allele analysis of all pseudoexfoliation patients (XFS+XFG) based on gender, the T allele of rs2165341 was detected in 75% of males and 49% of females (Table 4). Existence of T allele was associated with 3.2 times higher risk for men than women (p=6.78x10-5, $c^2=15.871$, OR=3.202 95% CI=1.719-5.989).

Discussion

After Thorleifsson et al.[5] from Iceland identified three associated polymorphisms of *LOXL1* in XFS/XFG, many studies were performed on Caucasian, Asian, and African populations.[10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,27,28,29,30,31,32] In our study we investigated the association between three SNPs of *LOXL1* (rs1048661, rs3825942, rs2165241) and XFS/XFG in the Turkish population. Our findings show a significant association with XFS, as in other recent studies. However, geographically Turkey is located in both Asia and Europe, and this association in our population was similar to that observed in Caucasians, as in European populations.

In our study, the relationship between G allele and GG genotype of rs3825942, G allele and GG genotype of rs1048661, and T allele and TT genotype of rs2165241 was found in XFS/XFG, as in the Caucasian population.[10,11,12,13,14,15,16,17,18,19,20,21,22] In the present study the G allele and GG genotype of rs3825942 was present in all XFS and XFG cases. According to the results of an African study and another Turkish study[11] for rs3825942, the A allele carries an increased risk for XFS.[11,32] However, in our study and another study from Turkey, the A allele was not detected in any XFS and XFG cases and was suggested to be protective.[10] Similarly, in another Turkish study, the G allele GG genotype of rs1048661 were detected in exon 1 of *LOXL1*, as seen in the patients in our study group.[12]

Studies in European and American populations reported that G allele and GG genotype of rs1048661 and T allele and TT genotype of rs2165241 were associated with XFS, whereas studies in Asian populations identified the opposite relationship for risk alleles and genotypes for these SNPs.[23,24,25,27,28,29,30,31] Our results appear to be similar to

Caucasians but different from Asians in terms of allelic and genotypic distributions of rs1048661 and rs2165241.[10,11,12,13,14,15,16,17,18,19,20,21,22] Another study from Turkey indicated that T allele and TT genotype of rs2165241 were associated with XFS/XFG, like our study, but revealed no significant relationship with G allele and GG genotype of rs1048661.[13] For this reason, the pathogenesis of XFS cannot be explained by genetic factors alone.

Table 2. Allele and genotype association analysis for the three single nucleotide polymorphisms of *LOXL1*

SNPs	Controls (n=171)	XFS (n=48)				XFG (n=58)			
	n (%)	n (%)	χ^2	p-value*	OR (95% CI)	n (%)	χ^2	p-value*	OR (95% CI)
rs3825942									
Allele									
G	273 (0.79)	96 (1.00)	21.495	$3.54x10^{-6}$	∞**	116 (1.00)	26.001	$3.41x10^{-7}$	∞**
A	69 (0.21)	0 (0.00)				0 (0.00)			
Genotype									
GG	108 (0.63)	48 (1.00)	23.061	$1.57x10^{-6}$	∞**	58 (1.00)	23.660	$1.45x10^{-6}$	∞**
GA	57 (0.33)	0 (0.00)				0 (0.00)			
AA	6 (0.04)	0 (0.00)				0 (0.00)			
rs1048661									
Allele									
G	238 (0.69)	80 (0.83)	7.117	0.008	2.18 (1.21-3.91)	104 (0.89)	18.438	$1.75x10^{-5}$	3.78 (1.99-7.18)
T	104 (0.31)	16 (0.17)				12 (0.11)			
Genotype									
GG	87 (0.51)	32 (0.67)	3.156	0.076	1.93 (0.98-3.77)	46 (0.79)	13.237	$2.75x10^{-14}$	3.71 (1.83-7.47)
GT	64 (0.37)	26 (0.33)				12 (0.21)			
TT	20 (0.12)	0 (0.00)				0 (0.00)			
rs2165341									
Allele									
T	150 (0.44)	74 (0.77)	33.114	$8.69x10^{-9}$	4.30 (2.55-7.25)	92 (0.75)	43.685	$3.85x10^{-11}$	4.90 (2.98-8.06)
C	192 (0.56)	22 (0.23)				24 (0.25)			
Genotype									
TT	31 (0.19)	28 (0.58)	28.771	$8.15x10^{-8}$	6.32 (3.16-12.64)	37 (0.63)	41.100	$1.45x10^{-10}$	7.95 (4.10-15.42)
CT	88 (0.51)	18 (0.38)				18 (0.31)			
CC	52 (0.30)	2 (0.04)				3 (0.05)			

*Pearson chi-square tests was used, **OR infinity, p-value of <0.05 was considered of statistical significance
SNPs: Single nucleotide polymorphisms, XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma, OR: Odds ratio, CI: Confidence interval

Table 3. Haplotype analysis of risk alleles at rs3825942, rs1048661 and rs2165341 in combined patients and controls

Haplotype	XFS/XFG (n=106)	Controls (n=171)			
	n (%)	n (%)	χ^2	p-value*	OR (95% CI)
rs3825942/rs1048661/rs2165341					
GGT	65 (0.61)	30 (0.17)	55.651	$8.65x10^{-14}$	7.45 (4.22-12.99)
rs3825942/rs1048661					
GG	78 (0.74)	42 (0.25)	64.049	$1.21x10^{-15}$	8.55 (4.91-14.90)
rs1048661/rs2165341					
GT	65 (0.61)	30 (0.17)	55.651	$8.65x10^{-14}$	7.45 (4.22-12.99)
rs3825942/rs2165341					
GT	65 (0.61)	31 (0.18)	53.905	$2.10x10^{-13}$	7.16 (4.12-12.43)

*Pearson Chi-Square test was used. p-value of <0.05 was considered of statistical significance.
XFS: Pseudoexfoliation syndrome, XFG: Pseudoexfoliation glaucoma, OR: Odds ratio, CI: Confidence interval

Table 4. The allele and genotype analysis of the pseudoexfoliation group based on gender					
SNPs	**Male (n=59)**	**Female (n=47)**			
	n (%)	**n (%)**	χ^2	**p-value***	**OR (95% CI)**
rs3825942					
G	118 (1.00)	94 (1.00)	0.000	1.000	∞
A	0 (0.00)	0 (0.00)			
rs1048661					
G	106 (0.90)	78 (0.83)	1.587	0.208	1.812 (0.759-4.358)
T	12 (0.10)	16 (0.17)			
rs2165341					
T	89 (0.75)	46 (0.49)	15.871	$6.78x10^{-5}$	3.202 (1.719-5.989)
C	29 (0.25)	48 (0.51)			
*Yates correction chi-square test was used, p-value of <0.05 was considered of statistical significance SNPs: Single nucleotide polymorphisms, OR: Odds ratio, CI: Confidence interval					

In several studies researching whether *LOXL1* gene polymorphism has any role in predicting XFG development, no significant association was found in the differentiation of XFS and XFG.[1] Likewise, in our study, no differences in *LOXL1* polymorphism were found between the XFS and XFG groups. On the other hand, recent studies have shown that females were affected more frequently by XFS than males, whereas XFG was more severe in males compared to females.[2] We observed a strong relationship between the T risk allele in the rs216341 SNP and gender in XFS and XFG, with men carrying the T allele showing at 3 times higher risk of disease. However, a study from Japan did not show significant gender differences in any of the three SNPs.[28]

In our study, the haplotype (GGT) consisting of all three risk alleles of *LOXL1* SNPs (rs3825942 G, rs1048661 G and rs2165341 T) was associated with a 7.45-fold higher risk of XFS/XFG. A study in an American population reported a 3-fold higher risk[6] and a study in a Polish population determined a 4-fold higher risk with the GGT haplotype.[22]

Conclusion

Our findings are similar to previous Turkish studies that investigated two non-synonymous coding SNPs rs3825942 and rs1048661, but we observed intronic SNP rs2165341 as well. Our results support the existence of a significant association between three SNPs of *LOXL1* with both XFS and XFG, though no significant differences were found between the XFS and XFG patients. Also different from the genotypes of exonic SNPs (rs3825942, rs1048661), the TT genotype of rs2165341 was detected more frequently in pseudoexfoliation and was associated with 6-fold and 7-fold increases in risk of XFS and XFG, respectively. Likewise, we observed a relationship between the T allele of rs2165341 and gender, as presence of the T allele was associated with 3 times higher risk for men compared to women. To the best of our knowledge, rs2165341 is an important and risk-modifying factor in our cohort. In conclusion, *LOXL1* gene polymorphism has a significant influence on XFS and XFG pathogenesis, but is inadequate to explain the exact mechanism. Therefore, further genetic and epigenetic studies are needed.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University Faculty of Medicine Ethics Review Board (2010/76).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yetkin Yaz, Yasemin Aydın Yaz, Nilgün Yıldırım, Zafer Yüksel, Oğuz Çilingir, Concept: Yetkin Yaz, Nilgün Yıldırım, Design: Yetkin Yaz, Nilgün Yıldırım, Data Collection or Processing: Yetkin Yaz, Yasemin Aydın Yaz, Analysis or Interpretation: Yetkin Yaz, Nilgün Yıldırım, Fezan Mutlu, Literature Search: Yetkin Yaz, Writing: Yetkin Yaz.

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Original Article

Does Fluid Temperature Affect Corneal Endothelium-Descemet Membrane Scroll Formation? An In Vitro Study

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Abstract

Objectives: To investigate whether unfolding time of Descemet membrane (DM) graft rolls changes at various fluid temperatures.

Materials and Methods: The study was prospective, ex vivo, and experimental. The study was conducted at the tertiary center for corneal disease in Adana Numune Training and Research Hospital between June 2014 and June 2015. DMs were divided into 4 categories according to baseline roll tightness and these were distributed among 4 different groups using 4 different balanced salt solution (BSS) temperatures (8, 16, 23, and 36 °C). Sixteen donor corneas were obtained from the hospital eye bank.

Results: DM roll formations may vary according to the donor cornea received. Some form tighter rolls while others can form a more open roll. No differences in roll tightness were observed in any of the DM rolls after 5 or 10 minutes in the different BBS temperatures. In all groups, neither tightening nor opening was observed in DM roll formations.

Conclusion: Different BSS temperatures were found to have no effects on DM unfolding time in this study.

Keywords: Descemet membrane endothelial keratoplasty, Descemet membrane, balanced salt solution, Descemet membrane unfolding time, donor cornea

Introduction

Descemet membrane endothelial keratoplasty (DMEK) was first described by Melles et al.[1,2] as the replacement of diseased endothelium and Descemet membrane (DM) using an isolated endothelium DM layer without adherent corneal stroma. Although the Descemet stripping automated endothelial keratoplasty (DSAEK) procedure involves well standardized and reproducible graft preparation and unfolding, DMEK remains challenging. The main step of the procedure, which involves unfolding the lamella to attach the graft to the posterior stroma, can be especially difficult. This step involves most of the manipulations to the graft.[3]

DMEK provides faster and more complete visual rehabilitation compared to DSAEK.[4,5,6] However, graft preparation and unfolding are less standardized. In DMEK, the graft preparation phase, injection of DM into the anterior chamber, and all the unfolding phases in the anterior chamber are performed in a fluid medium. We hypothesized that graft unfolding could be affected by the temperature of the fluid medium.

We observed a spontaneous opening of tight DM rolls that were difficult to open in the DMEK surgeries of some patients, and thought that it may be due to the warming effect of the microscope light. If DMEK surgery is prolonged, the microscope light can have a thermal effect. The major protein in DM is type IV collagen. With heat, the structure of collagen is disrupted by strong oscillations that break the bonds between molecules, and this may affect DM unfolding time.[7] Although there was no animal model or other research showing that temperature change can affect DM roll tightness, we investigated the effect of temperatures up to normal body temperatures on DM rolls in a laboratory setting.

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The study was presented in the XXXIV Congress of the European Society of Cataract and Refractive Surgeons as an e-poster.

This experimental study investigated whether the unfolding time of cornea DMEK graft rolls which could not be used due to positive serology changed in various fluid temperatures.

Materials and Methods

This study was prospective, *ex vivo*, and experimental in nature. Ethical approval was obtained from Adana Numune Training and Research Hospital, where the study was conducted. The study was carried out with 16 donor corneas which were obtained from the eye bank of the tertiary center for corneal disease in Adana Numune Training and Research Hospital between June 2014 and June 2015. The donors' ages were noted. The donor corneas were not appropriate for implantation due to positive results in serological tests ($HbsAg^+$ or $antiHCV^+$).

Corneoscleral buttons were excised and stored in a corneal chamber which contained Eusol-C (AlchimiA, Viale Austria, Italy) at 4 °C for 14 days. DM tissues were found to have no endothelial pathology by biomicroscopic examination (there was no evidence of corneal endothelial dystrophy or folds, and no history of intraocular surgery). The death-to-preservation time was not longer than 12 hours without refrigeration and the tissue was used within 7 days of harvesting.

Donor Preparation

All tissues were prepared by a single surgeon (Y.K.) in the operating room using the submerged cornea technique immediately before evaluation as described previously.[8] Corneoscleral buttons were positioned onto a Barron vacuum punch to prevent shifting during DM preparation (Katena Products, Inc., New Jersey, USA). All DM grafts underwent superficial trephination using an 8.0 mm punch, which is one of the most preferred diameters in DMEK surgery. The DM edges were stained with 0.06% trypan blue solution and the donor rim was filled with 23 °C balanced salt solution (BSS). Stripping was performed in this medium using tying forceps, working from edge to center, and the DM was harvested. The DM roll was then restained with trypan blue for 60 s (Figure 1).

DM Rolls

The DM grafts were divided into 4 categories according to initial roll tightness. Accordingly, 1/4 DM roll was very tight (about 1-2 mm width), 2/4 DM roll had about 3-4 mm width, 3/4 DM roll had about 5-6 mm width, and 4/4 DM roll was nearly completely open (about 7-8 mm width).

Using tying forceps, the prepared DM rolls were placed into closed glass containers containing BSS at different temperatures. Changes in DM roll formations and sizes were observed and photographed by ophthalmic surgical microscope at the beginning, at 5 minutes, and at 10 minutes.

The temperature of the operating room and liquids (relatively) in the room may vary between 22 and 24 °C during eye surgery.[9] The ambient temperature was ~23°C in the operating room where the current study was performed. In another study, it was determined that the mean temperature in the anterior chamber was 23.6 °C.[10] Therefore, 23 °C is a logical BSS temperature for stripping of DM graft. Considering the temperature range between 8 °C (4-8 °C is storage temperature of donor tissue) and 36 °C (human body temperature) suitable for this study, we evaluated temperatures of 8, 16, 23, and 36 °C to determine the optimal BSS temperature for DM grafts.

The study was conducted in 4 different groups, using 4 different BSS temperatures: 3 (20.0%) DM grafts were placed in 8 °C BSS (Group 1), 4 (26.7%) in 16 °C BSS (Group 2), 4 (26.7%) in 23 °C BSS (Group 3), and 4 (26.7%) in 36 °C BSS (Group 4). BSS temperatures in all groups were checked with a thermometer and kept stable throughout the 10-minute observation period. Changes in fold tightness of the DM grafts in BSS at different temperatures were observed for 10 minutes. In DMEK surgery, shorter DM graft unfolding time is desirable to ensure less endothelial loss and favorable postoperative prognosis. Thus, the effects of BSS temperature on the unfolding time of DM grafts in 10 minutes were observed and recorded in this study.

Statistical Analysis

SPSS version 16.0 software (SPSS, Inc., Chicago, IL) was utilized in the analysis of the data. The analysis included nonparametric tests. Median and range or mean ± standard deviations (SD) were demonstrated through descriptive statistics. The distribution of proportions was analysed using chi-square distribution. Statistical significance was accepted as $p<0.05$.

Results

The median donor age (16 corneas of 8 donors) was 69 years (range, 65-71 years). The male/female ratio was 6 (37.5%)/10 (62.5%). There were no significant differences between the groups in terms of age and gender ($p=0.114$, $p=0.362$, respectively).

The median time from death to corneal removal was 7 hours (range, 5-9 hours), while the median time from preservation to surgery was 5.5 days (range, 5-7 days). There were no statistical differences between the groups in terms of time from death to corneal removal or preservation to surgery ($p=0.687$, $p=0.887$, respectively).

Cause of death was cerebrovascular disease in 3 donors, myocardial infarction in 2 donors, and chronic kidney disease in 3 donors. It was thought that cause of death would affect DM roll formation. However, there were no statistical differences between the groups in terms of the donors' cause of death ($p=0.238$).

All tissues were stripped in the operating room and prepared immediately before evaluation. The median DM peeling time was 7.0 minutes (range, 5-20 minutes), with no statistically significant differences between the groups ($p=0.946$). Of the 16 corneas, the DM roll could not be obtained from only 1 (in Group 1). This lacerated DM was excluded from the study.

Prepared DM roll formations can vary according to the donor cornea. In the current study, some formed a tighter roll, while others formed a looser roll. At time of collection, there

was no statistical difference between the groups in DM roll tightness in the 23 °C BSS (p=0.273) (Table 1). In all groups, no differences were observed in the DM roll formations and width of the tissues in the different temperatures of BSS after 5 and 10 minutes. The DM graft rolls prepared in the 23 °C BSS temperature were not affected by increasing or decreasing the BSS temperature for 10 minutes. In all groups, neither tightening nor opening was observed in DM roll formations. Figure 2 displays the images of some DM rolls in groups at 0 and 10 minutes.

Discussion

DMEK preparation might be affected by some systemic conditions. Research shows that DMEK preparation can have higher failure rates with tissues from donors with diabetes mellitus (especially with longer duration of the disease) and hyperlipidemia or obesity. It is reported that failure rate can be reduced by eliminating the tissues from donors either with diabetes mellitus or with hyperlipidemia or obesity.[11] The related literature indicates general rate of failure as 5.2%.[8,12] In our study, we could not obtain DM graft from only one donor cornea (6.25%). There were lacerations resulting from the tightly cohesive nature of the stromal surface. This donor's cause of death was chronic kidney disease with diabetes mellitus, which is consistent with the information in the literature.[11]

Donor age, systemic diseases, and cause of death may have an impact on DM graft preparation, complications during harvesting, and DM roll formation.[3,11,13] In the current study, preoperative findings were similar and differences between groups were not statistically significant. Therefore, we were able to investigate only the effects of different BSS temperatures on DM roll formation in this study.

A statistically significant correlation was reported between relatively early postoperative endothelial cell loss and unfolding time, with longer unfolding time associated with greater endothelial cell loss.[3] Another study found no correlation between corneal donor characteristics and the degree of difficulty of unfolding with graft lamella older than 49 years. The same study indicated that there was a significant association between more difficult graft unfolding and rates of graft detachments and endothelial cell loss.[14] It was reported that graft orientation in DMEK surgery can be visualized and assessed with live intraoperative optical coherence tomography. In addition, faster graft positioning with less graft manipulation was reported in the presence of severe corneal edema.[15] Different ways to facilitate graft unfolding are still being sought.

When the DMEK graft is separated from the corneal stroma, it forms a roll with the DM inside and the endothelium facing outward. This formation is associated with type IV

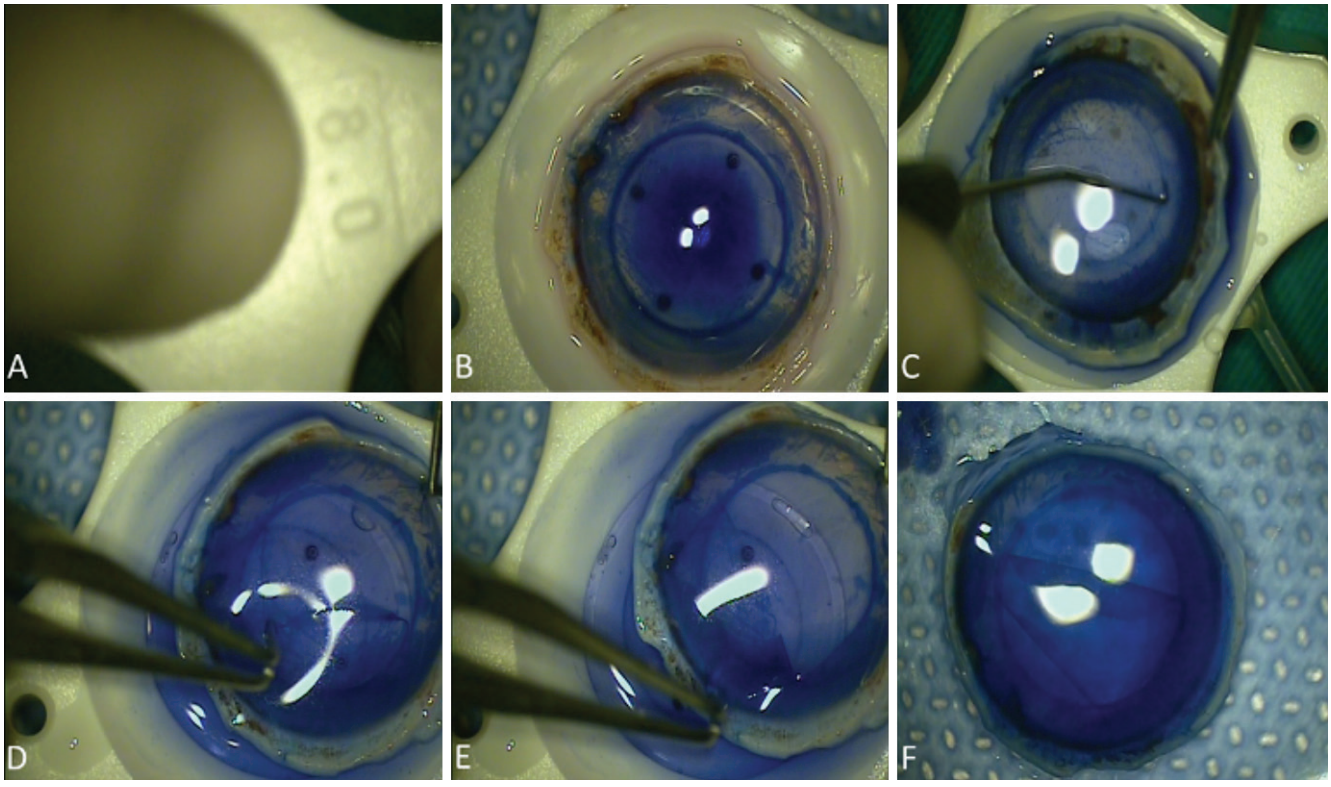

Figure 1. Harvesting of Descemet membrane (DM) roll. (A) Superficial trephination on the endothelial side; (B) staining DM edges with trypan blue; (C) finding edge of DM using Sinskey hook; (D) stripping toward the center using tying forceps; (E) completion of DM stripping; (F) restaining DM roll with trypan blue
DM: Descemet membrane

collagen in the DM and the behaviors of endothelial cells after leaving the cornea. More studies which demonstrate how graft properties affect graft unfolding time are needed. We were unable to find any animal model or other research in the literature showing that temperature change can affect DM roll tightness.

As the prognosis in the postoperative period depends on the remaining number of endothelium cells, DMEK surgery and DM unfolding times are important. The DM roll should be opened in the anterior chamber with minimum endothelial loss and attached to the recipient stroma. Recently, several maneuvers for atraumatic unrolling of DMEK grafts have been described.[16,17,18] An *in vitro* study showed that delivering DMEK tissue trifolded with the endothelium inward reduced surgical trauma to donor cells and facilitated spontaneous unfolding.[17] However, despite the maneuvers developed, there is no standardized method of graft unfolding which affects postoperative success, and DM unfolding time can be prolonged in some cases. Moreover, the factors affecting DM unfolding time have not been determined. Existing methods used for DM unfolding result in direct or indirect mechanical trauma to the graft, which can cause endothelium injury. Therefore, less traumatic methods need to be developed.

In some cases where we had difficulty in DM unfolding, in time we observed spontaneous unfolding. Supposing that this could be associated with heating under the microscope light, we put DM rolls obtained from this study into different BSS temperatures and observed whether any would open spontaneously. We refrained from any other maneuvers that would affect opening and investigated only the effect of the temperature. However, no changes were observed in DM rolls at 8 °C, 16 °C, 23 °C (BSS temperature we use routinely) or 36 °C BSS temperatures within the 10-minute period.

The DM rolls demonstrated neither tightening nor opening in our study. We had anticipated that 36 °C, which is normal physiological body temperature, would promote DM roll unfolding. However, we did not observe such an effect. Although we did not demonstrate the effect of BSS temperature on the DM rolls at the molecular level, it was observed that this effect did not change unfolding time of the graft. In a study using porcine corneal endothelial cells, it was found that the eye irrigation solution stored in the refrigerator better protected the corneal endothelial cells from heat damage than BSS stored in air-conditioned room.[19] Consequently, using BSS at a lower temperature may be advantageous and rational for DM graft since the higher BSS temperature offers no benefit in terms of DM graft unfolding time.

Study Limitations

This study has some limitations. First, we used biomicroscopic examination to detect endothelial pathology and we could not count endothelial cells. If we had a chance to perform specular microscopy, endothelial examination would be more valuable than biomicroscopic examination. Second, delivery of the tissue could not be simulated using an anterior chamber.

Conclusion

In conclusion, different BSS temperatures were found to have no effect on DM unfolding time in this study. Other methods which are less traumatic and facilitate DM unfolding should be investigated in order to reduce endothelial cell loss.

Table 1. Distributions of the Descemet membrane roll formation between the groups at the beginning

			Groups				Total
			Group 1 (8 °C)	Group 2 (16 °C)	Group 3 (23 °C)	Group 4 (36 °C)	
Baseline DM roll	1/4 roll	Number	2	0	2	2	6
		% within baseline DM roll	33.3%	0%	33.3%	33.3%	100.0%
		% within group	66.7%	0%	50.0%	50.0%	40.0%
	2/4 roll	Number	1	2	1	2	6
		% within baseline DM roll	16.7%	33.3%	16.7%	33.3%	100.0%
		% within group	33.3%	50.0%	25.0%	50.0%	40.0%
	3/4 roll	Number	0	2	0	0	2
		% within baseline DM roll	0%	100.0%	0%	0%	100.0%
		% within group	0%	50.0%	0%	0%	13.3%
	4/4 roll	Number	0	0	1	0	1
		% within baseline DM roll	0%	0%	100.0%	%0	100.0%
		% within group	0%	0%	25.0%	%0	6.7%
Total		Number	3	4	4	4	15
		% within baseline DM roll	20.0%	26.7%	26.7%	26.7%	100.0%
		% within group	100.0%	100.0%	100.0%	100.0%	100.0%

DM: Descemet membrane

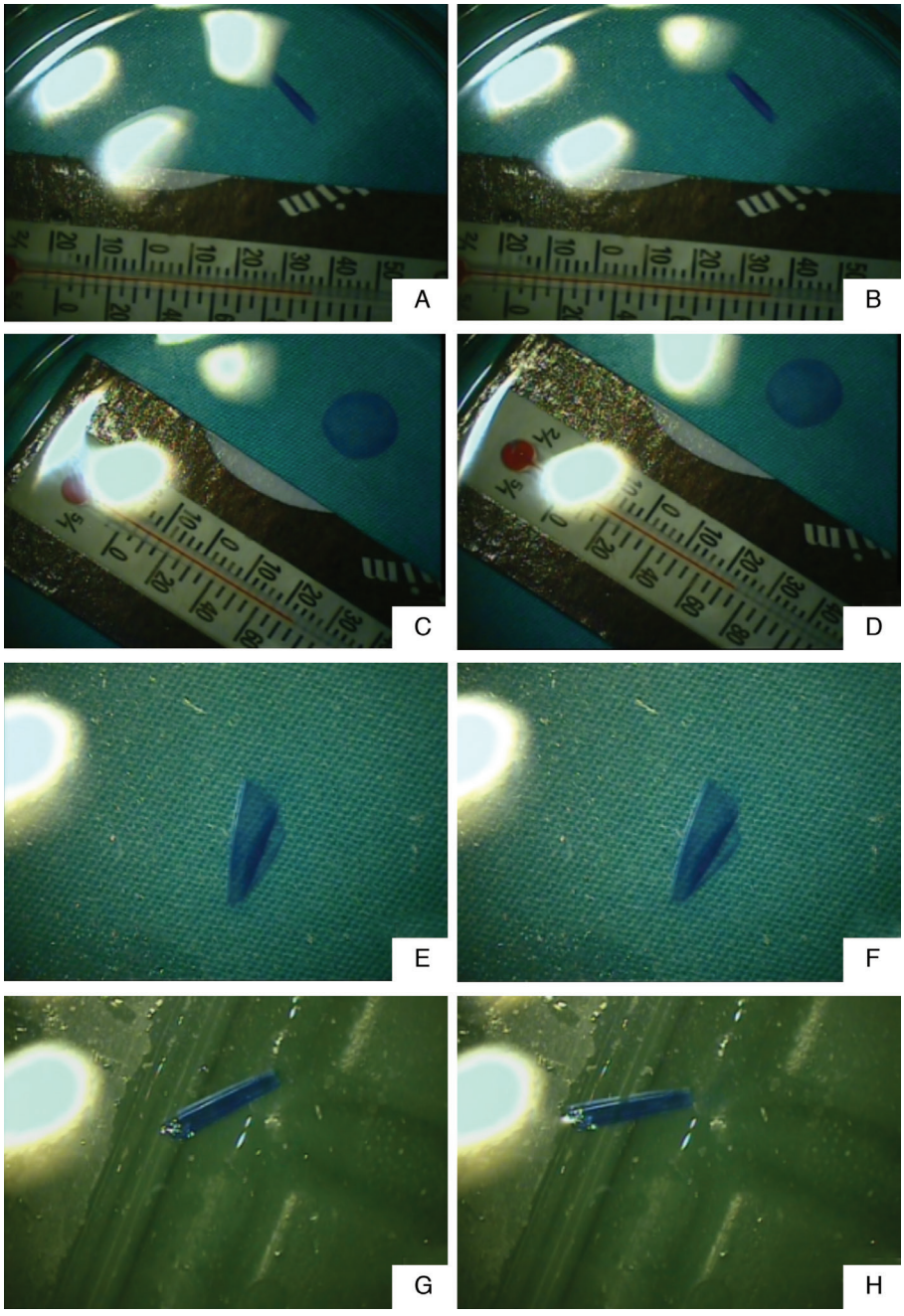

Figure 2. Demonstration of DM roll unfolding at baseline and the 10th minute after putting in different BSS temperatures; (A) DM roll in the 36 °C BSS temperature at baseline, (B) DM roll at the 10th minute after putting into the 36 °C BSS temperature, (C) DM roll in the 23 °C BSS temperature at baseline, (D) DM roll at the 10th minute after putting into the 23 °C BSS temperature, (E) DM roll in the 16 °C BSS temperature at baseline, (F) DM roll at the 10th minute after putting into the 16 °C BSS temperature, (G) DM roll in the 8 °C BSS temperature at baseline, (H) DM roll at the 10th minute after putting into the 8 °C BSS temperature.
DM: Descemet membrane, BSS: Balanced salt solution

Ethics

Ethics Committee Approval: Adana Numune Training and Research Hospital/174.

Informed Consent: This study was prospective, ex vivo, and experimental in nature.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yusuf Koçluk, Concept: Yusuf Koçluk, Emine Alyamaç Sukgen, Selim Cevher, Design: Yusuf Koçluk, Emine Alyamaç Sukgen, Selim Cevher, Data Collection or Processing: Yusuf Koçluk, Analysis or Interpretation: Yusuf Koçluk, Emine Alyamaç Sukgen, Selim Cevher, Literature

Search: Selim Cevher, Emine Alyamaç Sukgen, Writing: Yusuf Koçluk, Selim Cevher.

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

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Original Article

Evaluation of Anterior Segment Parameters in Pseudoexfoliative Glaucoma, Primary Angle-Closure Glaucoma, and Healthy Eyes

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Abstract

Objectives: To evaluate anterior segment parameters measured by dual Scheimpflug corneal topography in pseudoexfoliative glaucoma (PEXG), primary angle-closure glaucoma (PACG), and healthy eyes.

Materials and Methods: One hundred forty-three eyes of 86 patients were included in this study. Forty-seven eyes of 38 patients with PEXG, 30 eyes of 15 patients with PACG, and 66 eyes of 33 healthy subjects were evaluated. Patients who underwent previous ophthalmic surgery and contact lens wearers were excluded. After full ophthalmological examination, mean central corneal thickness (CCT), white-to-white horizontal corneal diameter (WTW), pupillary diameter (PD), anterior chamber volume (ACV), anterior chamber depth (ACD), and mean anterior chamber angle were measured by dual Scheimpflug corneal topography and compared between the three groups. Statistical analyses were done using Statistical Package for Social Sciences for Windows 18.0 program.

Results: No statistical difference was found in mean age or gender among the study groups ($p>0.05$). There were also no statistical differences in CCT, WTW, or PD among the groups ($p=0.568$, $p=0.064$, $p=0.321$, respectively). ACV, ACD, and mean anterior chamber angle values were significantly lower in the PACG group compared to the other groups ($p=0.000$ for all). There was no statistically significant difference in these measurements between the PEXG and normal eyes.

Conclusion: ACV and depth and mean anterior chamber angle were statistically different (lower) in PACG when compared with PEXG and healthy eyes. Dual Scheimpflug corneal topography can be used as an objective method for the measurement of anterior segment parameters in glaucoma.

Keywords: Pseudoexfoliative glaucoma, primary angle-closure glaucoma, dual Scheimpflug topography system

Introduction

Pseudoexfoliative glaucoma (PEXG) is a type of secondary glaucoma which is characterized by the production and accumulation of abnormal extracellular fibrillar material in the lens capsule, iris, non-pigmented ciliary epithelium, trabecular meshwork, and corneal endothelial cells. This accumulation causes intraocular complications including cataract, open-angle glaucoma, angle-closure glaucoma, lens decentration, and iridopathy.[1,2]

Primary angle-closure glaucoma (PACG) is a major blinding form of glaucoma in Asia.[3] The two main mechanisms of the disease are pupillary block and plateau iris syndrome. Besides these, anatomical differences in the iris, lens, and ciliary body have also been shown to play important roles in the pathogenesis. Shallow anterior chamber, thicker lens, anterior lens position, smaller corneal diameter, and anterior displacement of the lens-iris diaphragm are biometric characteristics of PACG.[3,4]

Intraocular pressure is an independent risk factor for glaucomatous progression and its measurement is affected by central corneal thickness (CCT). Therefore, we may say that CCT is associated with glaucoma because of its effect on tonometry. Ultrasonic pachymetry is widely used to measure CCT, but this method has some disadvantages. The accuracy and repeatability of measurements are dependent on accurate placement of the probe on the cornea. In addition, corneal indentation may result in an underestimated CCT value.[5,6] As a result, non-contact

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techniques are needed for the assessment of CCT. Prior studies have shown that highly reproducible CCT measurements can be obtained using dual Scheimpflug imaging systems.[7,8,9] Detailed anterior chamber angle (ACA) evaluation is essential for the diagnosis of PACG and PEXG. Gonioscopy is the gold standard technique for this evaluation. However, this technique requires a contact lens, topical anesthesia, and an experienced examiner to provide a confident diagnosis. Anterior segment imaging devices may be beneficial as a useful, non-contact method for angle closure screening. The parameters obtained with dual Scheimpflug imaging have been shown to correlate well with gonioscopy.[10] Anterior chamber depth (ACD) and anterior chamber volume (ACV) measurements are also important in both PACG and PEXG.[11,12]

The dual Scheimpflug imaging system is the basis for a number of devices that can image the anterior segment. It allows for photographic documentation of the anterior segment with a depth of focus ranging from the anterior cornea to the posterior lens surface. It is capable of estimating ACD, ACV, and ACA.[13]

In this study, we aimed to evaluate anterior segment parameters measured using the Galilei G4 Dual Scheimpflug Analyzer imaging device (Ziemer Ophthalmic Systems AG, Switzerland) in patients with PEXG and PACG and to compare these groups with healthy subjects.

Materials and Methods

This cross-sectional study was conducted at the Sakarya University Department of Ophthalmology. Prior approval was obtained from the Institutional Review Board (71522473/050.01.04/194) and written informed consent was obtained from each subject. The study was performed in adherence to the Declaration of Helsinki. Forty-seven eyes of 38 patients with PEXG (group 1), 30 eyes of 15 patients with PACG (group 2), and 66 eyes of 33 healthy subjects (group 3) were examined in this study.

Inclusion criteria for group 1 were high intraocular pressure (over 21 mmHg), visible pseudoexfoliation material on the anterior segment structures, glaucomatous optic nerve head changes (notching of optic disc rim, higher vertical cup-to-disc ratio, retinal nerve fiber layer hemorrhages), and glaucomatous visual field defects (scotomas indicating loss of the nerve fiber layer) detected by computerized visual field examination. Group 2 included patients with high intraocular pressure (over 21 mmHg), narrow ACA detected by gonioscopy, glaucomatous optic nerve head changes (notching of optic disc rim, higher vertical cup-to-disc ratio, retinal nerve fiber layer hemorrhages), glaucomatous visual field defects (scotomas indicating loss of the nerve fiber layer), and no history of laser peripheral iridotomy. Inclusion criteria for group 3 were normal intraocular pressure (under 21 mmHg) and no abnormal findings in anterior segment, fundus, or visual field examinations. Patients with corneal pathology (dry eye, keratoconus, history of contact lens use), uveitis, previous ocular surgery, history of contact lens use, previous ocular trauma, posterior segment pathology (retinal and optic nerve diseases which might affect visual field tests and retinal nerve fiber layer), and refractive errors greater than ±3 diopters were excluded from all groups.

All patients underwent full ophthalmic examination including best corrected visual acuity measured by Snellen chart, intraocular pressure measurement with Goldmann applanation tonometry, and detailed dilated fundus examination. In addition, Humphrey 30-2 SITA FAST visual field test and spectral-domain optical coherence tomography (SD-OCT) were performed.

The anterior segment was evaluated using a Galilei G4 Dual Scheimpflug Analyzer (Ziemer Ophthalmic Systems AG, Switzerland). Measurements were performed under scotopic conditions with undilated pupils by the same ophthalmologist (N.Ö.A). Mean ACA, ACD, ACV, CCT, pupil diameter, and horizontal white-to-white (WTW) corneal diameter values were obtained.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 18 (SPSS Inc, Chicago, IL, USA). All data were reported as means and standard deviation. Normality of continuous variables within the groups was determined by Shapiro-Wilk test. Chi-square test and ANOVA tests were used. A p value <0.05 was considered statistically significant.

Results

The demographic features of the three groups are summarized in Table 1. There was no statistically significant difference between the groups with respect to age or gender ($p>0.05$).

Mean ACA, ACD, ACV, pupil diameter, WTW corneal diameter, and CCT values of the three groups are shown in Table 2. Mean ACV and ACD were significantly lower and mean ACA was significantly narrower in the PACG group (group 2). There were no significant differences with respect to pupil diameter, WTW corneal diameter, or CCT among three groups. Mean CCT was markedly thinner in the PACG group (group 2) compared to the control group (group 3), but this difference was not statistically significant.

Table 1. Comparison of demographic data of patients in the pseudoexfoliative glaucoma, primary angle-closure glaucoma, and healthy control groups

	Group 1 (PEXG)	Group 2 (PACG)	Group 3 (control)	p value
Number of subjects, (n=86)	38	15	33	p>0.05
Eyes, n (143)	47	30	66	p>0.05
Gender Male (n=49) Female (n=37)	 17 (19.8%) 21 (24.4%)	 13 (15.1%) 2 (2.3%)	 19 (21.1%) 14 (16.3%)	0.247*
Age, years (Mean ± SD, range)	66.9±6.3 (56-80)	63.6±7.0 (54-79)	64.5±2.7 (60-70)	0.076**

*Chi-square test, **ANOVA
PEXG: Pseudoexfoliative glaucoma, PACG: Primary angle-closure glaucoma, SD: Standard deviation

Table 2. Comparison of anterior segment parameters in eyes with pseudoexfoliative glaucoma, eyes with primary angle-closure glaucoma, and healthy controls

	Mean ± SD			p-value		
	Group 1 (PEXG)	**Group 2 (PACG)**	**Group 3 (Control)**	**PEXG vs PACG**	**PEXG vs Control**	**PACG vs Control**
CCT	561.4±29.5	556.6±27.7	567.2±39.5	0.888	0.748	0.572
WTW	11.9±0.3	11.6±0.5	11.8±0.4	0.051	0.781	0.171
ACV	106.2±24.3	77.7±12.9	96.4±22.3	**0.000**	0.156	**0.021**
ACD	2.5±0.3	1.9±0.2	2.5±0.2	**0.000**	0.935	**0.000**
PD	2.8±0.4	2.1±0.4	2.6±0.4	0.396	0.461	**0.928**
Mean ACA	30.5±3.6	24.2±2.6	30.5±2.3	**0.000**	0.999	**0.000**

*ANOVA
PEXG: Pseudoexfoliative glaucoma, PACG: Primary angle-closure glaucoma, SD: Standard deviation, CCT: Central corneal thickness, WTW: White-to-white horizontal corneal diameter, ACV: Anterior chamber volume, ACD: Anterior chamber depth, PD: Pupil diameter, ACA: Anterior chamber angle

The patients in groups 1 and 2 used antiglaucomatous agents including prostaglandin analogues.

Discussion

Anterior chamber parameters such as ACD, ACV, and ACA have an important role in the diagnosis and evaluation of every type of glaucoma. Evaluation of the ACA is essential in glaucoma patients that can be subjectively evaluated with the Shaffer and Van Herick methods or gonioscopy. Different quantitative methods such as ultrasonic biomicroscopy, OCT, and Orbscan provide repeatable, accurate ACA measurements. Several studies have measured ACA and other anterior segment parameters in healthy and glaucomatous eyes using different methods.[12,14,15,16,17,18]

Pakravan et al.[14] evaluated anterior segment parameters in the unaffected fellow eyes of subjects with a previous episode of PACG using Pentacam and identified eyes at high risk of PACG among primary angle closure suspects. They claimed that ACV, ACA, and ACD are probably powerful indicators for determining the risk of acute angle closure (AAC) with cutoff values of ACV ≤100 µL, ACA ≤26°, and ACD ≤2.1 mm. Our findings in PACG subjects are consistent with their study.

Various parameters obtained with dual Scheimpflug imaging devices correlate well with gonioscopy.[13] However, ACA measurement by dual Scheimpflug devices may not be accurate because the entire angle is not fully visible due to total internal reflection. The correlation between ACA measurements and gonioscopic grade is better with anterior segment OCT (AS-OCT) and ultrasound biometry when compared to dual Scheimpflug.[19] Kurita et al.[11] compared Pentacam and ultrasound biomicroscopy and reported that Pentacam effectively measured ACD and ACV in eyes with PACG and PACG suspects, but not ACA. They reported that Pentacam ACA measurements were not reliable when evaluating eyes with a Shaffer grade of 2 or less. Grewal et al.[10] compared Pentacam and AS-OCT and reported that ACV had the highest discriminating ability (AUC=0.935) in detecting narrow angles. The Pentacam cannot directly visualize the angle; the breadth of three-dimensional data incorporated in its analyses is its disadvantage. In contrast, non-contact AS-OCT assessment limited to cross-sections of only the nasal and temporal angles may exclude representative information regarding the angle. To image the superior and inferior angles, contact would be required to move the eyelids obscuring visualization.[19] In a recent report, it was noted that non-contact imaging using OCT, dual Scheimpflug photography, or scanning peripheral ACD analyzer is superior to contact imaging using ultrasound biomicroscopy for large-scale primary angle closure screening.[20]

The high incidence of narrow angle configuration observed in patients with pseudoexfoliation may be associated with increased iris thickness, posterior synechiae, and zonular weakness. Doganay et al.[12] reported that the mean ACD measurement in patients with PEXG patients was found to be shallower than in healthy individuals. However, they found no statistical difference in ACD between PEXG and pseudoexfoliation syndrome. They also reported that there were no significant differences in ACV, ACA, or CCT parameters among patients with pseudoexfoliation syndrome, those with PEXG, and healthy controls.[12] Guneş et al.[15] evaluated anterior segment parameters in patients with pseudoexfoliation syndrome using dual Scheimpflug imaging and reported that there were no significant differences in ACA, ACD, or ACV values. Similarly, there were no statistically significant differences in ACA, ACD, or ACV between the patients with PEXG and the control group in our study.

Central corneal thickness is an important parameter in eyes with glaucoma. Studies evaluating differences in CCT among glaucoma types were performed previously. Some of these studies did not find any significant difference in CCT between PEXG and primary open-angle glaucoma (POAG).[16,17,18] Kitsos et al.[21], Bechmann et al.[22], Gorezis et al.[23], and Kniestedt et al.[24] found CCT to be significantly lower in PEXG compared to POAG. Pang et al.[25] and Tolesa and Gessesse[26] found no significant difference in CCT between PACG and POAG eyes, but Moghimi et al.[27] found thicker CCT in PACG than in normal healthy eyes. This variation in results could be due to differences in measurement methods, sample sizes, and ethnicities. In our study, there was no significant difference in CCT among groups.

Prostaglandin analogues have biological effects on extracellular matrix and collagen metabolism.[28] Altan et al.[29]

revealed that CCT was reduced with the use of 0.005% latanoprost, while ACD was not affected. In our study, patients were not classified according to antiglaucomatous medications used. This is a limitation of our study.

Dual Scheimpflug systems are able to provide highly repeatable CCT measurements.[5,7,8] In some studies, no difference has been observed in mean CCT obtained by ultrasound pachymetry or Pentacam.[6,30] In contrast, several other studies have revealed significant differences in mean CCT values measured by Pentacam and ultrasound pachymetry.[31,32] Although these differences may be small, comparing CCT values across different measurement platforms is not advised. Prior studies have shown that highly reproducible CCT measurements can be obtained by the Pentacam, Sirius, Galilei, and Corvis ST. Of these devices, the Galilei has the highest reported intraoperator repeatability. This may be due to its dual-rotating camera design, which can average the CCT estimated from two different dual Scheimpflug cameras.[5] In our study, we used Galilei for measuring CCT.

Conclusion

In conclusion, mean ACV, ACD, and ACA values measured with dual Scheimpflug imaging system were found to differ significantly in the PACG group. There were no statistically significant differences in anterior segment parameters between the PEXG group and healthy eyes. Therefore, dual Scheimpflug corneal topography can be used as an objective measurement method for anterior segment parameters in glaucoma.

Ethics

Ethics Committee Approval: Prior approval was obtained from the Institutional Review Board (71522473/050.01.04/194).

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Nilgün Özkan Aksoy, Burçin Çakır, Design: Nilgün Özkan Aksoy, Burçin Çakır, Emine Doğan, Gürsoy Alagöz, Data Collection or Processing: Nilgün Özkan Aksoy, Analysis or Interpretation: Nilgün Özkan Aksoy, Burçin Çakır, Gürsoy Alagöz, Literature Search: Nilgün Özkan Aksoy, Emine Doğan, Writing: Nilgün Özkan Aksoy, Burçin Çakır.

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Original Article

Real-World Outcomes of Anti-VEGF Treatment for Neovascular Age-Related Macular Degeneration in Turkey: A Multicenter Retrospective Study, Bosphorus Retina Study Group Report No: 1

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Abstract

Objectives: To evaluate the real-world outcomes of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment in neovascular age-related macular degeneration (nAMD) patients.

Materials and Methods: Multicenter, retrospective, interventional, non-comparative study. The records of nAMD patients treated with an anti-VEGF agent on a pro re nata treatment regimen basis between January 2013 and December 2015 were reviewed. The patients who completed a follow-up period of 12 months were included. Primary outcome measures of this study were the visit and injection numbers during the first year.

Results: Eight hundred eighty eyes of 783 patients met the inclusion criteria for the study. Mean number of visits at month 12 was 6.9±2.5 (range: 1-15). Mean number of injections at month 12 was 4.1±1.9 (range: 1-11). Mean visual acuity at baseline and months 3, 6, and 12 was 0.90±0.63 LogMAR (range: 0.0-3.0), 0.79±0.57 LogMAR (range: 0.0-3.0), 0.76±0.57 LogMAR (range: 0.0-3.0), and 0.79±0.59 LogMAR (range: 0.0-3.0), respectively. Mean central retinal thickness at baseline and months 6 and 12 was 395±153 µm (range: 91-1582), 330±115 µm (range: 99-975), and 332±114 µm (range: 106-1191), respectively.

Conclusion: The numbers of visits and injections were much lower than ideal and were insufficient with the pro re nata treatment regimen.

Keywords: Age-related macular degeneration, anti-vascular endothelial growth factor, treatment

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Introduction

Before the introduction of anti-vascular endothelial growth factors (anti-VEGF), the goal of treatment in neovascular age-related macular degeneration (nAMD) was only to prevent vision loss.[1,2,3,4,5,6,7] The first labeled intravitreal drug for the treatment of nAMD was pegaptanib, then off-label drug bevacizumab and approved drugs aflibercept and ranibizumab have led us to prevention of vision loss in most of the nAMD patients and vision gain in one third of them.[4,5,6,7,8] Several treatment regimens were evaluated in randomized controlled trials for each drug. Fixed monthly, pro re nata (PRN) with or without an initial 3 monthly loading doses, fixed bimonthly injection after the first 3 monthly loading doses, and "treat and extend" were some of the described treatment regimens.[5,6,7,8,9,10] The monthly and PRN regimens were the earliest described.[3,5,6,7] After the PrONTO study by Lalwani et al.[7], the PRN regimen became popular worldwide, including in Turkey.[8] Numerous studies were conducted to reevaluate the outcomes of this treatment regimen.[6,8,11,12] Physicians liked the idea of seeing the patients every month and injecting when required, because the PRN regimen seemed to have the advantage of individualized dosing.[8] However, most of the subsequently published real-world practice studies revealed that it was not possible to obey the strict follow-up and retreatment criteria of randomized controlled trials in daily practice.[10,11,13,14,15,16,17,18,19,20] Most of these studies showed that the PRN regimen resulted in less frequent patient monitoring and injections. Several single-center and multicenter national studies were conducted to evaluate this phenomenon.[13,14,15,16,17,18,19,20] Therefore, we conducted this multicenter study to assess the real-world outcomes of intravitreal anti-VEGF treatment in nAMD patients in 9 tertiary centers, all of which are located in or near İstanbul, the most populated city in Turkey, and we believe may reflect the general trends of treatment regimens in Turkey.

Materials and Methods

This was a retrospective, interventional, non-comparative real-life experience study conducted in 9 tertiary centers in Turkey. The records of nAMD patients who were treated with an anti-VEGF agent using a PRN treatment regimen between January 2013 and December 2015 were reviewed. Written informed consent was obtained from all patients before the treatment and the study adhered to the tenets of the Declaration of Helsinki. Ethical board approval was obtained from Kocaeli University Faculty of Medicine.

Patients who met the following criteria were included in the study: were ≥50 years of age, were diagnosed with nAMD, and had a minimum follow-up time of 12 months. Patients who had retinal disease other than nAMD (e.g., diabetic retinopathy, retinal vein occlusion) and those diagnosed with polypoidal choroidal vasculopathy or retinal angiomatous proliferation during follow-up were not included.

Data collected from the patients included age, gender, lens status, the drug used, whether they were treatment-naïve or -experienced, whether they received a loading dose of 3 injections, the period over which the 3 loading doses were administered, BCVA and central retinal thickness (CRT) at baseline and months 3, 6, 9, and 12 as well as number of visits and injections given during the first year.

All patients underwent a standardized examination including measurement of BCVA via the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or a projection chart at 4 meters, slit-lamp biomicroscopy and fundus examination, and measurement of intraocular pressure via applanation tonometry. Fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) imaging were performed before treatment. As this was a multicenter study, different brands of FA and OCT devices were used to assess the patients. All examinations were planned to be repeated monthly, except FA. FA was repeated only when the cause of visual acuity deterioration could not be clarified with clinical examination and other imaging methods. Optical coherence tomography was used for detecting subretinal fluid and measurement of CRT. CRT, defined as the mean thickness of the neurosensory retina in the central 1 mm diameter area, was computed using OCT mapping software generated by the device.

All injections were performed under sterile conditions in an operating room or an outpatient operating room (clean room). Topical anesthesia and 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT, USA) were applied to the lids and lashes, and 5% povidone-iodine was administered to the conjunctival sac. Intravitreal bevacizumab 1.25 mg/0.1 mL, ranibizumab 0.5 mL/0.1 mL, or aflibercept 2 mg/0.1 mL was injected through the pars plana 3.5-4 mm posterior to the limbus with a 30-gauge needle. After the injection, an ophthalmic solution of 0.5% moxifloxacin (Vigamox; Alcon Laboratories, Inc., Fort Worth, Texas, USA) was administered 5 times a day for 1 week. Patients were then instructed to consult the hospital if they experienced decreased vision, eye pain, or any new symptoms.

Some of the patients initially received the three monthly loading doses of anti-VEGF, while others did not. The decision to give a loading dose was not made according to strict criteria but was based on the physicians' preference. The patients were planned to be called for monthly visits. A single injection of a first preferred anti-VEGF agent was repeated when visual acuity decreased by one or more lines from the last visit or in the presence of newly developed macular hemorrhage, evidence of subretinal fluid, or persistent intraretinal fluid on OCT.

Primary outcome measures of this study included the numbers of visits and injections during the first year. Secondary outcome measures were change in BCVA and CRT from baseline to month 12.

Statistical Analysis

Visual acuity was converted from decimals to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Categorical variables were presented as numbers and percentages, while numerical variables were expressed as mean and standard deviation. The data were assessed for normality using the Kolmogorov-Smirnov test. As the distribution of the

data was found to be normal, changes in BCVA and CRT values between baseline and the other time points were assessed with repeated measures test. Categorical variables were compared using chi-square test. Statistical analyses were performed using SPSS (Version 21.0, SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

Eight hundred eighty eyes of 783 patients met the inclusion criteria for the study. The mean age was 73.2±8.8 years (range 50-94 years); 345 patients (44.0%) were women and 438 (56.0%) were men. One hundred thirty-eight eyes (15.7%) had been treated before, while 742 eyes (84.3%) were treatment-naïve. Thirty-six eyes (4.1%) received intravitreal bevacizumab, 222 eyes (25.2%) received intravitreal aflibercept, and 622 eyes (70.7%) received intravitreal ranibizumab as the initial treatment. The general characteristics of the patients are summarized in Table 1.

Mean number of visits at month 12 was 6.9±2.5 (range: 1-15). Mean number of injections at month 12 was 4.1±1.9 (range: 1-11). Two hundred eighteen eyes (24.8%) did not receive a loading dose of 3 consecutive monthly injections, whereas the other 662 eyes (75.2%) did. The mean duration for giving the loading dose of 3 injections was 83±22 days (range 56-150 days) in the subgroup of patients who received the loading doses.

Mean BCVA at baseline and months 3, 6, and 12 was 0.90±0.63 LogMAR (range: 0.0-3.0), 0.79±0.57 LogMAR (range: 0.0-3.0), 0.76±0.57 LogMAR (range: 0.0-3.0), and 0.79±0.59 LogMAR (range: 0.0-3.0), respectively (Figure 1) (p<0.0001 for all). As this was not principally a study of effectiveness, we did not use visual acuity cut-off values while including the patients. However, we calculated the rate of the eyes which were stable, or lost ≥3 lines of vision at month 12 in the subgroup of eyes which had a BCVA between 1.3 and 0.3 LogMAR. There were 580 eyes in this subgroup and 175 (30.2%) of them showed ≥3 lines of gain in vision, 336 (57.9%) showed stable vision (stable, or <3 lines of visual gain, or <3 lines of visual loss), and 69 (11.9%) showed ≥3 lines of loss in vision.

Mean CRT values at baseline and months 6 and 12 were 395±153 µm (range: 91-1582), 330±115 µm (range: 99-975), and 332±114 µm (range: 106-1191), respectively (p<0.0001 for month 6 and 12) (Figure 2).

All complications were limited to subconjunctival hemorrhage, punctate epitheliopathy, and mild anterior chamber reaction. No endophthalmitis was detected in any of the eyes during the study period.

Discussion

In the initial report of this multicenter study, we evaluated the real-world outcomes of intravitreal anti-VEGF treatment in nAMD patients, with the main focus on visit and injection numbers in the first year of treatment. All of the physicians who participated in this study reviewed the medical records of their patients and the data of 880 eyes of 783 patients were analyzed. The mean visit number was found to be 6.9 and injection number was 4.1. In the PrONTO study, the first year injection number was reported to be 5.6.[7] However, time-domain OCT was used at the time that study was conducted, and it was later shown that time-domain OCT devices could not detect anatomical disease activity in at least one-third of the patients when compared with spectral-domain OCT devices.[21] In other major prospective studies, the mean injection number required to treat nAMD during the first year was found to be 7-9 injections.[6,8,9,12] However, this number

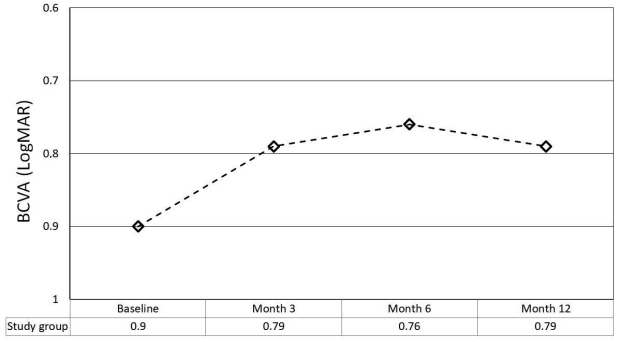

Figure 1. The change in mean best corrected visual acuity at different time points
BCVA: Best corrected visual acuity

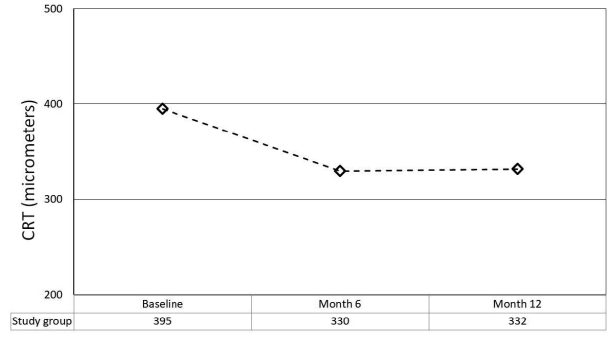

Figure 2. The change in mean central retinal thickness at different time points
CRT: Central retinal thickness

Table 1. General characteristics of patients	
General characteristics	
Age (mean ± SD) (range), years	73.2±8.8 (54-87)
Gender (F/M)	345/438
Baseline BCVA (mean ± SD) (range), LogMAR	0.90±0.63 (0.0-3.0)
Baseline CRT (mean ± SD) (range), µm	395±153 (91-1582)
Lens status (Phakic/pseudophakic/aphakic)	614/263/3
Initial drug (bevacizumab/aflibercept/ranibizumab)	36/222/622
Previous treatment (yes/no)	138/742
Loading dose (yes/no)	662/218

M/F: Male/female, BCVA: Best corrected visual acuity, LogMAR: Logarithm of minimal angle of resolution, CRT: Central retinal thickness, SD: Standard deviation

was reported as low as 3-4 in most of the real-world practice studies.[13,14,15,16,17,18,19,20] In addition, 12-13 visits are necessary in an ideal PRN treatment follow-up protocol.[6,7] The mean visit number was 6.9 in our study. In several previous real-world studies the mean visit number was found to be between 6 and 12.[13,14,15,16,17,18,19,20]

The importance of giving the first 3 loading doses at the beginning of treatment for nAMD was documented in a previous study.[17] The patients who received the first 3 loading doses demonstrated better visual outcomes than the patients who did not. The gain in visual acuity was 6 letters higher in the group of patients who received the loading dose than the patients who did not.[17] We also evaluated our data in this regard and 75.2% of the included patients received the first 3 loading injections, whereas 24.8% of them did not. The time period for giving the 3 loading doses varied between 56 and 150 days, with a mean of 83 days. This duration should be 60 days in an ideal scenario.[7]

Bevacizumab was preferred as the first-line treatment in 4.1% of the eyes, whereas aflibercept was preferred in 25.2% and ranibizumab was preferred in 70.7%. As this study was a retrospective and non-randomized study, the drug choice seemed to be made upon the physicians' preferences. Being an off-label drug, bevacizumab was used least frequently. Ranibizumab was the most frequently preferred drug, probably because it was the older of the two approved drugs.

As the primary objective was to assess and discuss follow-up visit and injection numbers, we did not analyze visual and anatomical outcomes deeply in this report. The mean visual acuity was found to be improved from 0.90 LogMAR to 0.79 at month 12 and the mean CRT was reduced from 395 µm to 332 µm.

In most real-world studies, visit and injection numbers were determined to be very far from the ideal.[13,14,15,16,17,18,19,20] This may be secondary to heavy patient load, visit and injection scheduling problems, and patient compliance. Therefore, we might suppose that the PRN treatment regimen may not be suitable for the treatment of nAMD in daily practice according to our results and most of the other studies results. Although the mean visual acuity was found to be increased by 1.1 lines in our study, this report was not designed as an effectiveness study and patients with very low visual acuity were included, which might cause this phenomenon. In randomized controlled studies in which the follow-up and treatment criteria were strictly obeyed, fixed monthly injections of ranibizumab or bevacizumab, fixed bimonthly injections of aflibercept after 3 loading injections, PRN treatment regimens, and more flexible treatment regimens such as treat-and-extend have resulted in visual gains of 5-12 ETDRS letters after 12 months of follow-up.[3,5,6,7,8,9,12] In the MARINA, ANCHOR, and CATT studies, monthly ranibizumab treatment regimen resulted in up to 11 letters of visual increase at month 12.[3,5,6] The PRN regimen was also as effective as monthly treatment regimens according to CATT and IVAN study treatment arms.[6,12] In addition to these treatment regimens, Wykoff et al.[22] reported that ranibizumab provided 10.5 letters of visual increase at month 12 of a treat-and-extend regimen.

Aflibercept has also been evaluated with several treatment regimens.[8,23,24] In the VIEW studies, monthly and bimonthly aflibercept treatment after 3 loading doses resulted in 8-9 letters of visual increase at month 12.[8] Yamamoto et al.[25] evaluated the efficacy of treat-and-extend regimen with aflibercept in nAMD and demonstrated 1.5 lines of visual increase at month 12. In all of these and other randomized controlled studies, the mean injection number during the first year was reported as at least 8.[6,8,12,23,24,25] On the other hand, reaching this injection number seems nearly impossible with the PRN treatment regimen in real life.[13,14,15,16,17,18,19,20] Most of the retrospective real-life studies reported the injection number as 3-4 during the first year.[13,14,15,16,17,18,19,20] In a multicenter study, the mean injection number at month 12 was reported between 4.3 and 5.7 in patients from different countries.[13] Two consecutive studies from France regarding real-life treatment of nAMD on a PRN regimen evaluated the results in two different time periods.[15] The authors compared the outcomes in the second study.[15] The LUMIERE study consisted of nAMD patients who were treated between 2006 and 2009 and the following TWIN study included patients who were treated between 2010 and 2011.[15,26] They concluded that although improvements were made in key parameters, the mean injection number was around 5.5 at month 12. In addition, they pointed out the importance of regular postinduction monitoring (after 3 loading doses) and reported that it was the most important determinant of successful treatment.[15,26] In a multinational real-life study by Holz et al.,[14] patients from Canada, France, Germany, Ireland, Italy, the Netherlands, United Kingdom, and Venezuela were assessed. The mean number of injections was reported to be 5.0 at month 12 and the mean visual change was 2.4 letters. In conjunction with this study, several national reports were published by using national patient data. In a German real-life study by Ziemssen et al.,[16] the mean number of anti-VEGF injections at month 12 was found to be 4.3, along with the 1.1 letters of visual increase. Among the countries involved the AURA study, the greatest mean injection number was reported from England.[17] The mean number of injections at month 12 was 5.8 and the mean change in visual acuity was 6.0 letters. In other retrospective real-life studies, the mean injection number at month 12 was reported as 5.7 by Kataja et al.,[18] 3.8 by Silva et al.,[19] and between 3.7 and 4.9 by Jain et al.[20] Nearly all of the real-life studies demonstrated that it was not possible to perform the proper number of visits and injections. After proving this fact, the performance of other treatment regimens was evaluated or compared with PRN regimen in new studies.[9,10,23] Ozturk et al.[23] retrospectively evaluated the outcomes of fixed bimonthly injection of aflibercept. They reported that 50% of the patients received the 8 obligatory injections during 12 months, and only 2 of the 42 patients were reported to receive 5 injections, which was the minimum injection number among the study patients. In another study from the United States by Lotery et al.,[24] the mean numbers of ranibizumab and aflibercept injections were reported as 6.7 and 7.0, respectively.

Two interesting studies compared the difference between the PRN and treat-and-extend regimens in nAMD.[9,10] In the TERRA study from the United Kingdom, the authors compared the mean injection number of patients previously treated PRN and then switched to treat-and-extend regimens.[9] Interestingly, the mean number of injections during a 12-month follow-up on the PRN regimen was 4.7, and increased to 8.9 after switching to the treat-and-extend regimen. Johnston et al.[10] conducted a real-life study based on the different treatment tendencies in Australia and the United Kingdom. They used Australia to analyze the treat-and-extend regimen and the United Kingdom for PRN. The mean injection numbers at month 12 were reported to be 9.2 in the treat-and-extend group and 6.0 in the PRN group.

Study Limitations

The present study has several limitations. We did not evaluate the visual and anatomical outcomes of the study in detail in this initial report of our study group. We are planning a deeper assessment of these outcomes in future reports. However, this is an important national study in terms of the demographics and injection characteristics, which is a major strength.

Conclusion

In conclusion, as proven by several multi- or single-center studies from different countries, it is very difficult to obey the strict follow-up and re-treatment criteria of the PRN regimen in nAMD patients.[13,14,15,16,17,18,19,20] This was the first multicenter study from Turkey to demonstrate this phenomenon. The number of patients included was satisfactory for a multicenter study conducted in a country between Europe and the Middle East to show the treatment tendencies in nAMD. The number of visits and injections were far from ideal with the PRN treatment regimen. It is likely that all of the centers included will have to organize their clinical approach to the treatment of nAMD, try to perform more frequent injections and visits, or switch to another treatment regimen such as treat-and-extend or fixed regimens.

Ethics

Ethics Committee Approval: Ethical board approval was obtained from Kocaeli University Faculty of Medicine.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Original Article

Evaluation of the Relationship Between Age-related Macular Degeneration and Refractive Error, Socio-demographic Features, and Biochemical Variables in a Turkish Population

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Abstract

Objectives: To investigate the relationship between age-related macular degeneration (AMD) and refractive error and axial length, as well as the socio-demographic characteristics and biochemical variables that may affect this relationship.

Materials and Methods: A total of 196 eyes of 98 patients over 50 years of age who were diagnosed with AMD at our clinic were included in this cross-sectional study. Early and late AMD findings were categorized according to the age-related eye disease study grading scale. Objective refractive error was measured by autorefractometer, confirmed by subjective examination, and spherical equivalent was calculated. Refractive errors of -0.50 D to 0.50 D were classified as emmetropia, <-0.50 D as myopia, and >0.50 D as hyperopia. Axial length was measured by ultrasonic biometry and values ≤23.00 mm were classified as short, >23.00 and <24.00 mm as normal, and ≥24.00 mm as long axial length. Demographic, systemic, and biochemical parameters of all patients were also investigated.

Results: Hypermetropic refractive error and shorter axial length were significantly more common than the other groups ($p<0.01$). No differences were observed between early and late stage groups in terms of refractive error and axial length. Patients with myopia had significantly lower values for total cholesterol, triglyceride, fasting blood glucose, and proportion of smokers. Rates of oral nutritional supplement use and fish consumption were significantly higher in the early AMD group. The most common comorbidity among the AMD patients in our study was essential hypertension.

Conclusion: Hyperopic refractive error and shorter axial length were found to be associated with AMD. Longitudinal studies including larger patient numbers are needed to elucidate the causal and temporal relationship between hyperopic refractive error and AMD.

Keywords: Axial length, refractive error, risk factors, age related macular degeneration

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Introduction

Age-related macular degeneration (AMD) is the most common cause of central vision loss among individuals aged 55 years and older in both developed and developing countries. The incidence of AMD is increasing due to the growing elderly population, and this constitutes a serious public health problem.[1,2]

AMD has two types, the wet form characterized by neovascularization and the dry form characterized by atrophy. These wet and dry forms account for approximately 20% and 80% of AMD cases, respectively. The wet type is responsible for 85% of AMD-related blindness.[3] AMD is also clinically classified as early and intermediate stage, which involve drusen and retinal pigment epithelium alterations, or advanced stage, which involves choroidal neovascularization (CNV) and/or geographic atrophy (GA).[4]

Today, AMD is considered a multifactorial disease associated with genetic and environmental factors. Age is the strongest non-modifiable risk factor. The risk of developing advanced AMD is 3 times higher among individuals aged 60-80 years than in those under the age of 60.[5] Smoking is another important but modifiable risk factor. Many studies have demonstrated the impact of smoking on AMD development and report that smokers are likely to develop AMD 5-10 years earlier than non-smokers.[6] Epidemiological studies have reported that AMD may be associated with genetics, family history, obesity, low education level, diet, history of cardiovascular and cerebrovascular disease, exposure to sunlight, and various other factors.[7,8,9,10,11,12,13,14] Possible associations between AMD and ocular factors such as light iris color, history of previous cataract surgery, short axial length, and hypermetropic refractive error have also been proposed.[15,16] However, there are inconsistencies among the literature data, and no studies have been conducted previously in the Turkish population.

Understanding how refractive error and axial length are related to AMD may elucidate its pathophysiology and lead to the development of new diagnostic and therapeutic options. The aim of this study was to examine the relationship between AMD and refractive error and axial length, and to investigate the systemic and demographic characteristics that may affect it.

Materials and Methods

This prospective study was approved by the Scientific Research Commission of Fatih Sultan Mehmet Training and Research Hospital with approval number 17073117-050.03-2268 on September 3, 2013 and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent forms were obtained from all patients. The study included 196 eyes of 98 patients who presented to our clinic between October 2013 and June 2014 and were diagnosed with AMD. All patients in the study underwent a complete ophthalmologic examination. Diagnosis of AMD was based on findings of biomicroscopic dilated fundus examination, optical coherence tomography (NIDEK RS-3000 Advance), and fluorescein angiography. AMD lesions were assessed from color fundus images and classified as follows according to the age-related eye disease study (AREDS) staging system.[7]

Category 1: No drusen or a few small drusen in both eyes.

Category 2: Extensive small drusen, a few intermediate-sized drusen, or pigmentary abnormalities associated with AMD in at least one eye.

Category 3: One or more large drusen or extensive intermediate-sized drusen in at least one eye.

Category 4: GA or CNV in at least one eye.

Patients evaluated as category 1 or 2 were classified as early AMD and patients in categories 3 and 4 were classified as advanced AMD.

Patients with ocular disease other than AMD or pterygium and/or nuclear cataracts that could affect refractive error; aphakic or pseudophakic patients; anisometropic patients; and patients with history of refractive or any other ocular surgery other than intravitreal injection were excluded from the study.

Objective refractive error was measured with an autorefractometer (Canon RK-F1 full auto ref-keratometer, Tokyo, Japan) and confirmed by subjective examination. Spherical equivalent refraction was calculated in diopters (D) by adding half of the cylindrical value to the spherical value. Values between +0.50 D and -0.50 D were defined as emmetropia, values below -0.50 D as myopia, and values above +0.50 D as hypermetropia. Axial length was measured with an ultrasonic biometry (NIDEK US-4000 Echoscan, Japan) device; values of 23 mm and below were assessed as short, values between 23 and 24 mm as normal, and values of 24 mm and above as long.

Data pertaining to the patients' sex, age, systemic comorbidities (diabetes mellitus, hypertension, hyperlipidemia), smoking history (pack-years), fish consumption (meals/month), use of oral nutritional supplement (ONS) (multivitamin and mineral supplement containing 5-10 mg of lutein and zeaxanthin, tablets/day), use of acetyl salicylic acid (ASA), and body mass index were recorded. In addition, lipid panel (total cholesterol, triglycerides [TG], low-density lipoproteins [LDL], high-density lipoproteins [HDL]), fasting blood sugar (FBS), and hemoglobin A1c (HbA1c) levels were assessed for all patients.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 software and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analyses. For quantitative data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used as well as Student's t-test for pairwise comparisons of parameters with normal distribution and Mann-Whitney U test for pairwise comparisons of parameters without normal distribution. A one-way ANOVA was used for the comparison of normally distributed data between three or more groups and Tukey HSD test was used to determine the source of the difference. A Kruskal-Wallis test was used for the comparison of non-normally distributed data between three or more groups and Mann-Whitney U test was used to

determine the source of the difference. Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test, and Yates' correction for continuity (Yates' corrected chi-square test) were used in comparisons of qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$.

Results

The study included 50 female and 48 male patients with a mean age of 70.18±6.90 (54-85) years. Of these, 85.8% of the patients had a low education level, 46.9% were smokers, 97.8% consumed fish, 44.7% used ONSs, 30.6% used ASA, and 71.4% had a comorbid systemic disease. The most common systemic comorbidity was hypertension. The patients' demographic characteristics are presented in Table 1 and their biochemical data in Table 2.

In terms of refractive status distribution, 10.2% of the patients were myopic, 18.4% were emmetropic, and 71.4% were hypermetropic. Hypermetropia was significantly more common than the other groups ($p<0.01$). Refractive values ranged between +0.50 D and +3.00 D in 94.3% of hypermetropic patients, while 5.7% of patients had values higher than +3.00 D. The refractive error rates of the patients who participated in the study are given in Table 3.

Short axial length was noted in 83.7% of the patients, which was significantly more common than normal or long axial length ($p<0.01$). The axial length rates of the patients who participated in the study are given in Table 4.

Evaluation of biochemical parameters based on refractive error revealed statistically significant differences in cholesterol and TG values ($p<0.05$). Paired evaluations done to determine the source of the difference showed that patients in the myopia group had significantly lower total cholesterol levels compared to patients in the hypermetropia group ($p=0.045$). There was no statistically significant difference between the emmetropia and hypermetropia groups ($p>0.05$). Patients in the myopia group had significantly lower TG values than patients in both the emmetropia and hypermetropia groups ($p=0.014$, $p=0.001$). There was no statistically significant difference between the emmetropia and hypermetropia groups ($p>0.05$). Analysis of FBS values in the refractive error groups showed a difference that was near statistical significance ($p=0.058$). According to paired evaluations, patients in the emmetropia and myopia groups had significantly lower FBS than patients in the hypermetropia group ($p=0.021$). There was no significant difference between the emmetropia and myopia groups ($p>0.05$). There were no statistically significant differences in HDL, LDL, or HbA1c values based on refractive error ($p>0.05$). The distribution of biochemical parameters based on refractive error is shown in Table 5.

There was a significant difference between the refractive error groups in the proportion of smokers ($p=0.001$, $p<0.01$). The rate of smoking was statistically significantly lower in the myopia group than in both the emmetropia and hypermetropia groups. ASA use was also significantly less common in the myopia group compared to the emmetropia and hypermetropia groups ($p=0.011$). No statistically significant differences were observed

Table 1. Demographic characteristics of the patients

		Min-Max	Mean ± SD
Age (years)		54-85	70.18±6.90
Height (cm)		150-183	164.54±8.18
Weight (kg)		54-105	75.59±10.86
BMI (kg/m^2)		21.26-37.89	27.98±4.07
Smoking (pack-years)		2.0-100.0	25.66±26.02
Fish consumption (meals/month)		0.25-8.00	2.46±2.04
		n	**%**
Gender	Female	50	51.0
	Male	48	49.0
Education	Illiterate	8	8.1
	Literate	8	8.1
	Elementary school	32	32.6
	Middle school	16	16.3
	High school	20	20.4
	University	14	14.2
Smoking		46	46.9
Fish consumption		96	97.8
ONS use		44	44.7
ASA use		30	30.6
Comorbidity		70	71.4
Essential hypertension		38	38.7
Diabetes mellitus		16	16.3
Coronary artery disease		14	14.2
Benign prostatic hyperplasia		10	10.2
Hodgkin's lymphoma		10	10.2
Alzheimer's disease		2	2.04
Hypothyroidism		2	2.04
Essential thrombocytosis		2	2.04
Asthma		2	2.04

BMI: Body mass index, ONS: Oral nutritional supplement, ASA: Acetyl salicylic acid, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Distribution of biochemical variables

	Min-Max	Mean ± SD
Total Cholesterol	138.0-312.0	222.41±35.79
HDL	34.0-91.0	51.82±14.11
LDL	75.0-207.0	142.29±31.01
TG	53.0-322.0	132.00±55.84
FBS	80.0-313.0	108.70±37.04
HbA1c	5.0-10.40	6.03±0.97

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerid, FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c, SD: Standard deviation, Min: Minimum, Max: Maximum

between the refractive error groups in terms of fish consumption, ONS use, or comorbidities (p>0.05).

Evaluations based on AMD stage revealed no statistically significant differences in terms of mean axial length, refractive error, total cholesterol, HDL, LDL, TG, FBS, HbA1c values, smoking, ASA use, or comorbidities (p>0.05). Fish consumption and ONS use were significantly more common among patients with early AMD compared to those with advanced AMD (p=0.046, p=0.001). Distributions of axial length, refractive error, biochemical parameters, and usage habits based on AMD stage are presented in Table 6.

Discussion

In this study, the relationship between refractive error and AMD was investigated in a Turkish population and a strong correlation was found between AMD and the prevalence of hypermetropic refractive error. The literature includes numerous cross-sectional studies and a few longitudinal studies that investigate the relationship between hypermetropia and AMD.

In the Beijing Eye study, conducted in an Asian population, it was reported that hypermetropia is the most significant risk factor for early AMD, independent of age.[17] In another study conducted on Asian multiethnic groups, the prevalence of AMD was lower in myopic males, but there was no increased risk in those with hypermetropia.[18] In the Rotterdam study, conducted in a white population, the prevalence of hypermetropia was found to be 65% and every 1 mm of decrease in axial length was associated with an increase in the incidence and prevalence of AMD.[19] The Eye Disease and AREDS cross-sectional case-control studies reported 1.5 and 2.3 times more exudative AMD in hypermetropic patients compared to myopic patients after correcting for age and other risk factors.[4,20]

According to the Singapore Malay Eye study, also conducted in an Asian population, every 1 D increase in refractive error and every 1 mm decrease in axial length increased the risk of early AMD by 8% and 29%, respectively. A similar relationship was not found for advanced AMD and it was reported that this could be due to the smaller number of patients with late stage disease.[21] In a 5-year longitudinal follow-up of the same group, this relationship between early AMD and refractive error was not apparent.[22] Similarly, a cross-sectional study conducted by the Blue Mountains Eye Study group showed a correlation between moderate and high hypermetropia values and the incidence of early AMD, but a longitudinal study involving the 5-year follow-up of the same patients revealed no significant correlation between hypermetropia and AMD incidence.[23,24] In the Beaver Dam Eye study, 5-year and 10-year follow-up also failed to show any correlation between refractive error and the incidence of AMD.[25,26]

Table 3. Refractive error rates

	n	%	Expected %	p
Myopia	20	10.2	65.3	0.001**
Emmetropia	36	18.4	65.3	
Hypermetropia	140	71.4	65.3	

Chi-square test, **p<0.01

Table 4. Axial length rates

	n	%	Expected %	p
Short	164	83.7	65.3	0.001**
Mean	28	14.3	65.3	
Long	4	2.0	65.3	

Chi-square test, **p<0.01

Table 5. Evaluations based on refractive error

	[1]Myopia (n=20)	[2]Emmetropia (n=36)	[3]Hypermetropia (n=140)	[a]p	[c]Post-hoc
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)		
Total cholesterol	209.38±18.40	221.75±39.86	224.31±37.14	[b]0.049*	[f]1<3
TG	91.00±24.28 (83.00)	126.57±49.54 (114.00)	137.23±57.84 (137.00)	0.002*	1<2,3
HDL	52.75±7.90 (53.00)	52.50±14.65 (50.50)	52.17±14.56 (50.00)	0.643	-
LDL	135.43±19.43	139.00±34.73	143.57±31.85	[b]0.587	-
FBS	102.10±18.61 (96.00)	100.27±21.42 (96.00)	104.62±15.47 (104.00)	0.058	2<3
HbA1c	5.93±0.54 (5.80)	5.81±0.70 (5.70)	5.95±0.67 (5.90)	0.286	-
	n (%)	n (%)	n (%)	[c]p	[g]Post-hoc
Smoking	0 (0.0)	12 (25)	64 (52.5)	0.001**	1<2,3
Fish consumption	18 (90.0)	36 (100.0)	124 (88.6)	[d]0.114	-
ONS use	8 (40.0)	20 (55.5)	60 (42.8)	0.225	-
ASA use	0 (0.0)	10 (27.8)	42 (30.0)	0.011*	1<2,3
Comorbidity	10 (50)	28 (77.8)	94 (67.1)	0.512	-

[a]Kruskal-Wallis test, [b]One-way ANOVA, [c]Pearson chi-square test, [d]Fisher-Freeman-Halton exact test, [e]Mann-Whitney U test, [f]Tukey's HSD test, [g]Yates' continuity correction test, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c, SD: Standard deviation, ONS: Oral nutritional supplement, ASA: Acetyl salicylic acid, *p<0.05, **p<0.01

Table 6. Evaluations according to stage of age-related macular degeneration				
		[1]Stage 1 and 2 (n=104)	[2]Stage 3 and 4 (n=92)	[c]p
		Mean ± SD (median)	Mean ± SD (median)	
Axial length		23.13±0.91	23.09±0.93	[h]0.725
Total cholesterol		224.86±31.31	219.00±40.97	[h]0.326
HDL		51.61±12.76 (52.50)	52.09±15.78 (50.00)	0.520
LDL		146.08±28.09	136.89±34.04	[h]0.088
TG		131.57±58.61 (121.00)	132.59±51.76 (133.50)	0.570
FBS		195.23±16.29 (104.00)	113.64±53.97 (96.00)	0.063
HbA1c		5.90±0.64 (5.80)	6.23±1.27 (5.90)	0.332
		n (%)	n (%)	cp
Refractive error	Myopia	10 (9.6)	10 (11.4)	0.246
	Emmetropia	24 (23.1)	12 (13.6)	
	Hypermetropia	72 (67.3)	68 (75.0)	
Axial length	Short	90 (86.5)	74 (80.4)	[d]0.020*
	Mean	10 (9.6)	18 (19.6)	
	Long	4 (3.8)	0 (0.0)	
Smoking		42 (47.7)	34 (44.7)	0.702
Fish consumption		98 (100.0)	82 (95.3)	[i]0.046*
ONS use		56 (56.0)	28 (31.8)	0.001**
ASA use		24 (24.0)	32 (36.4)	0.064
Comorbidity		66 (67.3)	70 (77.8)	0.110

[c]Pearson chi-square test, [d]Fisher-Freeman-Halton exact test, [e]Mann-Whitney U test, [h]Student's t-test, [i]Fisher's exact test, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c, SD: Standard deviation, ONS: Oral nutritional supplement, ASA: Acetyl salicylic acid, *p<0.05, **p<0.01

It appears that the correlations between AMD and hypermetropic refractive error observed in cross-sectional studies are not found in longitudinal studies. Some patients are lost over a follow-up period of 5-10 years, and therefore the lifespan factor may alter the outcomes of longitudinal studies. For example, the Blue Mountains group stated in their study that most of the patients who died during follow-up were hypermetropic, and that the results may have been different if these patients had survived.

In our study, the prevalence of hypermetropia was 71.4% among all AMD stages and 72% and 68% for early and advanced AMD, respectively, while the prevalence of myopia was found to be 10% among all AMD stages and in both early and late AMD. Short axial length was noted in 83.7% of our patients. The results of our study are comparable to those of the Singapore Malay Eye, Beijing Eye, Rotterdam, Blue Mountains, Eye Disease, and AREDS groups. The results of these studies suggest that hypermetropia generally increases the risk of early AMD but is not associated with a significant increase in the risk of late AMD. In our study, however, there was no significant difference between the early and late AMD groups in terms of short axial length and hypermetropic refractive error. This may be attributable to the insufficient size of our patient group, which is the main limitation of our study. There are several possible biological explanations for the relationship between refractive error, axial length, and the pathogenesis of AMD. Hypermetropic eyes with short axial length have greater scleral rigidity. This creates resistance in choroidal venous outflow, and reduced outflow may contribute to the development of AMD due to the accumulation of metabolic waste.[27,28,29] Vascular endothelial growth factor (VEGF) plays a key role in the pathophysiology of AMD. According to recent findings, intraocular VEGF level decreases as degree of myopia and axial length increase.[30,31] Longer axial length may lead to increased VEGF dilution and lower risk of disease. Myopic eyes are prone to posterior vitreous detachment (PVD).[32,33] PVD has been shown to reduce the progression of neovascularization in diabetic eyes.[34] Considered from this perspective, PVD may exert a protective effect against AMD through increased oxygen diffusion in the macular region. On the other hand, glasses and contact lenses used by myopic patients may reduce exposure to ultraviolet radiation, which is recognized as a significant risk factor in the etiology of AMD.[13,14,35]

The lower prevalence of AMD in the myopic patient group in our study may have been due to their lower cholesterol, TG, and FBS levels and lower smoking rate. Our comparison of the early and advanced disease groups revealed significantly higher rates of fish consumption and ONS use in the early disease group. This offers further evidence of the positive effect of antioxidant fatty acids and vitamins such as omega-3, lutein-zeaxanthin, and vitamins A, C, and E, which have been emphasized as important components of preventative treatment in many studies.

Conclusion

Our study showed short axial length and hypermetropic refractive error to be associated with AMD, independent of demographic and systemic findings. The major limitations of our study are its cross-sectional design and the small number of patients. The small patient number reduces the power of the study. Cross-sectional studies cannot demonstrate the temporal and causative relationship between a factor and an outcome. AMD itself may also cause changes in refractive status and axial length. Examining for and questioning ocular, systemic, and environmental factors in patients over the age of 50 is beneficial for early diagnosis and follow-up as well as providing opportunities for preventive therapy and the modification of environmental factors.

Ethics

Ethics Committee Approval: This prospective study was approved by the Scientific Research Commission of Fatih Sultan Mehmet Training and Research Hospital with approval number 17073117-050.03-2268 on September 3, 2013.

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Öznur Gürbüz Yurtseven, Aysu Karatay Arsan, Sibel Aksoy, Yelda Buyru Özkurt, Hatice Kübra Kökçen, Concept: Aysu Karatay Arsan, Design: Aysu Karatay Arsan, Öznur Gürbüz Yurtseven, Data Collection or Processing: Öznur Gürbüz Yurtseven, Analysis or Interpretation: Öznur Gürbüz Yurtseven, Aysu Karatay Arsan, Sibel Aksoy, Literature Search: Öznur Gürbüz Yurtseven, Sibel Aksoy, Writing: Öznur Gürbüz Yurtseven, Sibel Aksoy.

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Original Article

Short-term Efficacy of Micropulse Yellow Laser in Non-center-involving Diabetic Macular Edema: Preliminary Results

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Abstract

Objectives: The aim of this study was to evaluate the efficacy of micropulse yellow laser (MPL) on best corrected visual acuity (BCVA) and retinal thickness in patients with non-center-involving diabetic macular edema (DME).

Materials and Methods: We retrospectively reviewed 9 eyes of 8 patients with non-center-involving DME who underwent MPL treatment between January 2015 and December 2016. BCVA (logMAR) and retinal thickness were evaluated before and 3 months after treatment. Maximum retinal thickness was determined manually from simultaneous spectral-domain optical coherence tomography images and recorded. The change in the measurements from before to after treatment was analyzed statistically.

Results: Of the 8 patients, 3 were female and 5 were male. The mean age was 52.8 years. Two of the 9 eyes had received previous intravitreal anti-vascular endothelial growth factor injection(s). Median BCVA was improved 3 months after treatment, although the difference was not statistically significant (0.34 logMAR before and 0.29 logMAR after treatment). BCVA was improved in 4 eyes while it showed no change in the remaining 5 eyes. The mean retinal thickness was 470.6 µm at baseline and 416 µm at 3 months after MPL treatment (p=0.01). Retinal thickness decreased in all eyes after treatment.

Conclusion: In this study, parafoveal retinal thickness showed significant decrease after MPL treatment in patients with DME. The limited increase in BCVA may be due to the inclusion of a low number of patients and only those with non-center-involving macular edema. MPL may be used as an alternative to conventional argon laser in non-center-involving DME.

Keywords: Micropulse, laser, diabetic macular edema

Introduction

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetic retinopathy (DRP). Thermal laser photocoagulation has long been used as the standard treatment for clinically significant DME.[1] Despite its therapeutic effectiveness, it can lead to undesirable complications such as visual field loss, choroidal neovascularization, epiretinal fibrosis, and enlargement of laser scars.[2,3,4] Micropulse laser (MPL) is a method developed to reduce the laser-induced thermal damage caused by conventional laser therapy.[5] In the micropulse mode, laser is applied in short pulses, thereby reducing the thermal energy generated in the target area.[6] The coagulation scars seen after conventional laser application do not form with MPL treatment.[7] Today, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection has been embraced in the treatment of DME, and its efficacy has been reported in several studies.[8,9,10] However, in some cases the expected functional/anatomical success is not achieved with anti-VEGF administration.

The aim of this study was to investigate the effect of yellow (577 nm) MPL therapy on best corrected visual acuity (BCVA) and retinal thickness in patients with parafoveal macular edema that does not involve but threatens the central macula.

Materials and Methods

Ethics committee approval for the study was obtained from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (20-1249-17). The study was carried out in accordance with the tenets of the Declaration of Helsinki. The study included 9 eyes of 8 patients who were being followed

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for DRP in our retina outpatient clinic, had macular edema that did not involve but threatened the fovea, and underwent MPL therapy with a 577 nm yellow laser (Supra Scan, Quantel Medical, Cedex, France). A single-spot test shot in micropulse mode was applied to a non-edematous area of the macula outside the temporal vascular arcade. The laser power was gradually increased until it formed a faint laser spot. The power of the micropulse pattern laser was set at 50% of the power needed to form a barely visible laser spot. Laser parameters used were 200 ms duration, 160 µm spot diameter, low operating cycle (5%), and high density (contiguous laser spots). Optical coherence tomography (OCT) thickness maps were consulted to select the most suitable scanning pattern for the entire edematous area. BCVA (logMAR) was recorded before and 3 months after the treatment. Spectral-domain OCT (SD-OCT) and fundus autofluorescence (FAF) images were obtained at the same time points. The point of greatest retinal thickness was determined manually, and measurements were recorded. Pre- and post-treatment FAF images were compared in terms of laser-induced scar formation. The differences between pre-treatment and month 3 post-treatment median BCVA and mean retinal thickness were statistically compared using paired samples t-test.

Results

Of the 8 patients included in the study, 5 were male and 3 were female. Their mean age was 52.3 years. All 9 eyes were evaluated as having non-center-involving parafoveal macular edema using SD-OCT images. Two of the eyes had previously received intravitreal anti-VEGF therapy. Of these 2 eyes, 1 had received 4 anti-VEGF injections and the other had received 5 anti-VEGF injections. Both eyes underwent MPL treatment at least 3 months after the last injection. The other 7 eyes with DME had not received any previous treatment, and MPL was applied as initial therapy.

Median BCVA was 0.34 logMAR before treatment and 0.29 logMAR at 3 months after treatment. BCVA increased after treatment in 4 eyes and remained unchanged in the other 5 eyes. However, the increase in BCVA was not statistically significant (p=0.16). In the measurements made manually from the point of greatest parafoveal retinal thickness on SD-OCT images, mean retinal thickness was 470.5 µm before treatment and 416 µm at 3 months after treatment. Retinal thickness had decreased in all 9 eyes at 3 months after treatment (Figures 1a, b and 2a, b). The decrease in mean retinal thickness was statistically significant (p=0.01).

Discussion

The prevalence of diabetes mellitus is increasing rapidly worldwide. The main cause of vision loss in this patient group is DME.

Numerous systemic and local factors have been identified in the development of DRP and DME. One of these is the role

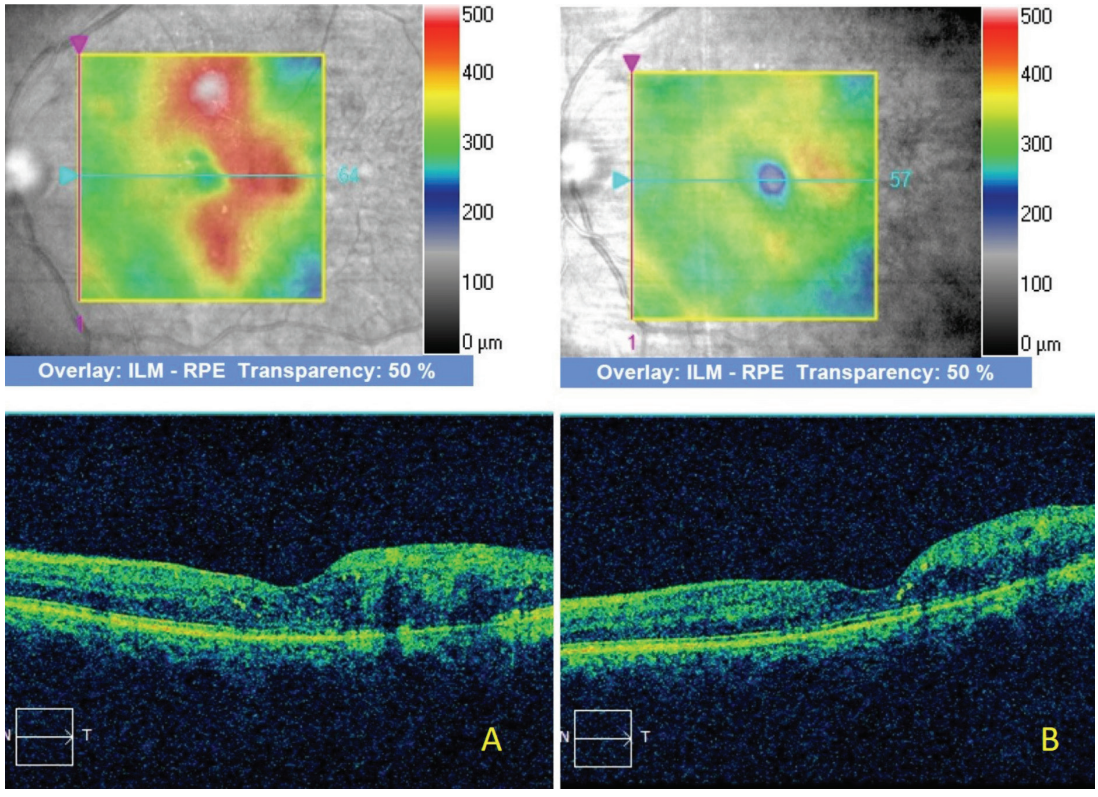

Figure 1. A) Optical coherence tomography images prior to micropulse laser treatment show retinal thickening in the temporal parafoveal area; B) optical coherence tomography images obtained 3 months after micropulse laser

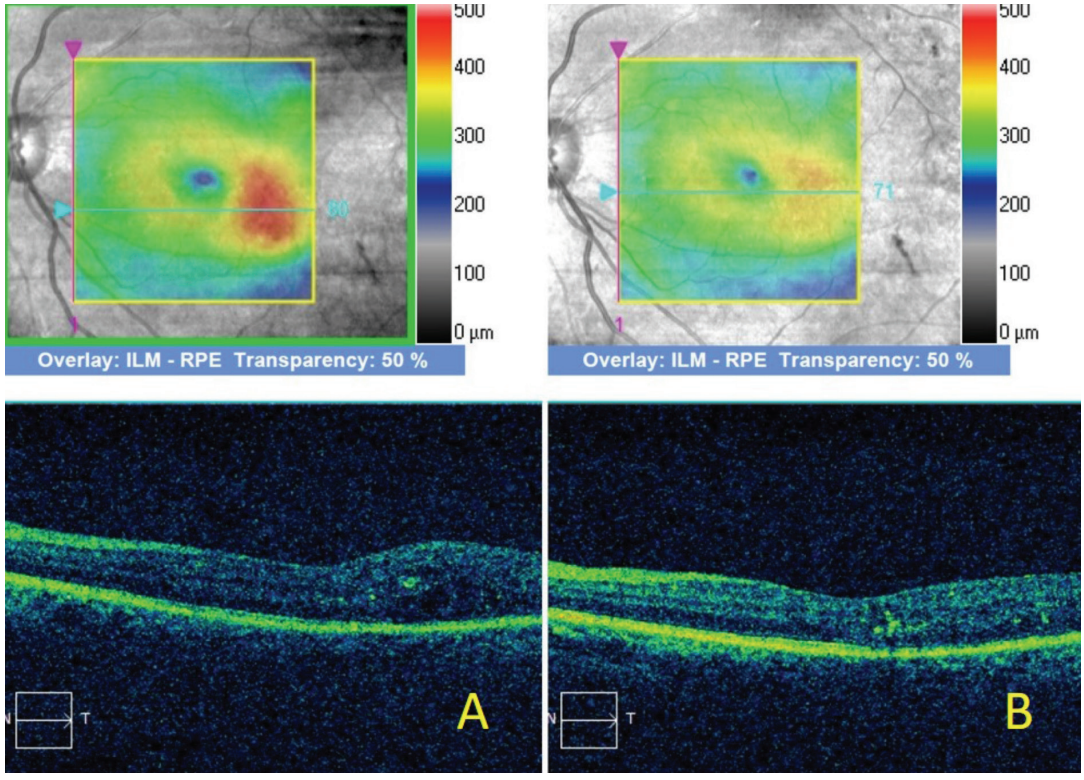

Figure 2. A) Optical coherence tomography images prior to micropulse laser treatment show retinal thickening in the temporal parafoveal area; B) optical coherence tomography images obtained 3 months after micropulse laser

of the retinal pigment epithelium (RPE). Electron microscope images obtained in diabetic human and animal studies have demonstrated cellular and subcellular damage in the RPE.[11,12] In addition, diabetes-related changes in RPE permeability and subsequent increase in fluid leakage has been reported in diabetic human and animal models.[12,13] The RPE releases a number of growth factors, anti/pro-angiogenic factors, and neurotrophic factors, some of which are known and others of which have been newly demonstrated in recent studies. Upregulation of VEGF occurs under hypoxic conditions.[14,15] VEGF levels in the aqueous and vitreous fluids are known to be correlated with DRP severity, retinal neovascularization, and edema formation.[16] In addition to the RPE, VEGF is also produced by Müller and ganglion cells. In fact, VEGF production from the neurosensory retinal tissue was shown to have a greater role in DRP than the RPE.[17]

Conventional laser photocoagulation has long been used in the treatment of DME, despite lacking a full understanding of its mechanism.[1] Unfortunately, this treatment has adverse effects in both the short and long term. Today, the standard treatment method for DME is intravitreal anti-VEGF injection, which is proven safe and effective.[8,9,10] Laser photocoagulation is still used for edema that does not involve the fovea or is resistant to anti-VEGF therapy.

Besides the pro-angiogenic VEGF molecule, another target in the treatment of macular edema is the RPE cells, which form the outer blood-retina barrier and incur damage and impairment of normal functions in diabetic patients. In the conventional laser procedure, laser light is absorbed by the RPE, resulting in cell damage. This is believed to reduce VEGF production in the RPE as well as decrease retinal oxygen demand and retinal hypoxia.[18] New laser methods are being investigated in order to reduce the side effects of laser application and increase the effectiveness of treatment.

It was observed in our study that following yellow wavelength (577 nm) MPL therapy in patients with non-center-involving DME that did not require anti-VEGF therapy, BCVA was preserved and/or increased and retinal thickness decreased significantly in the short term. Kwon et al.[19] applied yellow MPL therapy to 14 eyes with DME with foveal involvement and reported significant improvements in BCVA and central macular thickness at the end of a mean 7.9-month follow-up period. In another study, yellow MPL was applied to 26 patients and infrared MPL was applied to another group of 27 patients with center-involving DME. The eyes were evaluated before and after treatment using SD-OCT, FAF, fluorescein angiography, and microperimetry. No difference was reported between the groups in terms of morphological and functional safety and efficacy after treatment.[20] In our study, no change was observed in FAF images taken before and at 3 months after the laser procedure. In a study by Inagaki et al.[21] including 53 eyes with DME, some were treated with yellow MPL while others were treated with 810 nm MPL treatment, and the authors reported that macular

edema was decreased, visual acuity was preserved, and the need for additional treatments during the 12-month follow-up period had decreased in both groups.

MPL seems to be very advantageous compared to conventional laser treatment, especially in terms of side effects. In this relatively new technique, the photothermal effect is applied to the RPE in a more controlled way compared to conventional laser. As laser light is continuously applied in conventional laser treatment, tissue temperature increases rapidly, causing permanent photothermal damage to the neurosensory retina. In the MPL method, however, energy is delivered in repetitive "on"-"off" cycles. The short duration of laser light emission limits the increase in temperature, while the longer "off" period enables the reduction of tissue temperature, thus preventing thermal damage.[22] There is still no consensus on the ideal operating parameters for MPL. However, there are 2 methods of calculating laser power that are generally adopted in clinical practice. In the first method, the power of micropulse pattern is determined as 50% of the laser power that forms a barely visible spot in a single shot in micropulse mode. In the second method, laser power is determined as twice the power that forms a faint burn in a single shot in continuous mode. In the literature, laser parameters used in previous studies include operating cycle of 5%-15%, application time of 100-300 ms, and spot diameter of 100-200 µm, and no evidence of the superiority of any of these settings over the others has been reported.[23]

Study Limitations

The small number of patients, short follow-up period, and lack of a control group comprise limitations of our study. The limited increase in BCVA may be due to the small number of patients and the inclusion of eyes without foveal edema.

Prospective studies comparing MPL to anti-VEGF therapy in large patient groups and with long follow-up periods are needed to demonstrate the effectiveness and reliability of MPL in DME.

Conclusion

According to the results of our study, MPL can be considered as an alternative to conventional argon laser for the treatment of non-center-involving DME that threatens the central macula.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (20-1249-17).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sibel Demirel, Figen Batıoğlu, Emin Özmert, Concept: Mehmet Fatih Kağan Değirmenci, Sibel Demirel, Figen Batıoğlu, Emin Özmert, Design: Mehmet Fatih Kağan Değirmenci, Sibel Demirel, Figen Batıoğlu, Emin Özmert, Data Collection or Processing: Mehmet Fatih Kağan Değirmenci, Analysis or Interpretation: Mehmet Fatih Kağan Değirmenci, Sibel Demirel, Figen Batıoğlu, Emin Özmert, Literature Search: Mehmet Fatih Kağan Değirmenci, Writing: Mehmet Fatih Kağan Değirmenci.

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

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Case Report

Binocular Indirect Ophthalmoscopy Complements Non-contact Wide-field Imaging with Optos to Treat a Baby Outside ETROP Guidelines

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Abstract

We report a male premature baby who was born at 24 weeks gestation weighing 600 grams. There was bilateral stage 2, zone 2 retinopathy of prematurity (ROP) without plus disease at 38 weeks postmenstrual age. Ultra-wide-field Optomap images obtained 1 week later showed no change in ROP stage. At 40 weeks postmenstrual age, stage 3, zone 2 ROP was detected using binocular indirect ophthalmoscopy and documented using Optos. Minor tortuosity and dilation of vessels was interpreted as pre-plus disease. One week later, at 41 weeks postmenstrual age, Optomap images identified progressive extraretinal fibroproliferation in the nasal quadrant. As a result, the baby was treated with fundus laser photocoagulation.

Keywords: Binocular indirect ophthalmoscope, Optomap, Optos, retinopathy of prematurity, ultra wide-field imaging

Introduction

Retinopathy of prematurity (ROP) was first described by Terry[1] in 1942 under the name retrolental fibroplasia. ROP occurs because the retinal vessels and neural retina of a preterm newborn are incompletely developed at birth and do not grow normally. It is one of the leading preventable causes of childhood blindness, especially in high- and middle-income countries.[2,3,4]

At the present time, ROP screening is generally performed by binocular indirect ophthalmoscopy and/or wide-field digital imaging systems. There are 2 kinds of wide-field viewing systems in use for the pediatric age group: contact (3 nethra Neo, ICON, PanoCam, RetCam) and non-contact systems.[5] The Optos uses a non-contact ultra-wide-field dual wavelength laser camera that is able to capture high-quality images from infants with ROP.[6] The Optomap is a panoramic digital image generated by Optos scanning laser technology which shows approximately 82% of the retina.

In this report, we present a case of ROP managed using the Optos ultra-wide-field imaging system.

Case Report

A male baby was born at 24 weeks of gestation and birth weight of 600 g. Maternal history included no clear reason for prematurity such as preeclampsia or maternal chorioamnionitis. The baby needed oxygen therapy in the first weeks of life due to chronic lung disease.

ROP screening was started at 31 weeks postmenstrual age and no ROP was detected. The infant developed stage 2, zone 2 ROP without plus disease at 38 weeks postmenstrual age, and was followed at 1-week intervals. There was no change in terms of ROP at 39 weeks postmenstrual age. In follow-up examination at 40 weeks postmenstrual age, the patient exhibited stage 3, zone 2 ROP with pre-plus disease. Optomap images showed pre-plus disease with minor tortuosity and dilation of the vessels (Figure 1). One week later, an area of stage 3 ROP covering 3 clock hours was seen in zone 2 with pre-plus disease. Optomap images produced by the Optos® (Optos PLC, Dunfermline, Scotland, United Kingdom) imaging system demonstrated progression of the extraretinal fibroproliferation in the nasal

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quadrant. Binocular indirect ophthalmoscopy supported the decision to treat with laser therapy, as the neovascular areas were beginning to exert traction on the vitreous, suggesting a high risk of retinal detachment (Figure 2).

He was treated with fundus photocoagulation using a 514 nm wavelength argon laser. A total of 1320 laser spots were applied to the right eye and 1490 laser spots to the left eye, ranging from 140 to 200 milliwatts. There were no complications after laser treatment. Three weeks after argon laser therapy, the ROP and plus disease were fully resolved. Non-contact ultra-wide-field imaging confirmed retinal attachment with no vascular tortuosity or enlargement (Figure 3).

This case has been reported in accordance with the ethical principles in the Declaration of Helsinki and written informed consent for publication was received from the patient's parents.

Discussion

Ultra-wide-field imaging systems have brought about improvements in the management of ROP. They are useful for visualizing and documenting retinal features and determining ROP type.[5] The Optos ultra-wide-field imaging system is able to obtain clinically useful high-quality fundus images from ROP patients. The Optos scanning laser ophthalmoscope can be used to demonstrate ROP and plus disease, influence treatment decisions and timing, and document resolution postoperatively.[6] Non-contact scanning laser fundus imaging has become widely available globally in the management of adult ocular conditions such as diabetic retinopathy and retinal vascular occlusions.[7] The Optos system is a confocal scanning laser ophthalmoscope that uses the optics of an ellipsoid mirror to capture images of the retinal periphery. The Optomap delivers a detailed 200º image of the retina in less than half a second without the use of mydriatic agents.[8]

In our patient, stage 3 ROP was detected nasally in zone 2 with pre-plus disease using a binocular indirect ophthalmoscope at postmenstrual age of 41 weeks. We were able to image the posterior pole and retina periphery with Optomap images, even the avascular area anterior to the ROP line. The Optomap images showed the extraretinal fibroproliferation at the nasal quadrant could present a risk for future detachment or dragging. The high-resolution retinal images provided by this system gave us the opportunity to discuss how to manage the case. Even though the infant did not develop plus disease and was out of the Early Treatment for Retinopathy of Prematurity Study criteria, we decided to treat the ROP disease based on demonstrating progression of stage 3 ROP. An important point is that although the Optomap provides high-quality images, they are 2-dimensional. In contrast, an indirect ophthalmoscope enables 3-dimensional visualization of the fundus and ROP features.

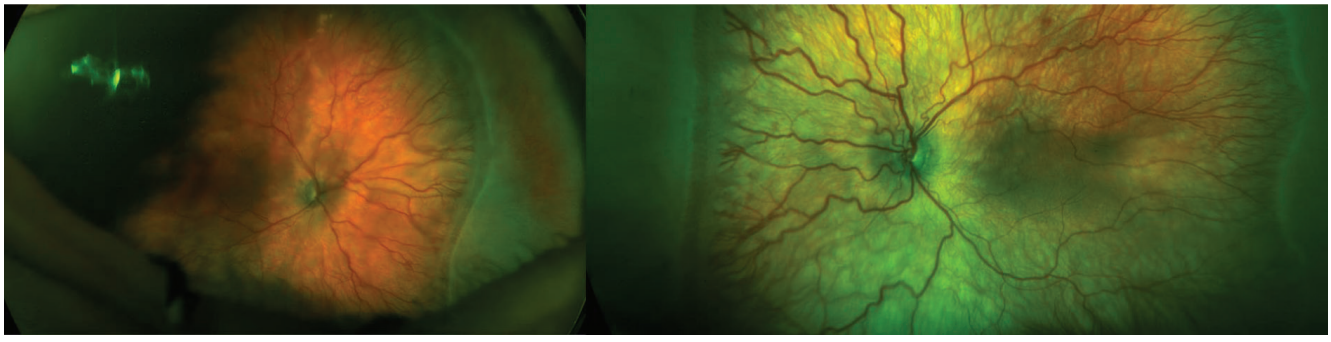

Figure 1. Pseudo-color fundus images obtained with Optos show bilateral extraretinal fibroproliferation in the nasal quadrant. Mild pre-plus disease is more significant in the left eye

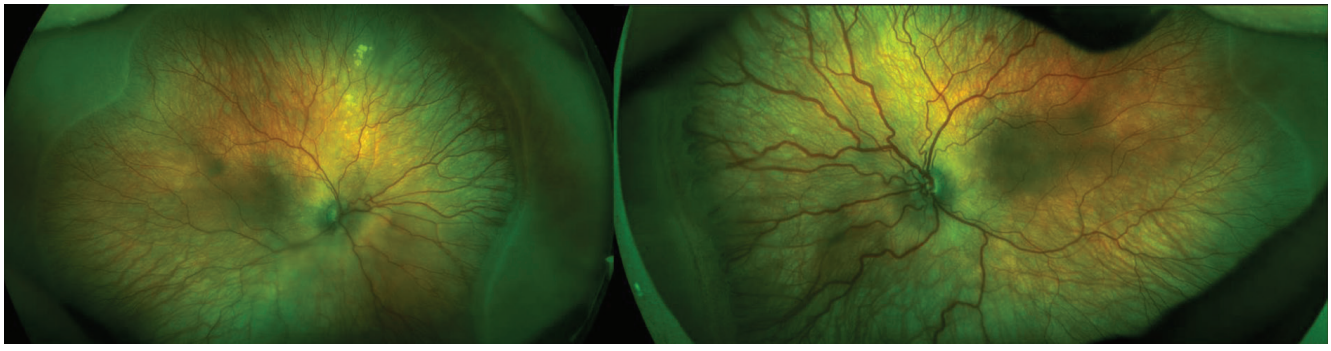

Figure 2. The Optomap images demonstrate stage 3 retinopathy of prematurity in zone 2 with pre-plus disease and extraretinal fibroproliferation in the nasal quadrant. There are ridge formations in the other quadrants

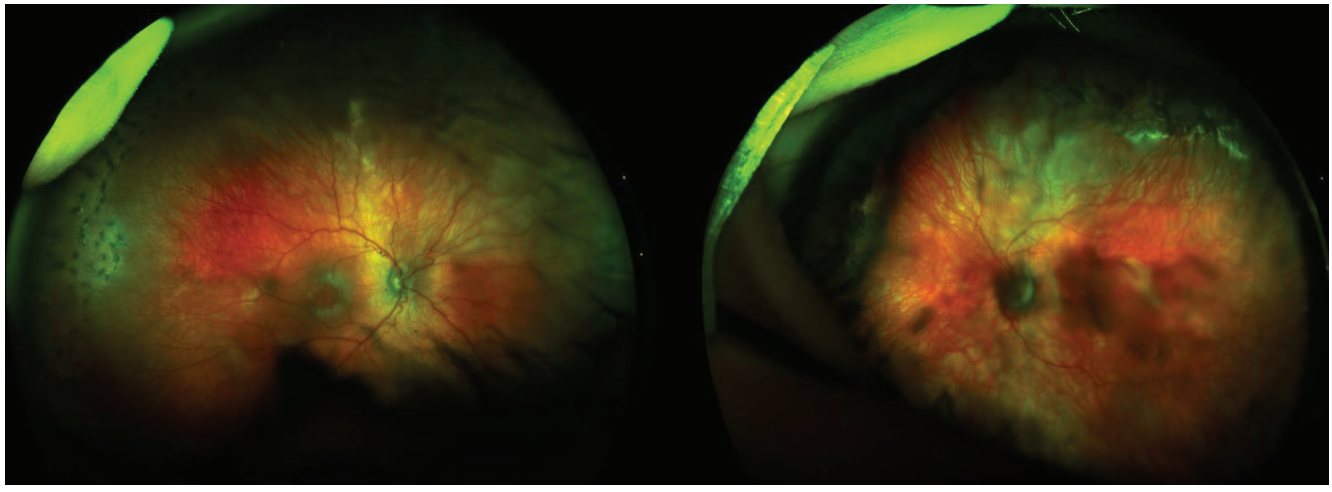

Figure 3. The Optomap images of both eyes show resolved stage 3 retinopathy of prematurity and regressed plus disease after argon laser photocoagulation

Retinal imaging in patients with ROP using ultra-wide-field imaging system has recently been popularized by Patel et al.[9] They were the first team to report that the Optos was capable of capturing high-quality images in infants with ROP. Patel et al.[9] showed that a large view of the infant's retina can be obtained with the Optos non-contact ultra-wide-field fundus imaging system. They demonstrated the different stages of ROP at the posterior pole and peripheral retina with Optos scanning laser ophthalmoscope using a modified "flying baby position". One of the important results from their study is that the Optomap can identify "skip areas" missed by initial laser treatment in the peripheral retina.[9] In the current case, we analyzed the patient's retina and the retinal periphery after laser photocoagulation and found no missed areas.

The non-contact high-resolution ultra-wide-field system has other advantages for pediatricians, neonatologists, and ophthalmologists in the evaluation of premature or full-term babies. Yusuf et al.[10] used Optomap images to show the retinal features of 10 eyes of 5 consecutive infants (aged 1-15 months) with suspected abusive head trauma. It is indisputable that to document and record any abnormalities in patients is a medicolegal obligation. It is also possible to acquire fluorescein angiograms in premature infants with ROP using the Optos system. Fung et al.[11] reported the fluorescein angiograms of 3 premature infants with ROP using oral fluorescein, at a dose of 25 mg/kg of body weight. The 2% fluorescein was mixed with infant formula milk and/or bottle-fed to the infants 30 minutes before the imaging process.

Although indirect ophthalmoscopy is still the gold standard method for ROP screening, non-contact ultra-wide-field fundus imaging offers new opportunities in the evaluation of pediatric retinal diseases. These 2 methods can be used together in the evaluation of ROP. In the present case, high-quality Optomap retinal images assisted us in effectively managing ROP.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Özdemir Özdemir, Chetan Kantibhai Patel, Design: Özdemir Özdemir, Chetan Kantibhai Patel, Data Collection or Processing: Özdemir Özdemir, Chetan Kantibhai Patel, Analysis or Interpretation: Özdemir Özdemir, Chetan Kantibhai Patel, Literature Search: Özdemir Özdemir, Writing: Özdemir Özdemir.

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

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

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Case Report

Bilateral Serous Macular Detachment After Attempted Suicide with Pregabalin

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Abstract

A 24-year-old female presented with bilateral vision loss following attempted suicide with pregabalin. Her best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/50 in the left eye. The bilateral visual disturbance was associated with serous macular detachment. Fundus examination of both eyes showed foveal serous retinal detachment, which was confirmed by optical coherence tomography. Topical nepafenac 0.1% eye drops were started as single drop every 8 hours for 4 weeks. One month later, the serous macular detachment had regressed and BCVA increased to 20/20 in both eyes. To the best of our knowledge, this is the first reported case of bilateral serous macular detachment presumably caused by pregabalin intoxication.

Keywords: Optical coherence tomography, pregabalin, serous macular detachment, suicide

Introduction

Pregabalin is a gamma-aminobutyric acid (GABA) analogue with antiepileptic, analgesic, and anxiolytic effects.[1,2] These effects occur when pregabalin binds to presynaptic voltage-gated calcium channels to regulate calcium entry into the cell, thereby reducing the release of neurotransmitters such as glutamate, norepinephrine, substance P, and calcitonin gene-related peptide.[3,4]

There has been an increase in publications regarding the abuse of pregabalin in recent years.[5,6] When taken in high doses, pregabalin may result in side effects such as affective disorders, somnolence, confusional state, agitation, and restlessness.[7]

Common ocular side effects of pregabalin include blurred vision[7] and diplopia.[8] Less frequent side effects such as ocular pain, photopsia, and irritation have also been reported.[7]

In this case report, we present a patient with bilateral serous macular detachment following attempted suicide with oral pregabalin.

Case Report

A 24-year-old female patient presented with complaints of blurred vision for 2 weeks. According to the patient's history, she had attempted suicide 2 weeks earlier by taking 15 tablets of pregabalin (Lyrica, 300 mg; Pfizer, Tadwort; United Kingdom) and was brought to the emergency department of another center with loss of consciousness and seizures. According to the patient's discharge report, her blood pressure was 100/60 mmHg, heart rate was 165/minute, respiration rate was 34/minute, and body temperature was 36.8 °C in the initial examination done in emergency services. Hemogram and biochemical values were within normal limits. Arterial blood gas analysis done during follow-up in intensive care showed pH: 6.79, PaO_2: 45 mmHg, $PaCO_2$: 55 mmHg, HCO_3: 7.9 mmol/L, and BE: -33.6 mmol/L. Blood drug level was not analyzed. The patient exhibited deep metabolic acidosis and convulsions and was treated with intravenous hydration, 20 ampules of $NaHCO_3$ and 0.05 mg/kg midazolam (Dormicum, Roche). After treatment, arterial blood gas analysis showed pH: 7.41, PaO_2: 145 mmHg, $PaCO_2$: 31.8

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mmHg, HCO_3: 18.8 mmol/L, and BE: -3.3 mmol/L. On day 3 of follow-up, the patient's general condition was improved and she was conscious and alert. She had developed blurred vision during this time, and was referred to the ophthalmology department upon discharge. Ophthalmologic examination revealed bilateral serous exudative macular detachment, upon which the patient was referred to our clinic for further examination and treatment.

On examination in our clinic, her best corrected visual acuity (BCVA) was 20/40 in the right eye and 20/50 in the left eyes. Anterior segment examination was normal. Intraocular pressure was within normal limits. Foveal reflex was absent bilaterally on fundoscopic examination (Figures 1a, b). Fundus fluorescein angiography revealed foci of hypofluorescence in the posterior pole starting in the early phases and continuing in the late phases (Figures 1c, d, e, f). Optical coherence tomography (OCT) images obtained in the other center and in our clinic

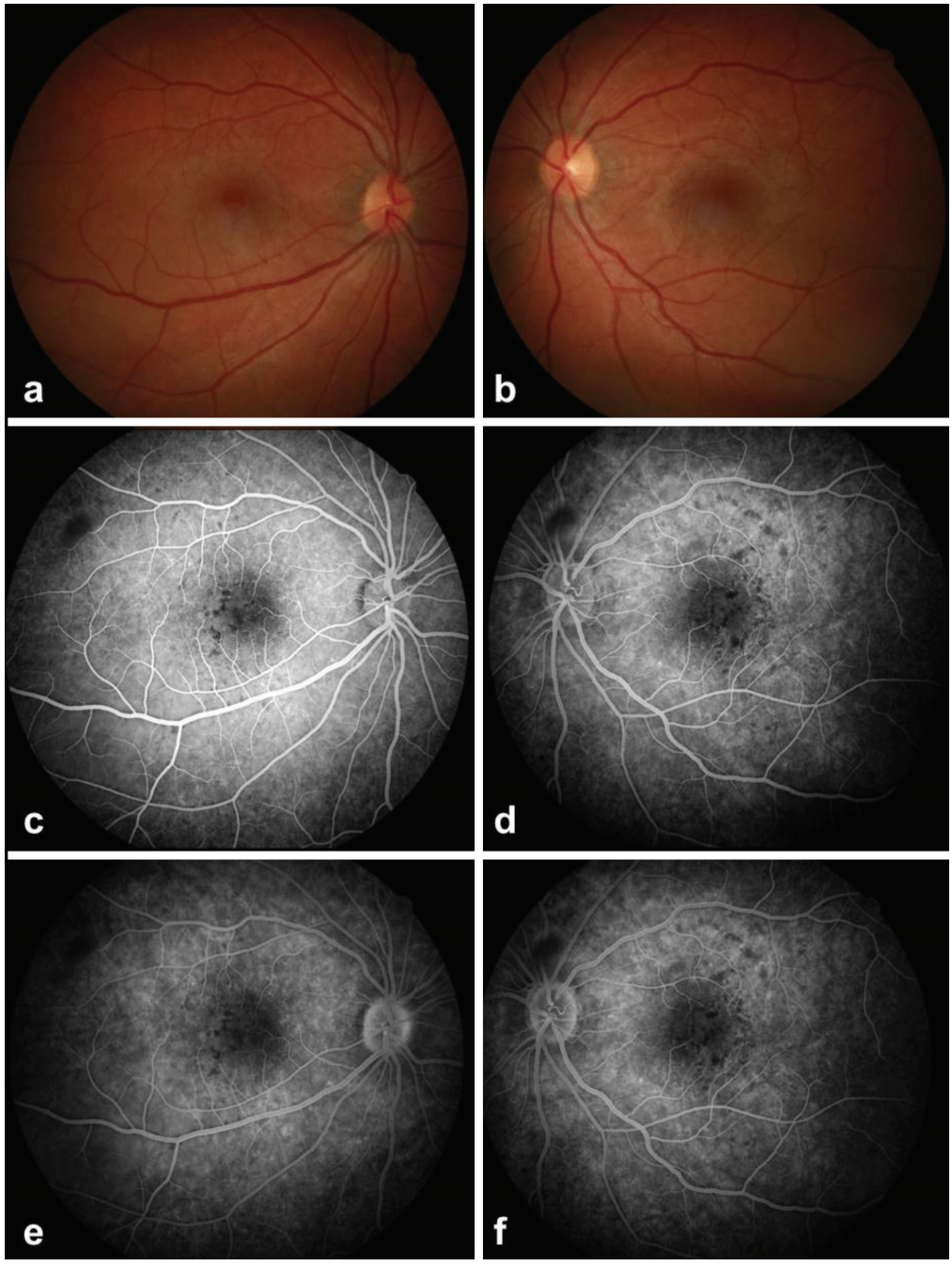

Figure 1. Color fundus photography and fundus fluorescein angiography of a 24-year-old female patient at her initial presentation to our clinic; (a, b) color fundus image shows absent foveal reflex in both eyes due to subretinal fluid; (c, d) fundus fluorescein angiography shows bilateral spots of hypofluorescence starting in early phases and continuing in late phases (e, f) in the posterior pole.

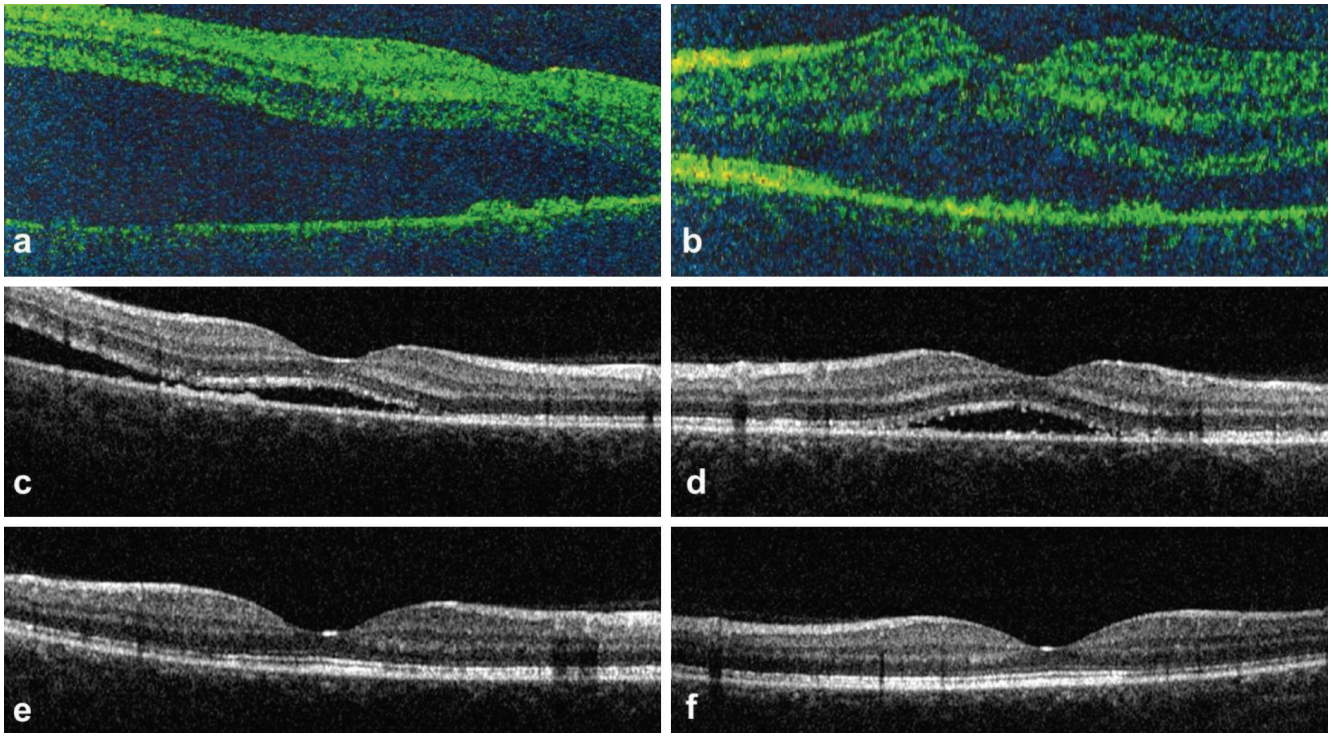

Figure 2. Optical coherence tomography images obtained in another center and in our center after discharge from intensive care; (a, b) optical coherence tomography taken in the other center 3 days after the suicide attempt shows bilateral serous detachment that is more pronounced in the right eye; (c, d) optical coherence tomography taken in our clinic 1 week later shows significant reduction of the subretinal fluid in both eyes compared to the initial images; (e, f) in optical coherence tomography taken 1 month later the subretinal fluid had totally regressed

showed subretinal fluid in both eyes (Figures 2a, b, c, d). Based on the patient's history and examination findings, the serous macular detachment was believed to be a result of pregabalin intoxication. Treatment was started with topical nepafenac 0.1% (Nevanac Alcon, Forth Worth, Texas, United States of America) 3 times a day. The subretinal fluid was totally resolved after 1 month of treatment (Figures 2e, f). Topical treatment was discontinued. On examination 3 months after her initial presentation, BCVA was 20/20 in both eyes and no subretinal fluid was evident on OCT.

Discussion

Pregabalin is a structural analogue of GABA. It binds to the alpha-2-delta subunits of voltage-gated calcium channels to block calcium influx, resulting in reduced release of excitatory neurotransmitters such as glutamate, norepinephrine, substance P, and calcitonin gene-related peptide.[9] This mechanism of action led to the use of pregabalin in disorders such as neuropathic pain, epilepsy, and anxiety.[9,10,11]

In the case presented here, a 24-year-old woman developed blurred vision due to serous macular detachment after attempting suicide using pregabalin. Her lack of any relevant medical or family history and the absence of significant systemic pathology other than metabolic acidosis during her stay in intensive care suggest that the serous detachment occurred as a result of the effect of pregabalin. In the literature there is another case reported from Turkey in which unilateral hemorrhagic macular infarct occurred following a suicide attempt using pregabalin, alcohol, and marijuana.[12] The authors proposed that the macular ischemia in this case developed secondary to marijuana-related arteritis and impaired vascular autoregulation as well as pregabalin-related systemic hypotension. In our case, we suspect the hypofluorescent spots observed in fluorescein angiography and the subretinal fluid observed in OCT may have resulted from a vascular filling defect in the choroidal vessels and increased choroidal vascular permeability which likely developed due to the effect of pregabalin. However, data about the choroidal circulation and thickness were insufficient due to our inability to perform indocyanine green angiography and OCT with enhanced depth imaging.

Pregabalin has a wide range of indications for therapeutic use. It is indicated for patients with peripheral neuropathic pain, fibromyalgia, epilepsy, generalized anxiety disorder, and partial convulsions.[7] The number of publications reported on the misuse and abuse of pregabalin has increased in recent years.[5,13,14] Individuals with a history of opioid abuse are particularly prone to abuse pregabalin.[14] In conclusion, consumption at high doses due to misuse or abuse is possible with pregabalin, which has such a wide range of indications. Although there are limited reports in the literature regarding

the potential ocular side effects of pregabalin, a detailed drug use history must be obtained whenever ophthalmologists detect serous macular detachment or macular infarct. Randomized controlled studies are needed in order to better understand the dose-dependent or dose-independent effects of pregabalin on the retina and choroid.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Burak Tanyıldız, Baran Kandemir, Mehmet Serhat Mangan, Aise Tangılntız, Eren Göktaş, Şaban Şimşek, Concept: Burak Tanyıldız, Design: Burak Tanyıldız, Baran Kandemir, Data Collection or Processing: Burak Tanyıldız, Eren Göktaş, Analysis or Interpretation: Burak Tanyıldız, Şaban Şimşek, Literature Search: Burak Tanyıldız, Mehmet Serhat Mangan, Aise Tangılntız, Writing: Burak Tanyıldız.

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

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Case Report

Toxocara Neuroretinitis Associated with Raw Meat Consumption

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Abstract

Neuroretinitis characterized by optic disc edema and star-like exudates in the macula was detected in a patient who presented with sudden unilateral painless vision loss and had a history of raw meat consumption. The patient tested seropositive for *Toxocara*. Combination therapy with steroid and albendazole resulted in an increase in visual acuity and complete resolution of clinical signs.

Keywords: *Toxocara*, neuroretinitis, optic neuropathy, raw meat

Introduction

Toxocara infection is a zoonotic disease caused by *Toxocara canis* or *Toxocara cati* nematodes. Transmission to humans occurs either through oral intake of eggs in soil contaminated with cat or dog feces, or especially in adults, via consumption of raw or undercooked liver and other meat from animals infected with *Toxocara* larvae.[1] Ocular toxocariasis is frequently seen in children, although the reported prevalence is also rising in Asian adults in recent years.[2]

Ocular toxocariasis is characterized by chorioretinal granulomas at the posterior pole or at the periphery, focal chorioretinal lesions, and chronic endophthalmitis.[3] *Toxocara* larvae may also present clinically with vitritis, panuveitis, intermediate or posterior uveitis, and secondary vitreous hemorrhage.[1,4,5,6] However, optic nerve involvement due to *Toxocara* infection and development of neuroretinitis is rare in the literature.

This report presents the clinical manifestations and treatment results of a patient diagnosed as *Toxocara* neuroretinitis due to consumption of raw meat.

Case Report

A 36-year-old male patient presented to our clinic with a complaint of sudden, painless vision loss in his left eye for 1 week. His history was unremarkable except for raw meat consumption. Best corrected visual acuity (BCVA) was 20/20 and 20/125 and intraocular pressure was 16 mmHg and 14 mmHg in his right and left eyes, respectively. Anterior segment examination was normal bilaterally. Pupillary light reflexes showed relative afferent pupillary defect in his left eye. The optic nerve head was edematous with indistinct margins and star-like macular exudates were detected in left fundus examination (Figure 1). In addition, spectral-domain optical coherence tomography (SD-OCT) (Topcon 3D-OCT 2000 Corporation, Tokyo, Japan) showed subretinal fluid in the macula. Right fundus examination was normal. Visual evoked potential was consistent with delayed conduction and Humphrey visual fields showed an inferior arcuate scotoma in the central 20 degrees in the left eye.

Etiological investigation was conducted, including complete blood count, biochemical, viral, bacterial, and parasitological serological tests. Detailed evaluation was performed, including

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This study was presented as a poster in Turkish Ophthalmology Society Meeting in 2016, Antalya, Turkey.

chest x-ray and quantiferon test for tuberculosis, lysozyme and angiotensin converting enzyme level analysis for sarcoidosis, and relevant serological tests for cat-scratch and Lyme disease, along with consultations for rheumatologic and neurological diseases. Cranial magnetic resonance imaging and laboratory tests were all in normal range except *Toxocara* immunoglobulin (Ig) G seropositivity with increased avidity (ELISA and Western Blot) and elevated total IgE (Total IgE = 140 IU/mL) without eosinophilia.

Intravenous methylprednisolone therapy (1 g daily for 1 week) was administered with a preliminary diagnosis of neuroretinitis. After 1 week, BCVA in the left eye increased to 20/30. Considering his history of raw meat consumption, the neuroretinitis was thought to be related to *Toxocara* infection, and oral albendazole treatment (400 mg twice daily) was given in addition to the maintenance corticosteroid regimen for 1 month.

After 1.5 months, BCVA in the left eye was 20/20 and clinical signs including optic nerve head edema and macular exudates had completely resolved. The subretinal fluid in the macula had also disappeared on SD-OCT (Figure 2).

Discussion

In this case report, an adult patient with a history of raw meat consumption presented with unilateral neuroretinitis. Detailed investigation revealed that his optic neuropathy was associated with *Toxocara* infection confirmed with Western blot technique. Elevated total IgE levels also supported the diagnosis. Common causes of neuroretinitis such as cat-scratch disease, caused by *Bartonella* species, syphilis, Lyme disease, and toxoplasmosis

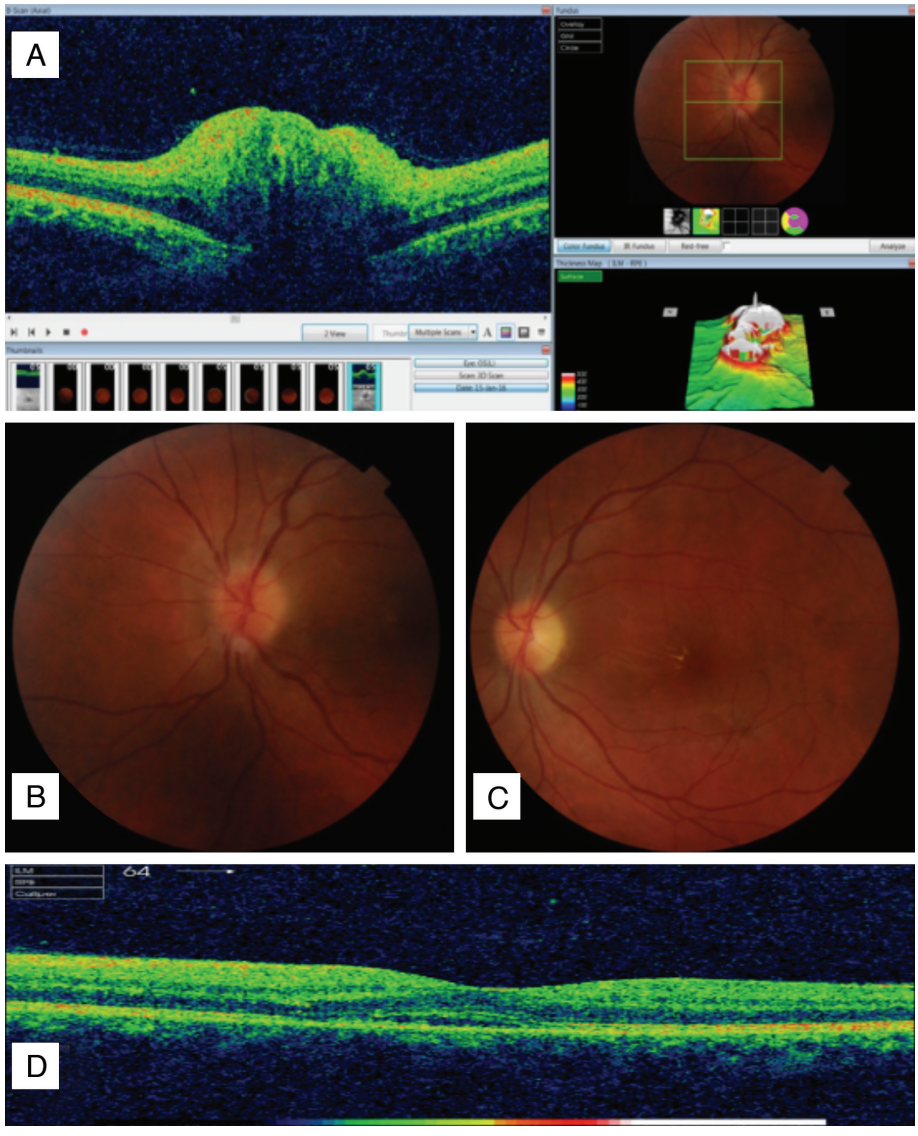

Figure 1. Initial posterior segment findings: A and B) Optic disc edema with indistinct margins; C) Star-like exudates in the macula; D) Subretinal fluid in spectral-domain optical coherence tomography

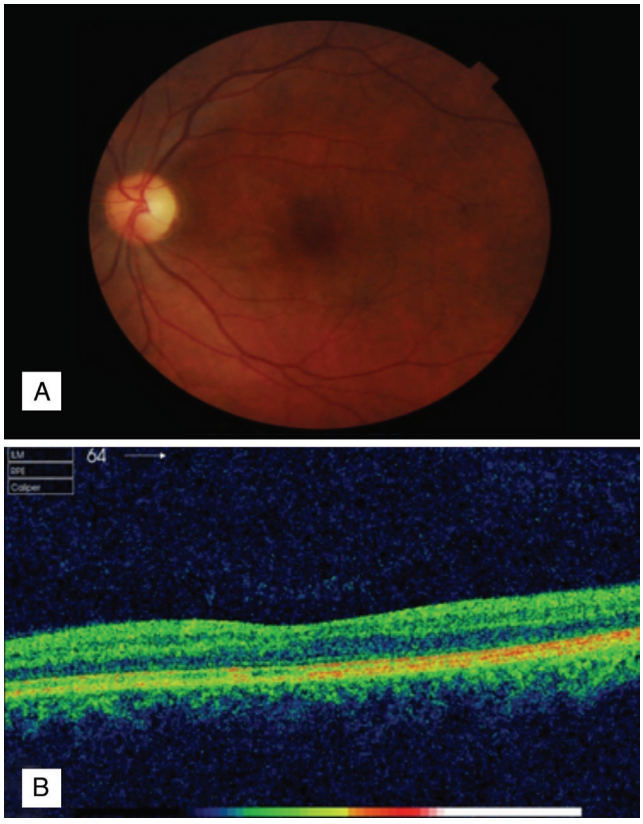

Figure 2. Posterior segment findings after treatment: A) Optic disc and macular region; B) Spectral-domain optical coherence tomography

were all excluded by negative serological test results. In addition, there was no history of exposure to cats. Other possible causes of macular star include hypertensive retinopathy, papilledema, anterior ischemic optic neuropathy, diabetic papillopathy, and toxic etiologies. However, many of these tend to be bilateral, unlike neuroretinitis, and systemic evaluation of our patient was unremarkable for those diseases.

Chronic ocular toxocariasis is usually diagnosed based on clinical findings of granulomas in the retina or at the optic disc together with *Toxocara* seropositivity. Rarely, definitive diagnosis can be made by direct observation of larvae in an ophthalmological examination. For this reason, diagnosis of ocular toxocariasis is presumptive and is usually based on careful history and clinical observation.[3] Detection of IgG antibodies against *Toxocara* larval antigens with ELISA and confirmation with Western blot technique was also reported to be sufficient for the diagnosis. Chronic increase in total IgE and eosinophilia usually accompany helminthic infections including toxocariasis. However, it was reported that a single larva causing ocular toxocariasis resulted in local eosinophil accumulation in the tissue. Therefore, blood eosinophil count was within normal range in that case.[7] In our case, total IgE levels were increased and blood eosinophil count was normal.

In the literature, ocular toxocariasis can be seen in adults especially if their history is consistent with raw meat and liver consumption.[2] Jee et al.[8] also reported that consumption of raw meat products was more common than history of cat or dog contact in their case series. Thus, history of raw meat consumption along with positive serology also strongly suggested a diagnosis of *Toxocara* neuroretinitis in our patient.

The prevalence of neuroretinitis in ocular toxocariasis was reported as 7.2%.[8] Yang et al.[9] related raw meat consumption to *Toxocara* optic neuropathy in their 5 cases, stated as the largest series in the literature. In addition, granuloma in the retina or at the optic disc, peripapillary subretinal exudates, and localized serous retinal detachment along with positive *Toxocara* serology, raw meat consumption, and recurrent vitritis episodes were reported to be distinguishing features of *Toxocara*-related optic neuropathy.

There is no consensus on the management of ocular toxocariasis; however, corticosteroids are usually recommended because they decrease the inflammatory response, thus preventing the development of tractional retinal detachment in these cases.[10] The use of antihelminthic drugs is controversial, as they may lead to severe reaction in the tissue due to dead larvae. However, albendazole can pass through the blood-retina barrier and reduce recurrence through its intraocular parasiticidal effect. Combination therapy with albendazole and oral prednisolone significantly reduced 6-month recurrence rates as compared to corticosteroid monotherapy and was thought to be successful.[11] In our case, pulse methylprednisolone therapy resulted in significant improvement in BCVA and the addition of oral albendazole to the regimen resulted in complete resolution of exudates and subretinal fluid.

Ocular toxocariasis has diverse clinical manifestations both in the acute and chronic stages. Thus, clinical signs of neuroretinitis along with a history of raw meat consumption should raise suspicion of *Toxocara* infection.

Ethics

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Irmak Karaca, Jale Menteş, Serhad Nalçacı, Concept: Irmak Karaca, Jale Menteş, Design: Irmak Karaca, Jale Menteş, Data Collection or Processing: Irmak Karaca, Jale Menteş, Serhad Nalçacı, Analysis or Interpretation: Irmak Karaca, Jale Menteş, Literature Search: Irmak Karaca, Jale Menteş, Writing: Irmak Karaca, Jale Menteş.

Conflict of Interest: Jale Menteş has served as a consultant for Allergan, Bayer and Novartis, Thea Pharma.

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

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Case Report

Multimodal Imaging in Pachychoroid Neovasculopathy: A Case Report

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Abstract

Pachychoroid neovasculopathy (PNV) is a form of type 1 neovascularization characterized by dilated choroidal vessels in areas of increased choroidal thickness. In this article, we describe a patient diagnosed with PNV. A 50-year-old male with a 2-month history of blurred vision was referred to our clinic. His best corrected visual acuity was 20/100 in both eyes. Retinal pigment epithelium alterations, which were more prominent in fundus autofluorescence, were detected in both eyes on dilated fundus examination. Characteristic findings of PNV were detected in fundus fluorescein angiography, indocyanine green angiography, spectral domain optical coherence tomography, and optical coherence tomography angiography.

Keywords: Pachychoroid neovasculopathy, choroidal neovascularization, optical coherence tomography angiography

Introduction

Pachychoroid spectrum diseases were first recognized in 2013 when Warrow et al.[1] described pachychoroid pigment epitheliopathy. The pachychoroid spectrum includes 4 disease groups: pachychoroid pigment epitheliopathy, central serous chorioretinopathy, pachychoroid neovasculopathy (PNV), and polypoidal choroidal vasculopathy. Pachychoroid spectrum diseases are characterized by increased choroidal thickness, dilation of the outer choroidal veins (pachy-veins), and thinning of Sattler's and choriocapillaris layers.[2]

Multimodal imaging methods are used to understand the disease pathophysiology and in diagnosis. Indocyanine green angiography (ICGA) is shown to be superior to fundus fluorescein angiography (FFA) for detailed imaging of choroid neovascularization (CNV) and diagnosis of choroidal polyps. Thanks to its longer wavelength, ICGA enables better visualization of lesions underlying the retinal pigment epithelium (RPE), even in the presence of blood, exudate, and pigment epithelium detachment (PED).[3,4] Advances in the field of optical coherence tomography (OCT) have also enabled imaging of choroidal structures in addition to the retina.[5,6] OCT angiography (OCT-A), a relatively new technology, provides structural information about the retinal and choroidal vessels without the need for contrast material injection.[7]

In this case report, we analyze the findings obtained with various imaging modalities from a patient with PNV who presented with a 2-month history of blurred vision.

Case Report

A 58-year-old male patient with no other known disease presented to our clinic with blurred vision for the last 2 months. His best corrected visual acuity was 20/100 in both eyes. Pupils were isochoric and light reflexes were present bilaterally. There was no afferent pupillary defect. Slit-lamp anterior segment examination was normal and intraocular pressure values were within normal limits. Fundus examination revealed RPE changes in the macula of both eyes.

Irregular hyperfluorescent areas were observed in both eyes in the early and late phases of FFA (Heidelberg retinal angiograph 2) (Figure 1).

On ICGA, both eyes were found to have dilated choroidal vessels in the early phase and appearance consistent with plaque CNV in the late phase (Figure 2).

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Fundus autofluorescence revealed hyperautofluorescent spots were seen in the central fovea and superonasal to the fovea (Figure 3).

Bilateral subretinal fluid, shallow irregular PED, and pachy-veins were observed on spectral domain OCT (Heidelberg). Subfoveal choroid thickness was 307 µm in the right eye and 254 µm in the left. Pachy-vein thickness was measured as 285 µm in the right eye and 206 µm in the left (Figure 4).

OCT-A (RTVue XR "Avanti", Optovue, Fremont, California, United States of America) imaging revealed tangled hyperreflective neovascular network compatible with type 1 CNV in the choroid slab of both eyes. The selected CNV area was 4.671 mm^2 in the right eye and 3.533 mm^2 in the left. The flow area through the selected CNV area was 2.847 mm^2 in the right eye and 2.211 mm^2 in the left. The largest diameter of the selected CNV area was 1.26 mm in the right eye and 1.28 mm in the left (Figure 5).

Discussion

PNV was first described by Pang and Freund[8] in 2015. The disease may consist of type 1 CNV that develops secondary to central serous chorioretinopathy or pachychoroid pigment epitheliopathy. PNV should be suspected in cases of thickened choroid with type 1 CNV without characteristic findings of age-related macular degeneration (AMD) such as drusen or hemorrhages. It is characterized by the presence of shallow, irregular PED.

In a study by Miyake et al.[9] including 200 patients diagnosed with PNV and AMD, 19.5% of the cases were diagnosed with PNV. Subfoveal choroid thickness was found to be greater in patients with PNV than in those with AMD. They reported that genetic mutations were detected less frequently in patients with PNV. In addition, PNV was observed in younger patients compared to AMD.[10]

The etiopathogenesis of pachychoroid spectrum diseases involves microtrauma to the Bruch's membrane from the enlarged

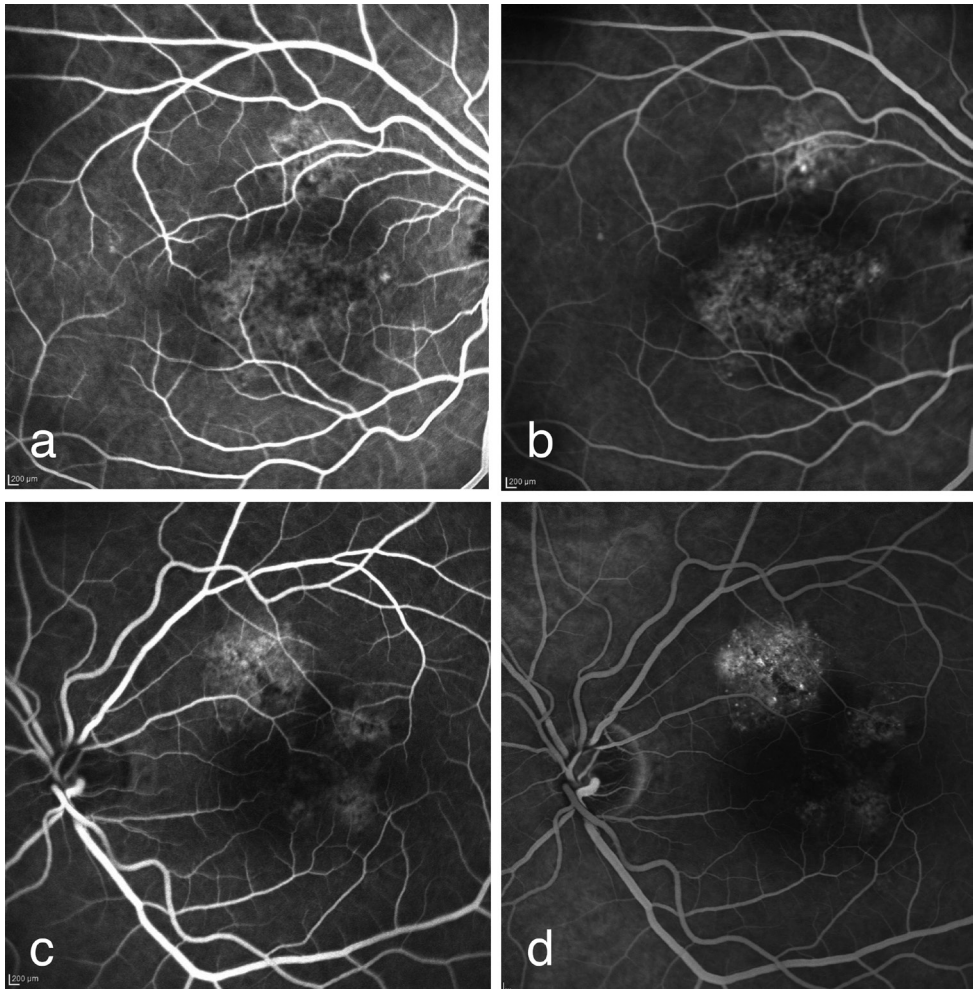

Figure 1. a) Faint hyperfluorescence in the central and superior parafoveal area starting at second 28 of fundus fluorescein angiography in the right eye; b) irregular hyperfluorescence in the central and superior parafoveal area continuing at 4 minutes, 32 seconds of fundus fluorescein angiography in the right eye; c) irregular hyperflorescence in the parafoveal areas at second 37 of fundus fluorescein angiography in the left eye; d) irregular hyperflorescence in the parafoveal areas continuing at minute 5 of fundus fluorescein angiography in the left eye

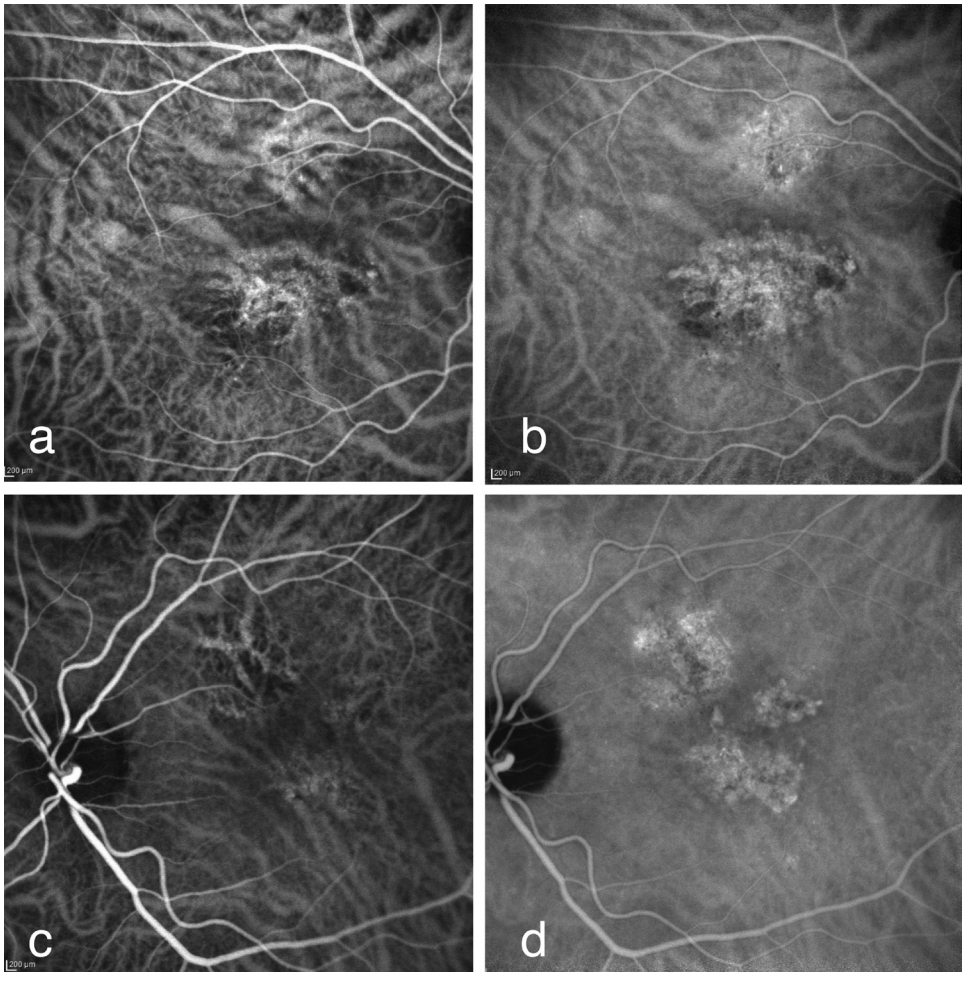

Figure 2. a) The appearance of dilated choroidal vessels and hyperfluorescence in the central area starting at second 28 of indocyanine green angiography in the right eye; b) plaque choroid neovascularization with contours clarifying in the central area and having polypoid expansion in the nasal at 4 minutes, 47 seconds of indocyanine green angiography in the right eye; c) dilated choroidal vessels in the macula at 37 seconds of indocyanine green angiography in the left eye; d) two plaques of choroid neovascularization in the subtemporal and temporal parafoveal areas and retinal pigment epithelium irregularity and hyperflorescence due to atrophy in the superior parafoveal area at 8 minutes, 39 seconds of indocyanine green angiography in the left eye

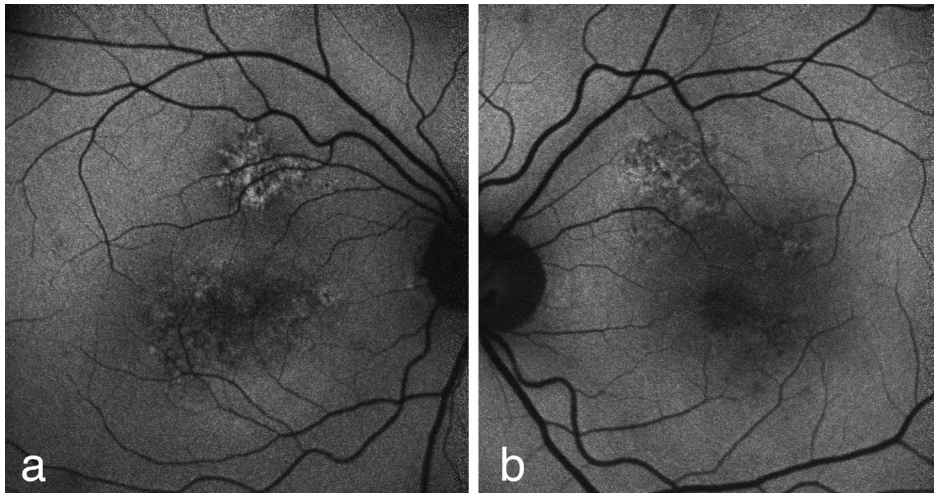

Figure 3. Hypo and hyper signal changes in fundus autofluorescence; a) in foveal and superior parafoveal areas of the right eye; b) and in the superior and temporal parafoveal areas of the left eye

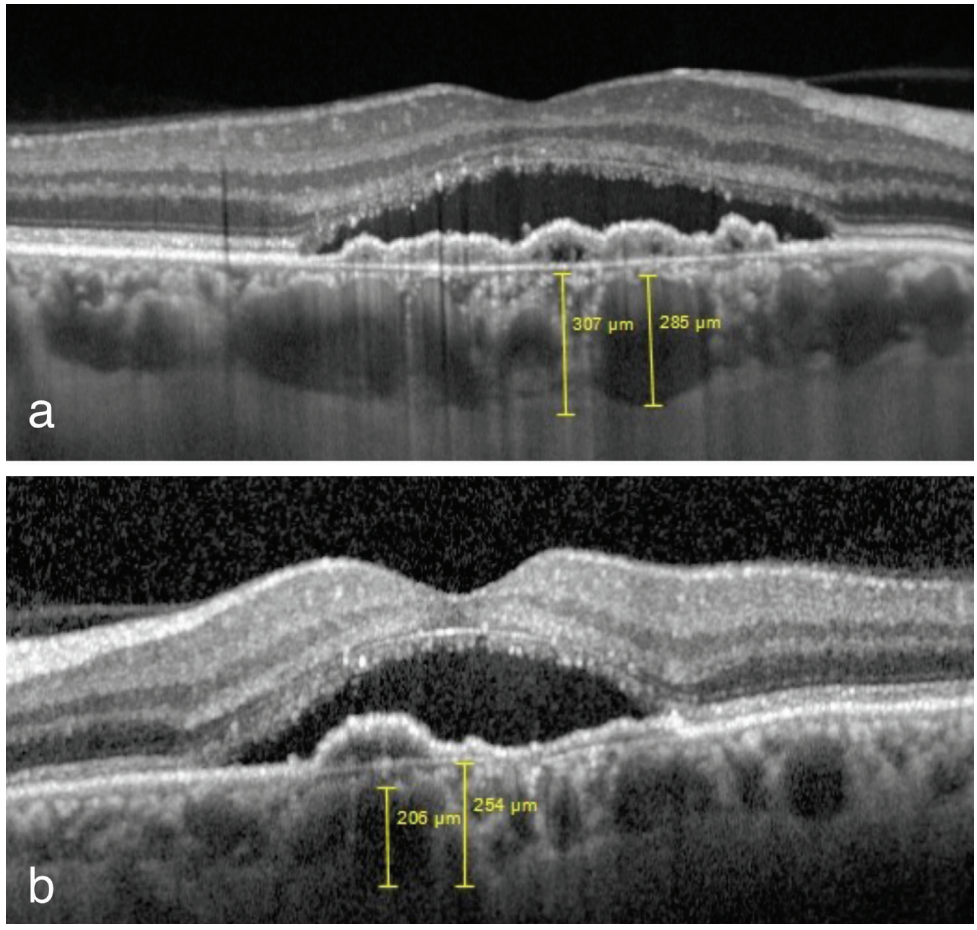

Figure 4. Shallow irregular pigment epithelium detachment, subretinal fluid and pachy-veins on spectral domain optical coherence tomography; a) subfoveal choroid thickness and pachy-vein thickness are 307 µm and 285 µm in the right eye; b) 254 µm and 206 µm in the left eye, respectively

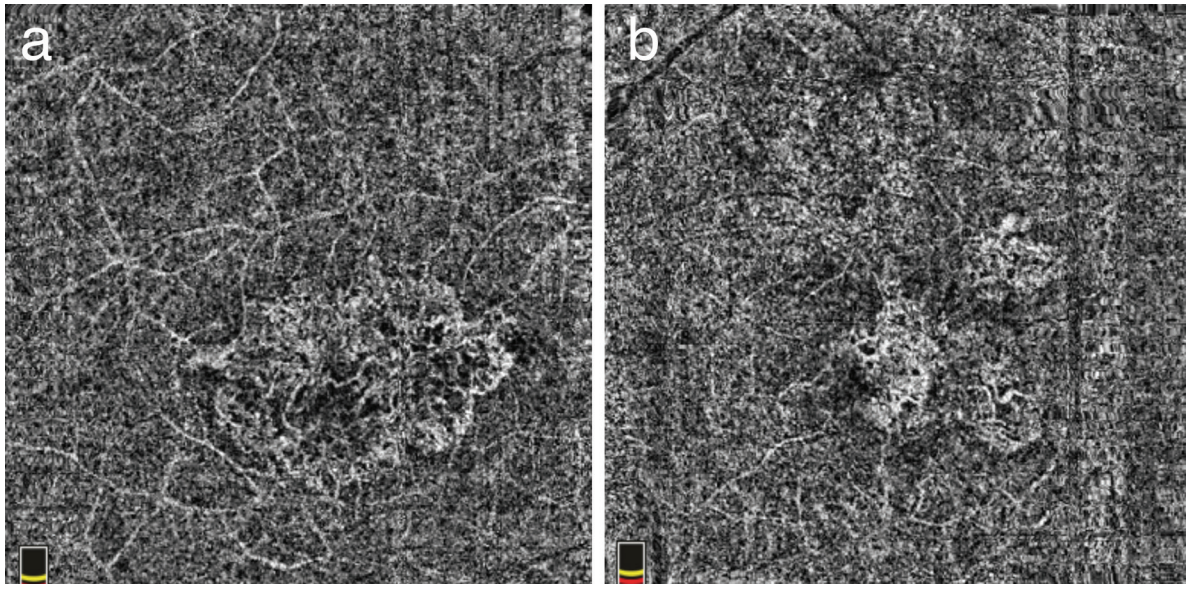

Figure 5. a) Optical coherence tomography angiography image of a single vascular network of type 1 choroid neovascularization; b) optical coherence tomography angiography image of 2 vascular network of type 1 choroid neovascularization

pachy-veins in the Haller's layer. This causes choriocapillaris loss and RPE changes. Neovasculopathy develops as a result of extension of neovascularization beneath the RPE.[1]

FFA and ICGA are used in the diagnosis of CNV and are known to cause nausea and anaphylaxis in rare cases.[11] OCT-A enables image acquisition by serial OCT scanning and is a reliable method that allows imaging of retinal and choroidal vasculature without needing any dye injection.[7] The tangled vascular network under the shallow irregular PED can be imaged with OCT-A. In a study including 16 patients (22 eyes) with shallow irregular PED, CNV was detected in 95% of the patients with OCT-A. Compared to other angiography techniques, OCT-A is shown to be more successful in demonstrating type 1 CNV.[12]

Similarly, in the present case we observed shallow PED, subretinal fluid, thickened choroid, and pachy-veins on spectral domain OCT and appearance consistent with type 1 CNV in FFA and ICGA. OCTA showed a CNV network in the areas corresponding to the type 1 CNV observed on ICGA. In a case series by Azar et al.[13] including 5 PNV patients, the presence of neovascularization could not be fully identified with FFA and ICGA in 2 patients, whereas the presence of tangled filamentous vascular network was detected in all of the patients with OCT-A. Therefore, these findings indicate that OCT-A can detect CNV before FFA and ICGA in pachychoroid spectrum diseases.

In conclusion, as we have also observed in our case, non-invasive OCT-A imaging generally supports fundus angiography images with regard to the diagnosis of type 1 CNV in PNV. OCT-A should be used in combination with other methods for the detection of vascularization in AMD presenting with shallow PED and in pachychoroid spectrum diseases.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özlem Biçer, Figen Batıoğlu, Sibel Demirel, Emin Özment, Concept: Özlem Biçer, Figen Batıoğlu, Design: Özlem Biçer, Figen Batıoğlu, Data Collection or Processing: Özlem Biçer, Figen Batıoğlu, Analysis or Interpretation: Özlem Biçer, Figen Batıoğlu, Literature Search: Özlem Biçer, Writing: Özlem Biçer, Figen Batıoğlu.

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

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Turk J Ophthalmol 2018;48:267-273

Case Report

Clinical Features and Surgical Results in Harada-Ito Surgery Patients

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Abstract
Symptomatic excyclotorsion is an important clinical problem, especially in acquired superior oblique muscle palsy. Excyclotorsion can disrupt the fusion and cause torsional diplopia. Harada-Ito surgery (HI) is a widely used method for treating excyclotorsions. This method relieves the torsional diplopia by increasing the effect of the incyclotorsion. In this study, we aimed to report the clinical features of patients with torsional diplopia due to acquired trochlear nerve palsy and the results of HI surgery in these patients.
Keywords: Superior oblique muscle palsy, trochlear nerve, excyclotorsion, Harada-Ito

Introduction

The Harada-Ito (HI) procedure is a strabismus surgical technique developed to treat torsional diplopia caused by excyclotorsion resulting from superior oblique (SO) muscle palsy. The main indication for the procedure is acquired trochlear nerve palsy following closed head injury, particularly due to traffic accidents.[1] In acquired SO palsy, torsional diplopia occurs as a result of weakened intorsional effect and the greater extorsional effect of the inferior oblique (IO) muscle. The HI procedure is an effective surgical method, especially in cases of bilateral SO palsy with a large amount of torsion.[2] In the original technique described by Harada and Ito[4] in 1964, the anterior fibers are advanced anteriorly without disinsertion.[3] In 1974, Fells modified the technique and described the form that is commonly used today.[3,5] In this modified technique, the SO muscle tendon is bisected and the anterior fibers are disinserted and transposed anterolaterally to increase the intorsional effect.[5] The procedure can be applied unilaterally or bilaterally, depending on amount of torsion and laterality. In 1981, Metz and Lerner described the use of an adjustable suture technique with this procedure.[6]

Although there are internationally published studies concerning HI surgery, to the best of our knowledge there is no nationally published study on this subject. The existing publications are mostly from retrospective studies and the surgical techniques are usually described in these reports in writing or illustrations.[1,2,3,4,5,6] In this study, we aimed to report the clinical features and outcomes of HI surgery in three patients who developed torsional diplopia due to acquired trochlear nerve palsy. In addition, one of our patients was evaluated with pre- and postoperative tests together with images showing the technique in order to make this rarely practiced surgical procedure more comprehensible.

The medical records of three patients who underwent the HI procedure due to torsional diplopia were retrospectively evaluated. Written consent forms were obtained from all patients prior to surgery. Medical procedures, data collection, and all stages of the study were carried out according to the Declaration of Helsinki and ethics committee approval was obtained.

For all patients, detailed medical history, examination findings, and the etiology, clinical presentation, and duration of disease were recorded. Visual acuity, anterior and posterior segment findings, eye movements, angle of deviation, abnormal

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head positions, oblique muscle functions, and amount of torsion were assessed pre- and postoperatively. Deviation was measured with a prism cover test, torsion was measured by double Maddox rod test, and extraocular muscle function was assessed using a Hess screen. Diagnosis of SO palsy was made based on limited depression on adduction, IO hyperfunction, V-pattern, hypertropia, abnormal head position, excyclotorsion findings, and medical history. Patients who had symptoms for at least six months underwent surgical treatment.

All patients underwent Fells' modified HI procedure. A conjunctival incision was made in the superotemporal quadrant 8 mm from the limbus, the superior rectus (SR) muscle was isolated and the SO muscle was exposed from the lateral side. The SO tendon was split longitudinally 10 mm posterior from the insertion. The anterior fibers were separated from the insertion by suspending with 6.0 vicryl suture. The lateral rectus (LR) muscle was then isolated using a muscle hook and the anterior fibers of the SO tendon were sutured to the sclera adjacent to the superior margin 8 mm posterior to the LR insertion.

Case Reports

The records of three patients were retrospectively reviewed in this study (Table 1). All of the patients had torsional and vertical diplopia. The etiology in all cases was closed head trauma due to vehicular accident. Based on examination findings, two patients were diagnosed with SO palsy due to bilateral trochlear nerve injury and the other patient due to unilateral trochlear nerve injury. HI surgery was performed on the affected eyes to treat diplopia.

Case 1

A 28-year-old male patient presented with diplopia that was more pronounced in downgaze and had developed after a motorcycle accident a year earlier. The patient exhibited a chin-down head position and had 20/20 visual acuity and normal anterior and posterior segment examination findings in both eyes. He had minimal V pattern esotropia with -1 limited depression in adduction on the right and -2 limited depression in adduction on the left, and +1 IO hyperfunction bilaterally (Figure 1). Double Maddox rod test revealed 20 degrees of extorsion (Figure 2A) and fundus photograph revealed +3 extorsion (Figure 2B). Bilaterally reduced SO muscle function was observed on Hess screen test (Figure 2C), while binocular visual field test revealed single vision in the superior visual field (Figure 2D). Based on ophthalmic examination findings, the patient was diagnosed with bilateral SO palsy and underwent modified HI with adjustable suture technique in the right eye and modified HI procedure in the left eye (Figure 3). On postoperative day 1, double Maddox rod test revealed 5 degrees of extorsion and the suture was adjusted to eliminate this remaining torsion. On postoperative day 3, the patient's head position was improved, he was orthotropic in primary gaze, and fundus photography showed +1 intorsion. At postoperative 4 months, the patient was orthotropic with no limitation or torsion in any gaze position, and maintained straight gaze (Figure 4). There was no torsion in fundus images. Extraocular muscle functions were normal in the Hess screen test and his field of single vision in binocular visual field testing had expanded (Figure 5).

Table 1. Pre- and postoperative characteristics of the patients

	Patient 1	Patient 2	Patient 3
Age (years)/Gender	28/M	53/M	58/F
Visual acuity	20/20	20/20	20/20
Diplopia	T, V	T, V, H	T, V
Involvement	Bilateral	Bilateral	Unilateral
Strabismus pattern	V-pattern + ET	V-pattern + ET	Right HT
Head position	Chin down	Chin down	Left head tilt
Extorsion	20°	20°	10°
Treatment	Adjustable HI	Modified HI	Modified HI + SR recession
Postop extorsion	0	2°	0
Complications	None	IO limitation	None

M: Male, F: Female, T: Torsional, V: Vertical, H: Horizontal, XT: Exotropia, ET: Esotropia, HT: Hypertropia, HI: Harada-Ito, SR: Superior rectus, IO: Inferior oblique, Postop: Postoperative

Case 2

A 53-year-old male patient presenting with diplopia stated that his complaint had started after a traffic accident 6 months earlier. He had 20/20 vision in both eyes and normal biomicroscopic and fundoscopic examination findings. The patient exhibited a chin down head position and had torsional diplopia as well as V-pattern esotropia of 12 prism diopters on downgaze. He had limited depression in adduction (-2) in both eyes, but no IO hyperfunction. Double Maddox rod test revealed 20 degrees of extorsion and fundus photography revealed +2 extorsion. Bilateral SO muscle hypofunction was observed in Hess screen test and binocular visual field testing revealed diplopia on downgaze. The patient was diagnosed with bilateral SO palsy based on examination findings, and the modified HI surgery was performed in both eyes. At postoperative week 1, the patient showed improved head position, fundus images showed no extorsion, and 2 degrees of extorsion were observed in the double Maddox rod test. Hess screen test showed normal SO muscle function bilaterally and slight IO hypofunction. Diplopia on downgaze was not detected in binocular visual field testing. At postoperative 4 months, the patient exhibited normal head position and was orthotropic in primary gaze. No torsion was observed in double Maddox rod test and fundus images. The patient described slight diplopia on upgaze. Hess screen test showed normal SO function with -1 hypofunction in the IO muscles. No additional intervention was done.

Case 3

A 58-year-old female patient reported developing double vision following a traffic accident 1 year earlier, and that later her right eye gradually developed an upward deviation.

Her vision was 20/20 in both eyes and her anterior segment examination and fundoscopy findings were normal. She exhibited a left head tilt. In primary gaze position, hypertropia of 14 prism diopters at distance and 12 prism diopters at near was measured in the right eye. Depression in adduction was -2 limited and IO hyperfunction was not observed in the right eye. Double Maddox rod test revealed 10 degrees of extorsion and +2 extorsion was measured on fundus photography of the right eye. Hess screen test revealed reduced SO muscle function in the right eye and binocular visual field testing revealed diplopia on downgaze. She was diagnosed with right SO palsy and modified HI surgery with 5.5-mm SR recession was performed. At postoperative 1 week, the patient showed improved head position and extorsion. Minimal hypertropia was observed on the right eye in primary gaze position, while Hess screen test revealed improved SO muscle function in the right eye and binocular visual field testing demonstrated reduction in the area of diplopia on downgaze. Examination findings at the first postoperative month showed no further changes, and the patient continued follow-up in a different city.

Discussion

The long intracranial course of the trochlear nerve makes it especially prone to injury in closed head traumas. Acquired trochlear nerve palsy may cause symptomatic excyclotorsion, also referred to as torsional diplopia, which is rarely seen in congenital cases.[7] Managing patients with this complaint is difficult. The main goal of surgical treatment in these patients is to provide single vision in primary and downgaze and to correct abnormal head position.[7] While various surgical techniques have been described for the treatment of SO palsy due to acquired trochlear nerve injury, the modified HI procedure is very effective in reducing excyclotorsion and treating torsional diplopia.[7] In the modified HI technique, the anterior fibers of the SO muscle are transposed anterotemporally, strengthening the intorsion effect of the muscle.[2]

In our study, HI surgery was successfully performed on five eyes of three patients with torsional diplopia. Postoperative diplopia was not observed with distant or near fixation in the primary gaze position. However, surgical success rates of 43-68% have been reported in previous studies.[2,3] Preoperatively, our patients exhibited abnormal head positions they had developed to prevent diplopia and achieve fusion. We found that in all cases, head position was improved and fusion achieved postoperatively. Bradfield et al.[8] demonstrated that the presence of fusion prior to surgery was associated with surgical success.

Another factor determining surgical success is preoperative amount of torsion. Bradfield et al.[8] reported that surgical success increased as the amount of torsion decreased. Torsion usually does not exceed 10 degrees in unilateral SO palsy; as in our third case, patients with complaints of diplopia

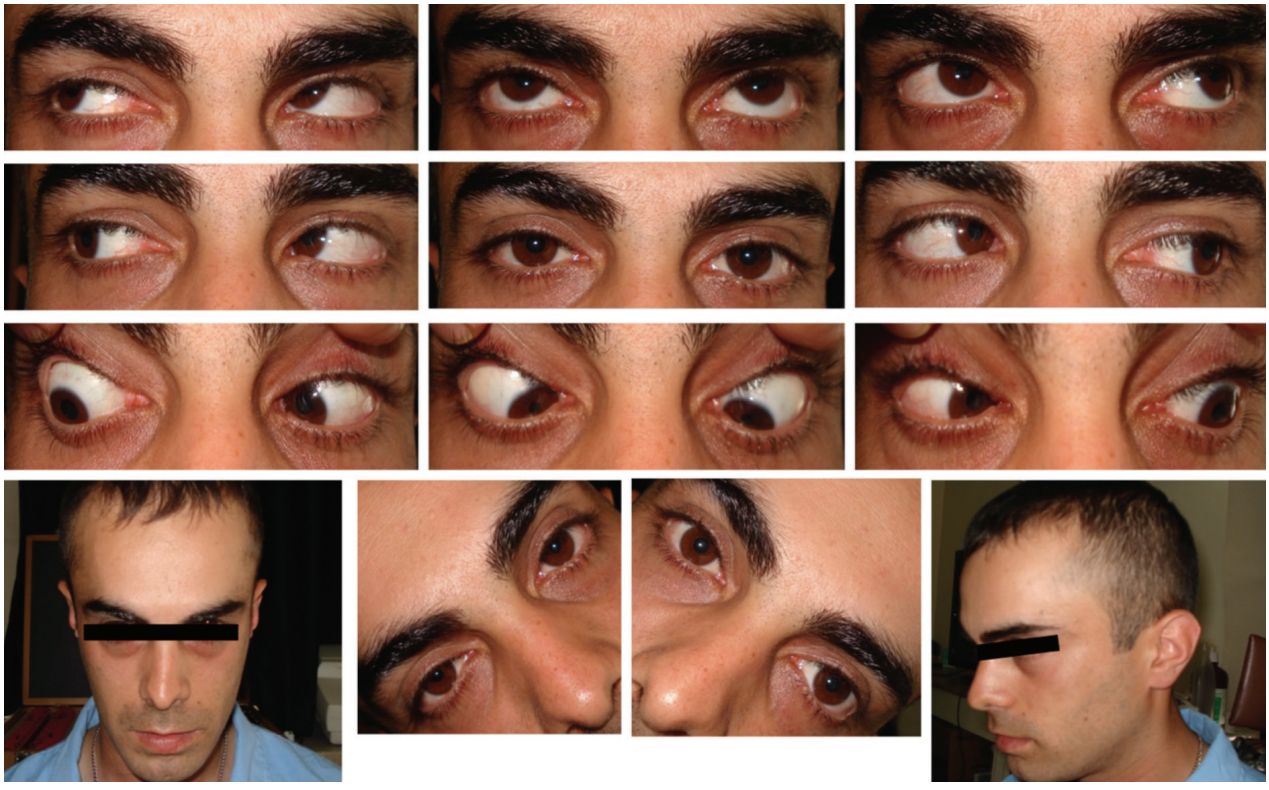

Figure 1. Preoperative images of patient 1. The patient had chin down head position and minimal V-pattern esotropia. Depression in adduction was -1 limited in the right eye and -2 limited in the left eye. There was +1 inferior oblique hyperfunction in both eyes

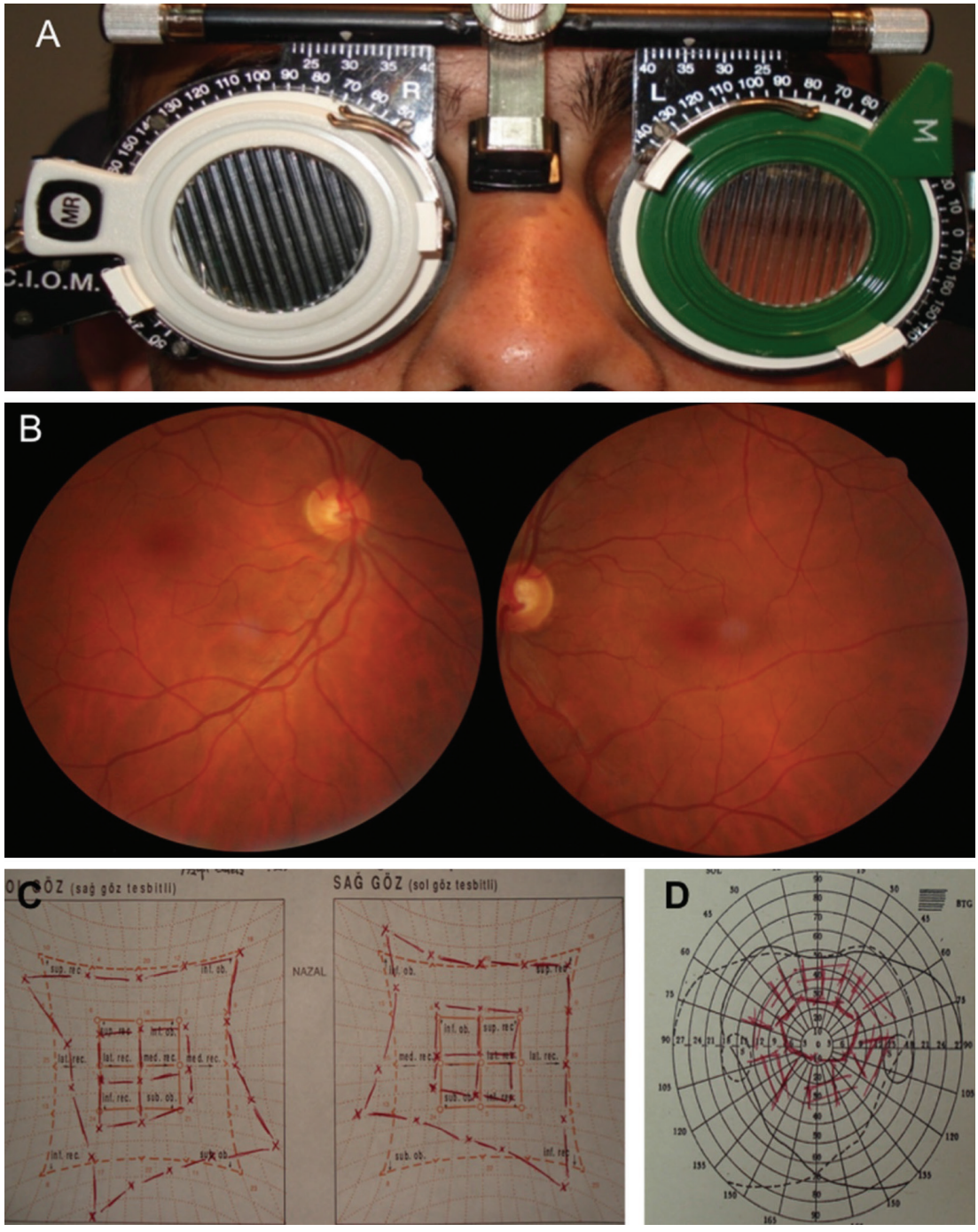

Figure 2. Preoperative test results in patient 1. The patient exhibited 20 degrees of extorsion in the double Maddox rod test (A) and +3 extorsion was observed in fundus images (B). Bilateral superior oblique muscle hypofunction was observed in Hess screen testing (C) and binocular visual field test revealed single vision in the superior visual field (D)

occurring immediately after head trauma later report unilateral hypertropia.[1] In these patients, SR recession or IO muscle weakening to correct hypertropia can be performed concurrently with the HI procedure to correct torsion. Our third patient, whose right eye was hypertropic in addition to having 10 degrees of torsion, underwent HI surgery and concurrent SR recession due to the absence of IO hyperfunction. Patients with more than 10 degrees of excyclotorsion are usually symptomatic, as in our other 2 cases. Such patients have a chin down head position, and bilateral SO muscle palsy should be suspected.[2] Together with a history of head trauma, examination findings of V-pattern, more than 10 degrees of

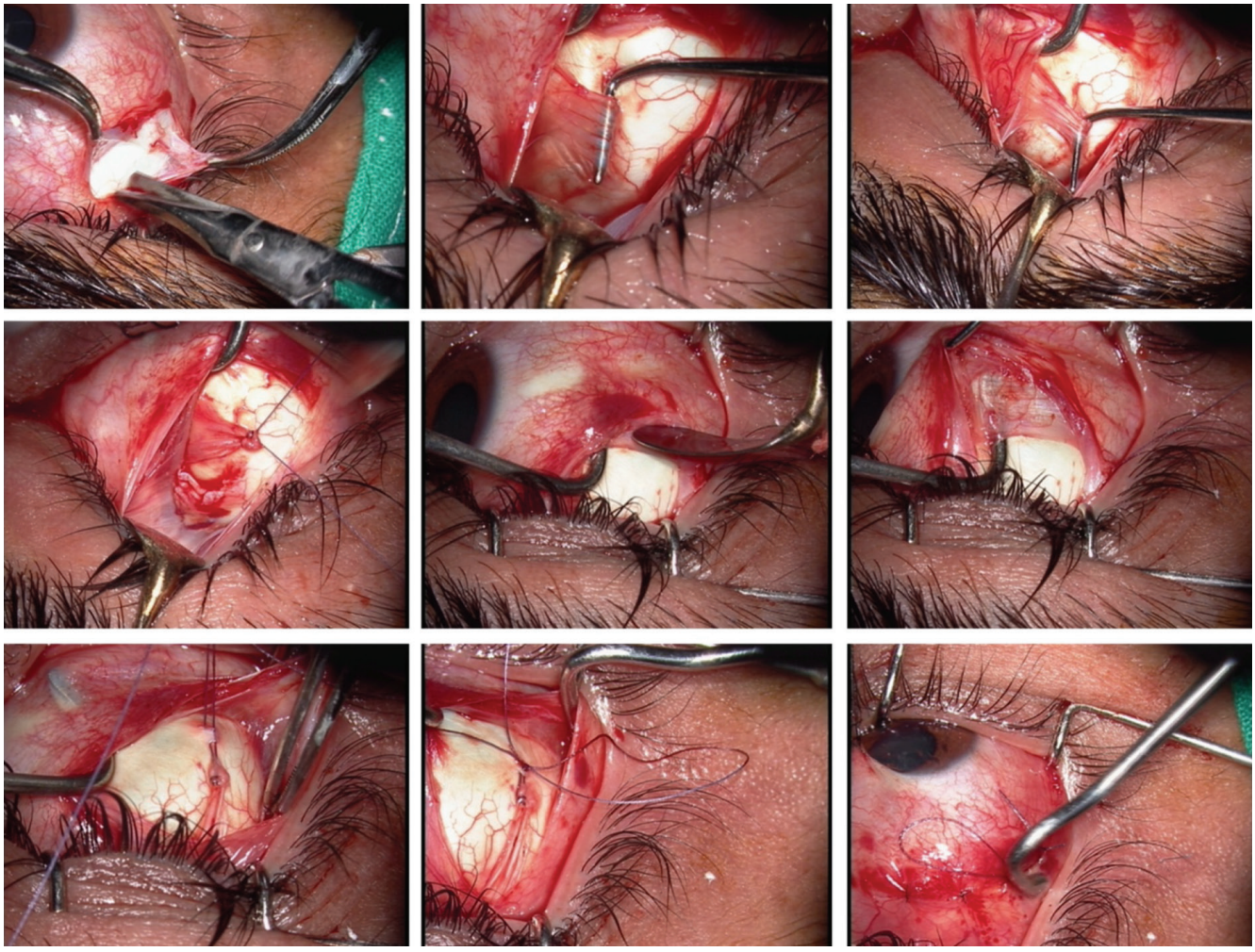

Figure 3. Modified Harada-Ito procedure with adjustable suture technique

excyclotorsion, and left hypertropia in right gaze and right hypertropia in left gaze are suggestive of bilateral SO palsy.[1] Managing bilateral acquired SO palsy may be difficult because of the considerable amount of torsion, but bilateral HI surgery can successfully reduce extorsion and alleviate symptoms in these patients.[2] To improve the success of surgical treatment, the HI procedure should be used in patients with primary complaints of torsion in particular.

Taking into account coexisting vertical and horizontal deviations, V-pattern, and IO hyperfunction during surgical planning influences surgical success. Tendon transposition of the rectus muscles, inferior or superior rectus recession, and IO muscle weakening surgery to correct V-pattern can also be performed together with the HI procedure.

As with our second patient, there are patients who postoperatively develop limitation of movement in the IO muscle field and diplopia on upgaze, similar to Brown's syndrome.[8] Patients undergoing surgery should be informed about complications such as iatrogenic restriction and under- or overcorrection. As in our first case, intorsion may develop in the early postoperative period following HI surgery for symptomatic extorsion. Intorsion usually regresses during follow-up. Postoperative recurrence of symptomatic extorsion has been reported in several studies; therefore, an overcorrection of up to 10 degrees of intorsion is recommended.[2,3,9] Residual excyclotropia occurring later in the postoperative period, as in our second case, is common.[1,3,9] It has been reported that patients with acquired cyclotropia exhibit retinal sensory reorientation to overcome torsion and are only symptomatic in dissociated environments.[10]

Limitations of our study include the fact that it was a retrospective chart review. In addition, statistical analyses could not be done due to the small number of patients and paucity of data, and follow-up was short.

In conclusion, HI surgery successfully treated torsional diplopia, especially in primary gaze position, in all three of our patients. Preoperative amount of torsion and the presence of fusion can affect surgical success. Prior to surgery, patients should

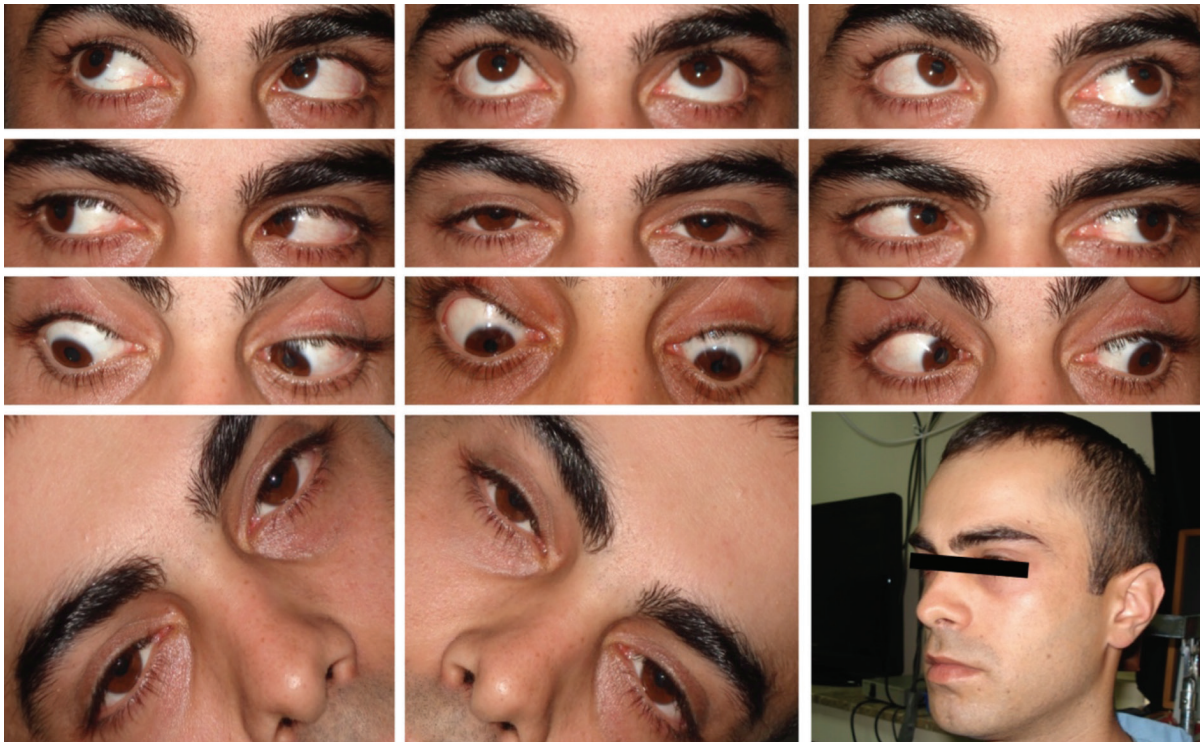

Figure 4. Images of patient 1 at postoperative month 4. The patient is orthotropic in primary gaze with normal head position and no torsion or limitation in the gaze positions

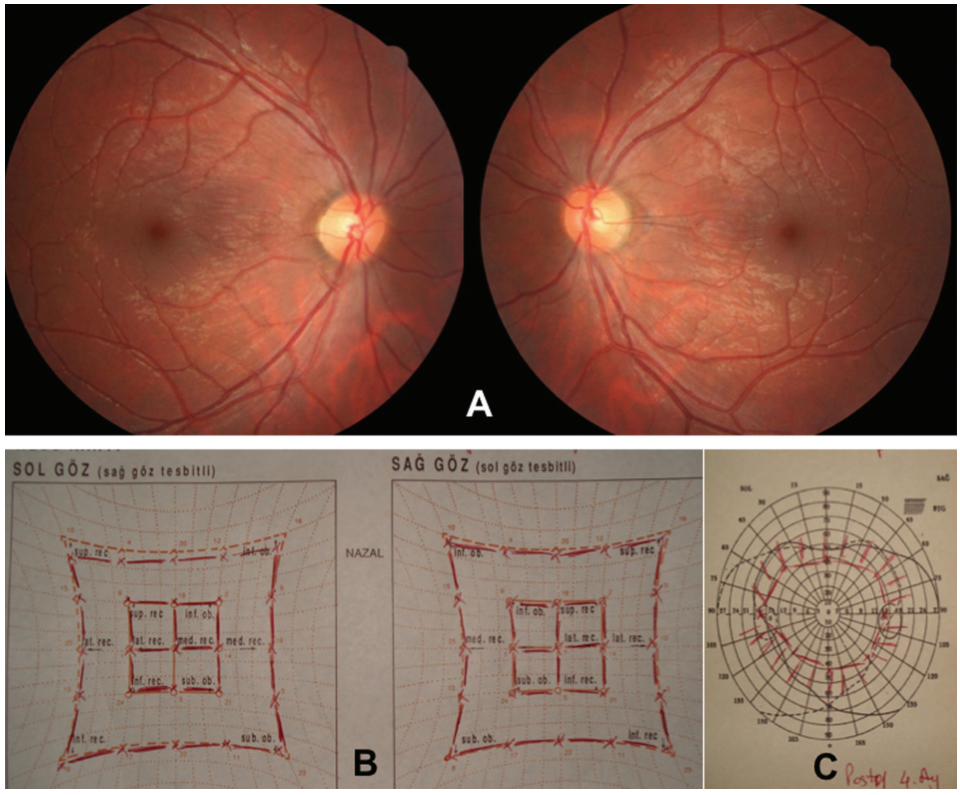

Figure 5. Test results of patient 1 at postoperative month 4. No torsion was observed in fundus images (A). Extraocular muscle functions were normal in Hess screen testing (B) and the area of single vision had expanded in binocular visual field testing (C)

be informed that diplopia may persist postoperatively, especially in downgaze, that this may necessitate an additional intervention or the use of prisms, and that iatrogenic Brown's syndrome may develop and cause diplopia in upward gaze.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Önder Ayyıldız, Fatih Mehmet Mutlu, Halil İbrahim Altınsoy, Concept: Önder Ayyıldız, Fatih Mehmet Mutlu, Halil İbrahim Altınsoy, Design: Önder Ayyıldız, Fatih Mehmet Mutlu, Gökçen Gökçe, Data Collection or Processing: Önder Ayyıldız, Murat Küçükevcilioğlu, Gökçen Gökçe, Analysis or Interpretation: Önder Ayyıldız, Fatih Mehmet Mutlu, Literature Search: Önder Ayyıldız, Murat Küçükevcilioğlu, Gökçen Gökçe, Writing: Önder Ayyıldız.

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

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Letter to the Editor

Topography and Higher Order Corneal Aberrations of the Fellow Eye in Unilateral Keratoconus

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Dear Editor,

We congratulate Aksoy et al.[1] for their study entitled "Topography and Higher Order Corneal Aberrations of the Fellow Eye in Unilateral Keratoconus". We have read the article with interest. They evaluated and compared the topographic data and corneal higher order aberrations of fellow eyes of unilateral keratoconus patients with keratoconic eyes and control group. They retrospectively reviewed the medical records of 392 eyes of 196 patients with keratoconus and identified 20 patients (%11.2) with unilateral keratoconus. The diagnosis of unilateral keratoconus was defined as having a keratometric astigmatism below 1.5 diopter (D), vertical keratometry (K) value below 47.0 D, and no keratoconus patterns on corneal topography in this study. The results of the study revealed that there is no statistical difference in best corrected visual acuity between fellow eyes and control, whereas K_1, K_2, and cylindrical power values were significantly higher in the fellow eyes. Comparison of quantitative topographic indices showed that all indices except the inferior-superior ratio are significantly higher in the fellow eyes in keratoconic patients than in the control group ($p<0.05$). We express our gratitude to the authors regarding this study. However, we want to specify some matters and our thoughts related to this article.

First, we would like to emphasize that the term of 'unilateral keratoconus' is not appropriate. Because, according to the global consensus on keratoconus and ectatic diseases, keratoconus is a bilateral corneal disease.[2] However, clinical and topographical findings of the disease may not be evident one of the eyes. Many different terms such as *subclinical keratoconus, keratoconus suspect, and forme fruste keratoconus* have been employed to describe the preclinical stages of keratoconus.[3] We think that the term of "unilateral keratoconus" in this study may be confused with "subclinical keratoconus". Additionally we believe that posterior corneal elevation and pachymetric index are more sensitive index for the early diagnosis of keratoconus. Hence, the patients in the study must be evaluated by using these analyses. The studies by us[4] and Bae et al.[5] revealed that even these analyses are not adequate to detect the subclinical keratoconus. We examined the medical records of 3474 patients with keratoconus and 116 (3.3%) cases with subclinical keratoconus were detected. The diagnosis of subclinical keratoconus was defined as having a central mean K value less than 47.2 D, an inferior-superior asymmetry for the average K less than 1.4 D, a keratoconus percentage index (KISA%) of less than 60%, and no clinical evidence. After that, these patients were analyzed with the Belin-Ambrósio Enhanced Ectasia Display (BAD) III, which evaluates the pachymetric progression and anterior and posterior elevation values of the cornea. Normal BAD analysis were detected in only 38 (1.1%) of these patients. We found that there were no statistically significant differences between the eyes with subclinical keratoconus who had normal BAD analysis and the controls in visual acuity, topographic, topometric and tomographic parameters (for all, $p>0.05$). We only detected statistically significant differences with regard to corneal densitometry values. Accordingly, we think that if the authors would take into account the posterior corneal surface and pachymetric indices, the prevalence of subclinical keratoconus in their study may be reduced and the keratometry values as well as some of the topographic parameters and surface index parameters might not be statistically significantly different between the fellow eyes and normal eyes.

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Keywords: Corneal aberrations, topography, unilateral keratoconus

Ethic

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Mustafa Koç, Kemal Tekin, Design: Mustafa Koç, Kemal Tekin, Data Collection or Processing: Mustafa Koç, Kemal Tekin, Analysis or Interpretation: Mustafa Koç, Kemal Tekin, Literature Search: Mustafa Koç, Kemal Tekin, Writing: Mustafa Koç, Kemal Tekin.

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

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Response from the Authors

Dear Editor,

In a Letter to the Editor written in response to our article entitled "Topography and Higher Order Corneal Aberrations of the Fellow eye in Unilateral Keratoconus" published in the Turkish Journal of Ophthalmology issue 2017/5 (reference no: TJO-45220), the author claimed that the term "unilateral keratoconus" is inappropriate, and that the term 'subclinical keratoconus' should be used instead. The author stated that posterior elevation and pachymetry data are more sensitive indexes in the detection of subclinical keratoconus, and the use of these data would reduce the rate of subclinical keratoconus in our study.

The term unilateral keratoconus is used in the literature. These publications were also cited in our article. We stated that the eyes considered topographically and clinically normal in unilateral cases may eventually develop signs of keratoconus findings if followed long enough. The NIDEK Magellan Mapper, which is available in our clinic and was used in our study, is a Placido-based system that only provides data regarding the anterior cornea surface. The lack of posterior corneal surface data was given as one of the limitations of our study. The points criticized by the author have already been addressed in our article, as shown below:

Introduction, paragraph 2: "The progressive course of the disease ultimately affects both eyes, though only one eye may be affected initially. The prevalence of true unilateral keratoconus has been reported to range from 0.5-4% in studies using computerized videokeratography[1,2] and was 4.5% in a more recent study using slit scanning corneal topography (Orbscan 2).[3] Holland[2] reported that patients with unilateral keratoconus developed keratoconus symptoms in their apparently healthy fellow eyes 4 years later, while Li et al.[4] found that keratoconus developed in 50% of cases within 16 years. Therefore, it may be concluded that the fellow eyes of patients with unilateral keratoconus may seem normal with regard to clinical and topographical pattern but have subclinical keratoconus."

Discussion, last paragraph: "In our study, the unilateral keratoconus ratio was found to be 11.2%. The prevalence of true unilateral keratoconus is reported in the international literature as ranging between 0.5% and 4.5%. In a study conducted in Turkey, a unilateral keratoconus prevalence of 14.9% was determined using Pentacam.[5] The main limitation of our study was that the elevation data provided by our topography device was not adequate and not able to evaluate the posterior corneal surface. Another limitation is that long-term patient follow-up data was not available. The suspected keratoconus eyes that we determined to be normal may exhibit signs that would lead to a keratoconus diagnosis if examined using more advanced topography systems."

Best Regards,

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