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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/);

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CONTENTS

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EDITORIAL

2016 issue 5 at a glance;

This issue includes six original articles, a review, and five case reports concerning various ocular segments which we believe will make valuable contributions to our national and international knowledge base.

The small-incision lenticule extraction (SMILE) procedure is a relatively new development in refractive surgery and has been introduced into practice in some Turkish centers in recent years. In SMILE, an intrastromal lenticule is created with a femtosecond laser and manually removed through a small peripheral incision. Yıldırım et al. evaluated the 2-year results of SMILE performed in 45 high-myopic eyes with refractive errors of over 6 diopters (D). They found that the mean postoperative spheric equivalent was -0.30±0.50 D and that visual acuity of 20/20 or better was achieved in 86% of the eyes. Only 2% of the patients lost one line in corrected visual acuity, while a moderate increase in corneal high-order aberrations was observed. These results suggest that SMILE is a safe and effective refractive surgical procedure (see pages 200-204).

Posterior capsular opacification is the most common complication after pediatric cataract surgery, and its incidence increases with younger age. It is therefore recommended to perform posterior capsulotomy and anterior vitrectomy in the same surgical session as cataract extraction. Batur et al. retrospectively evaluated preschool- and school-age children (4-12 years old) who underwent cataract surgery without posterior capsulotomy and reported that 21 of 30 eyes developed posterior capsular opacification and 15 (50%) required Nd:YAG laser capsulotomy. Due to the high incidence of posterior capsular opacification, the authors advise performing posterior capsulotomy and anterior vitrectomy in the same surgical session as cataract extraction (see pages 205-208).

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy arising from the avascular retina which occurs primarily in premature neonates with low gestational age and birth weight. Currently, the most effective and reliable treatment for ROP is laser photocoagulation of the avascular retinal field. Şekeroğlu et al. applied bedside laser photocoagulation under remifentanil analgesia to 195 eyes of 99 premature infants and achieved good anatomic results in 96.9% of the eyes after one year. Other than minor lens and corneal opacities after laser application (in 3 patients), no anterior segment complications were observed; 3 patients required repeat laser therapy, and 6 eyes of 6 patients required vitreoretinal surgery due to retinal detachment. The authors identified aggressive posterior ROP, delayed laser treatment (stage 4a), tunica vasculosa lentis prior to treatment, and iris vascular dilation/tortuosity as significant risk factors for unfavorable anatomic outcomes (see pages 209-214).

Peripheral exudative hemorrhagic chorioretinopathy (PEHC) is a disease of the peripheral retina that emerges with advancing age and is frequently mistaken for an intraocular mass. In their retrospective evaluation of 21 eyes of 12 patients with PEHC, Cebeci et al. observed subretinal hemorrhage and hemorrhagic/serous retinal pigment epithelium detachment (71.4%), lipid exudation (52.4%), chronic retinal pigment epithelium alterations (23.8%), subretinal fibrosis (9.5%) and intravitreal hemorrhage (4.8%) localized to the temporal quadrant. Half of the patients exhibited findings of age-related macular degeneration (AMD) such as drusen, geographic atrophy and choroidal neovascularization. Patients whose peripheral lesions did not threaten the macula were followed without treatment and their lesions showed no progression. The authors concluded that PEHC patients should be followed closely and examined regularly for sight-threatening macular pathologies (see pages 215-220).

Diabetic retinopathy (DR) is among the foremost causes of vision loss among working-age adults in developed countries. Alagöz et al. evaluated the efficacy of intravitreal bevacizumab (IVB) therapy in patients with vitreous hemorrhage associated with proliferative diabetic retinopathy. Panretinal photocoagulation was able to be performed within the first month in 86% of eyes treated with IVB, compared to 58% of eyes that were not treated with IVB (p=0.016). Fewer patients from the IVB group required surgery (see pages 221-225).

Coats' disease is a nonhereditary disease characterized by retinal capillary telangiectasia, arterial aneurysms, exudation and exudative retinal detachment. The condition is generally unilateral and is more prevalent in male children. Cebeci et al. observed in their retrospective analysis that of 27 patients diagnosed with Coats' disease, most were referred with an initial diagnosis of intraocular tumor and the most common symptoms were low vision, strabismus and leukocoria. The patients were treated with therapies such as laser photocoagulation, cryotherapy, intravitreal injections (bevacizumab, triamcinolone acetonide) and intravitreal dexamethasone implants either alone or in combination, as well as surgical interventions like scleral buckling and pars plana vitrectomy; some eyes that developed neovascular glaucoma and phthisis were enucleated. The authors' main objective was to avoid vascular anomalies and their associated complications through repeated combined therapies. Treatment in the early stages can increase functional success, while treatment in advanced stages may be beneficial in preserving the eye (see pages 226-231).

For this issue, Tuğcu and Özdemir reviewed the literature regarding imaging methods used in the diagnosis of optic disk drusen (ODD), which may be encountered with optic nerve edema. With imaging tests such as B-scan ultrasonography, fundus fluorescein angiography, computed tomography, fundus autofluorescence as well as the recently developed technology of optical coherence tomography, it is possible to examine in detail the structure and location of ODD and quantitatively follow changes over time (see pages 232-236).

In this issue's first case report, Şimşek et al. report the clinical findings and treatment of a 13-year-old female patient with pupillary block and angle-closure glaucoma due to a small, spherical crystalline lens and discuss the case together with the literature. For cases in which medical antiglaucomatous therapy and laser iridotomy are ineffective, clear lens extraction with or without goniosynechiolysis, filtering surgery and shunt surgery may be applied (see pages 237-240).

Lyme disease is an infectious disease caused by Borrelia burgdorferii transmitted by arthropod vectors. Ocular involvement can feature conjunctivitis, episcleritis, uveitis, neuroretinitis, retinal vasculitis and cranial nerve paralysis. In their case report, Müftüoğlu et al. discuss a Lyme patient with peripheral retinal vasculitis and intermediate uveitis as well as multifocal white dots in the posterior pole. Though rare, Lyme disease should be considered in the differential diagnosis of white dot syndromes (see pages 241-243).

Aktaş et al. present a case of idiopathic, isolated cilioretinal artery occlusion in a 26-year-old male patient. After 20 sessions of hyperbaric oxygen (HBO) therapy, the patient's retinal edema had regressed, fundus fluorescein angiography showed recanalization of the cilioretinal artery, the inferior hemivisual field defect on computerized visual field testing had substantially decreased, and his visual acuity improved to 20/20 (see pages 244-247).

Ticks act as vectors of many disease agents and can transmit the potentially deadly Crimean Congo Hemorrhagic Fever. Infestation of ocular tissues by ticks is a rare occurrence. In their case report discussing the diagnosis and treatment of two patients with tick infestation of the eyelid, Uzun et al. state that mechanically removing the tick as a whole using blunt-tipped forceps is a safe and effective treatment approach (see pages 248-250).

Finally, Marangoz et al. discuss a patient who presented with a painless mass in the medial left upper eyelid. Orbital magnetic resonance imaging with contrast revealed a nonenhancing, smooth-bordered cystic mass lesion. The mass was completely excised preserving the capsule and was later diagnosed by pathologic examination as eccrine hidrocystoma (see pages 251-254).

Respectfully on behalf of the Editorial Board,
Banu Bozkurt, MD

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Original Article

Long-term Results of Small-incision Lenticule Extraction in High Myopia

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Summary

Objectives: To evaluate two-year results of small-incision lenticule extraction (SMILE) for correction of high myopia.

Materials and Methods: Forty-five eyes of 35 patients with mean spherical equivalent (SE) of -7.10±0.95 D who underwent routine SMILE by a single surgeon and were followed for at least 2 years were analyzed by retrospective chart review. SMILE was performed with a Visumax femtosecond laser (Carl Zeiss Meditec, Jena, Germany). Follow-up intervals were at 1, 6, 12, and 24 months after surgery. Uncorrected and best corrected distance visual acuity (CDVA), corneal wavefront measurements, and all complications were recorded.

Results: After 2 years, 86% of eyes with plano target had an uncorrected distant visual acuity (VA) of 20/20 or better. Two percent of eyes lost 1 line of CDVA, while 32% gained 1 line. The mean SE after 2 years was -0.30±0.50 D. Corneal total high-order aberrations (HOA) increased from 0.43 to 0.92 µm at postoperative 12 months. There were metallic foreign bodies at the corneal interface in 1 eye of 1 patient which caused no decrease in VA.

Conclusion: SMILE for high myopia seems safe and effective in light of two-year follow-up results. The procedure caused a moderate increase in HOA.

Keywords: Small-incision lenticule extraction, high myopia, high-order aberrations

Introduction

Current femtosecond laser technology enables the predictable, effective and safe creation of corneal lamellar incisions.[1] Femtosecond laser systems are increasingly used in refractive lenticule extraction (RELEX). Based on how the lenticule is removed, RELEX procedures are classified as either femtosecond lenticule extraction (FLEX) or small-incision lenticule extraction (SMILE). In the SMILE procedure, an intrastromal lenticule is created with a femtosecond laser and manually removed through a small peripheral incision.[2] SMILE is used to treat myopia and astigmatism.[3,4]

Corneal refractive surgery and phakic intraocular lens (IOL) implantation are options for the correction of high myopia.[5] The use of SMILE for high myopia presents several advantages, namely avoiding the flap created during laser-assisted in situ keratomileusis (LASIK) and subsequent risk of ectasia, the risk of haze in high-myopic patients after photorefractive keratectomy and the invasive procedure on phakic IOL surgery.

In this study we aimed to evaluate the long-term visual and refractive outcomes, the effect on high-order aberrations (HOA) and the complications of SMILE for the correction of high myopia.

Materials and Methods

This retrospective study included 45 eyes of 35 patients who underwent SMILE in the Refractive Surgery unit of the Beyoğlu Eye Research and Training Hospital between 2011 and 2013. All procedures were performed by the same surgeon. The study was performed in accordance with the Declaration of Helsinki and was approved by the Beyoğlu Eye Research and Training

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Hospital Ethics Committee. Informed consent forms were obtained from all patients.

All patients included in the study were over 18 years old, had a spherical equivalent (SE) refraction value over 6.0 diopters (D), and had myopia or myopic astigmatism. Other inclusion criteria were absence of other ocular disease, having normal topography and regular retinoscopic reflex, a smallest pachymetry value greater than 500 µm, having stable refraction for the previous 2 years, and a cylindrical value smaller than 1.5 D. Prior to the procedure, the regularity of each patients' topography pattern was confirmed using a Sirius™ topography system (Costruzione Strumenti Oftalmici, Firenze, Italy). Mesopic (4 lux) pupil diameter was 6.5 mm or less in all patients. The calculated residual stromal bed thickness was greater than 250 µm.

Pre- and Postoperative Evaluations

Visual acuity (VA) was assessed using illuminated Early Treatment Diabetic Retinopathy Study chart (Optec 3500 Vision Tester, Stereo Optical Co., USA). Objective cycloplegic refraction measurements were done using an autorefractometer (KR-1 Auto Kerato-Refractometer, Topcon, Japan). The Sirius® corneal topography and aberrometry system (6 mm pupil diameter, Costruzioni Strumenti Oftalmici, Italy) was used for corneal topography, dynamic infrared pupillography, ocular wavefront analysis and corneal wavefront analysis.

IOP was measured with a Goldmann applanation tonometer. All patients underwent detailed slit-lamp examination of the anterior and posterior segments.

Surgical Technique

All procedures within the scope of this study were performed by the same surgeon using the VisuMax® (Carl Zeiss Meditec, Germany) femtosecond laser platform using the same laser settings. Spot size was 3 µm for lamellar incisions and 2 µm for sidecuts. Other settings were as follows: spot energy was 140 nJ, minimum lenticule edge thickness was 15 µm, lenticule sidecut angle was 120° and optical zone was 6.5 mm. The cap was planned to have a diameter of 7.5 mm with a 50° side cut in the superior region. A small interface was used for all patients. After making the lenticule cut and sidecut and moving the patient under the surgical microscope, a blunt spatula was used to enter the area of anterior lamellar photodisruption and remove any residual material. The same procedure was performed on the posterior lamellar photodisruption surface. After ensuring the complete separation of the lenticule from the overlying and underlying stroma, the lenticule was removed through the sidecut using forceps.

Statistical Analysis

Mean and standard deviation were used in descriptive statistical analyses. Normality of data distribution was determined by Kolmogorov-Smirnov test. Dependent samples t-test was used to analyze repeated measures. Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, USA) software was used for all analyses.

Results

Visual and Refractive Results

Uncorrected VA was 1.45±0.17 logMAR before the procedure, compared to 0.03±0.04 at 12 months after the procedure and 0.03±0.07 logMAR at 24 months after the procedure ($p<0.001$ for both). Corrected VA (CVA) was 0.06±0.08 logMAR before the procedure, compared to 0.01±0.02 at 12 months after the procedure and 0.01±0.03 logMAR at 24 months after the procedure ($p<0.001$ for both). Pre- and post-procedure VA values are summarized in Table 1.

As illustrated in Figure 1, at 1 year after the procedure, CVA decreased by 1 row in 2% of eyes and increased by 1 row in 32%. At 24 months after the procedure, CVA decreased by 1 row in 2% of eyes and increased by 1 row in 38%.

Emmetropia was the goal in all 45 eyes. At 1, 6, 12 and 24 months, VA was 20/20 or better in 78%, 82%, 88% and 86% of eyes, respectively. At final examination, VA was 20/25 or better in 96% of the eyes (Table 2). At 12 months after the procedure, 94% of the eyes were within ±0.5 D of the objective refraction and 100% of patients were within ±1.0 D. At 24 months after the procedure, 92% of the eyes were within ±0.5 D of the objective refraction and 100% of patients were still within ±1.0 D (Figure 2).

There were significant differences between baseline and postoperative 24-month values for SE, spherical value and cylindrical value ($p<0.001$ for all). Pre- and postoperative refractive values are presented in Table 3.

Corneal High-order Aberrations

Total corneal HOA increased from 0.43±0.10 µm before the procedure to 0.92±0.17 µm at 12 months after the procedure. Mean spherical aberration was -0.20±0.05 µm preoperatively and -0.56±0.2 µm at 12 months postoperatively ($p<0.001$). Mean coma aberration was 0.25±0.01 µm preoperatively and 0.66±0.3 µm at 12 months postoperatively ($p<0.001$), while trefoil aberration was 0.20±0.1 µm preoperatively and 0.22±0.1 µm at 12 months postoperatively ($p<0.04$) (Table 4).

Table 1. Pre- and postoperative visual acuity

	Preop Mean ± SD (n=45)	Postop 1 month Mean ± SD (n=45)	p	Postop 6 months Mean ± SD (n=45)	p	Postop 12 months Mean ± SD (n=45)	p	Postop 24 months Mean ± SD (n=45)	p
VA	1.45±0.17	0.07±0.05	<0.001	0.05±0.06	<0.001	0.03±0.04	<0.001	0.03±0.07	<0.001
CVA	0.06±0.08	0.05±0.06	<0.001	0.03±0.04	<0.001	0.01±0.02	<0.001	0.01±0.03	<0.001

Preop: Preoperative, Postop: Postoperative, VA: Visual acuity, CVA: Corrected visual acuity, SD: Standard deviation

Table 2. Relative comparison of postoperative visual acuities					
SMILE	**≥20/20**	**≥20/25**	**≥20/32**	**≥20/40**	**≥20/50**
Preop CVA (n=45)	88%	100%	100%	100%	100%
Postop 1 mo VA (n=45)	78%	90%	96%	98%	100%
Postop 6 mo VA (n=45)	82%	94%	100%	100%	100%
Postop 12 mo VA (n=45)	88%	92%	98%	100%	100%
Postop 24 mo VA (n=45)	86%	96%	100%	100%	100%
SMILE: Small-incision lenticule extraction, Preop: Preoperative, Postop: Postoperative, CVA: Corrected visual acuity, mo: month, VA: Visual acuity					

Table 3. Pre- and postoperative refractive values									
	Preop Mean ± SD (n=45)	**Postop 1 month Mean ± SD (n=45)**	**p**	**Postop 6 months Mean ± SD (n=45)**	**p**	**Postop 12 months Mean ± SD (n=45)**	**p**	**Postop 24 months Mean ± SD (n=45)**	**p**
Mean SE (D)	-7.10±0.95	-0.27±0.58	**<0.001**	-0.31±0.65	<0.001	-0.22±0.47	<0.001	-0.30±0.50	**<0.001***
Mean spherical value (D)	-6.64±0.88	-0.19±0.47	**<0.001**	-0.21±0.60	<0.001	-0.13±0.40	<0.001	-0.20±0.56	**<0.001***
Mean cylindrical value (D)	-0.82±0.55	-0.16±0.35	**<0.001**	-0.19±0.34	<0.001	-0.19±0.31	<0.001	-0.18±0.40	**<0.001***
Preop: Preoperative, Postop: Postoperative, SD: Standard deviation, D: Diopter, SE: Spherical equivalent, p: Dependent samples t-test									

Table 4. Pre- and postoperative high-order corneal aberrations			
HOA-6 mm	**Preoperative Mean ± SD**	**Postoperative 12 months Mean ± SD**	**p**
Total (µm) (RMS)	0.43±0.10	0.92±0.17	<0.001
Coma (µm)	0.25±0.10	0.66±0.30	<0.001
Spherical aberration (µm)	-0.20±0.05	-0.56±0.20	<0.001
Trefoil (µm)	0.20±0.10	0.22±0.10	0.04
HOA: High-order aberrations, SD: Standard deviation, RMS: Root mean square, p: Dependent samples t-test			

Side Effects and Complications

Suction loss occured in 1 eye of 1 patient while performing the cap cut. The procedure was completed successfully after suction was restored. In 1 eye of 1 patient, a 1 mm tear occured in the sidecut intraoperatively, while removing the lenticule. In the same eye, metallic deposits were observed postoperatively in the interface near the sidecut (Figure 3). None of the patients exhibited corneal epithelium ingrowth or topographic signs of corneal ectasia during follow-up.

Discussion

SMILE is a new femtosecond laser-based keratorefractive surgical procedure used to treat myopia without the creation of a flap, unlike the LASIK and FLEX procedures.[6] There are few studies on the long-term effects of SMILE for the correction of high myopia.[7] In the present study we evaluated the results from 2 years of follow-up from high myopic patients who underwent SMILE.

There are many studies in the literature reporting short-term outcomes of SMILE for myopia correction and comparing SMILE

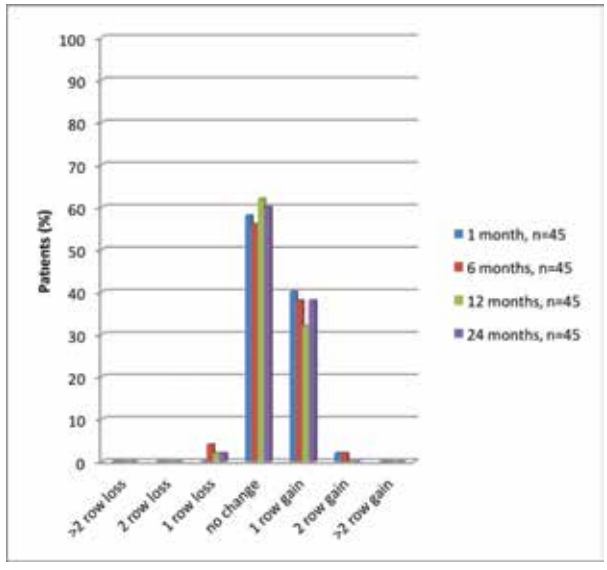

Figure 1. Rates of visual acuity gains and losses (in rows) in postoperative follow-up

with FLEX and LASIK.[8,9,10] Vestergaard et al.[10] investigated the short-term results of 35 patients who underwent FLEX in 1 eye and SMILE in the fellow eye. The patients' preoperative mean SE value was -7.6±1.0 D; VA was 20/40 or better in 90% of patients at postoperative day 1, and 100% at 6 months. At postoperative month 6, there was a significant improvement in CVA of about 1.5 rows. None of the eyes had more than 2 rows of gain or loss. The SMILE group achieved a postoperative mean refractive value of -0.09±0.39 D. After both procedures, final refraction at postoperative month 6 was within ±0.50 D in 88% of eyes. In another study, Vestergaard et al.[11] performed SMILE

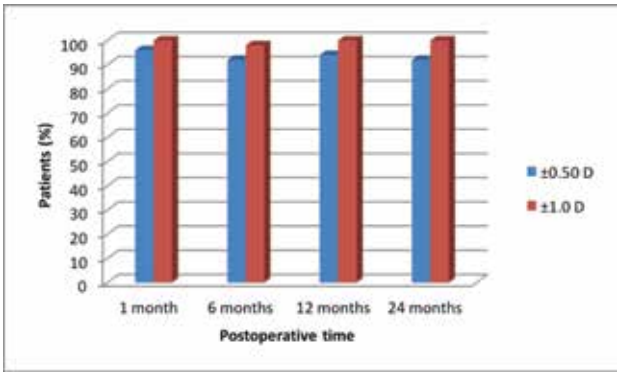

Figure 2. Refractive deviation from target spherical equivalent in postoperative follow-up

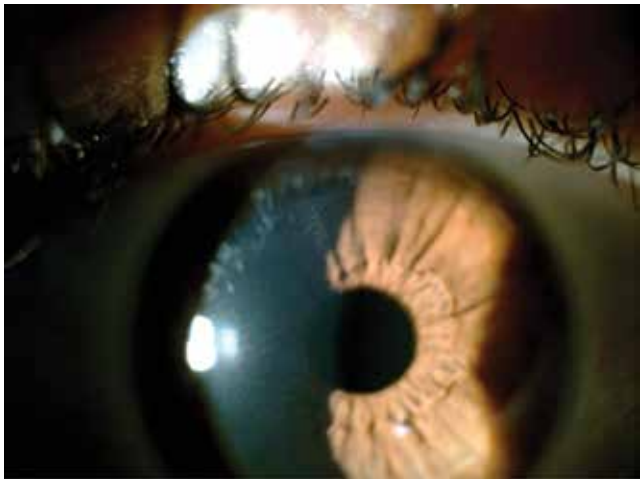

Figure 3. Postoperative 1-month photograph of eye that had intraoperative tearing of the side cut; metallic particles beneath the side cut and healed tear are visible

in a randomly selected eye of 144 patients and followed them for 3 months. Forty percent of patients had a VA better than 0.1 logMAR at postoperative day 1, compared to 73% of patients at 3 months. CVA ranged from -0.01 logMAR to -0.03 logMAR. One patient gained 2 rows, 24 patients gained 1 row, and 6 patients lost 1 row of VA. The patients' mean SE was -7.18±1.57 D preoperatively and reached -0.09±0.5 D by final follow-up examination. Final refraction values were within ±0.50 D in 77% of patients and within ±1.00 D in 95%. Ivarsen et al.[6] evaluated the 3-month CVA results in 1,547 patients who had SMILE in both eyes. The patients' mean SE was -7.25±1.84 D preoperatively and their postoperative refraction was -0.09±0.5 D. After 3 months, CVA was better or the same in 86% of patients. A loss of more than 2 rows was observed in 1.5% of the patients. The refractive and visual outcomes found in our study are consistent with those reported in these short-term studies.

Study Limitations

A recent study by Pedersen et al.[7] evaluating the 3-year results of SMILE in high-myopic patients revealed a mean SE of -7.30±1.40 D preoperatively, -0.30±0.50 D at postoperative 3 months and 0.40±0.60 D at postoperative 36 months. At the end of the 3-year follow-up period, 78% of their patients had an SE within ±0.50 D and 90% within ±1.00 D. This large study demonstrated that postoperative CVA continued to improve for 3 years after the procedure. Similarly, we observed that CVA was significantly higher in postoperative follow-up examinations compared to preoperative values. Pedersen et al.[7] proposed restructuring of the corneal stroma, neural adaptation or the reduction of corneal haze over time as possible explanations for this phenomenon. The small number of cases in our study may also have negatively impacted our statistical evaluation.

Increases in corneal HOA adversely influence visual outcomes due to glare, halo and reduced contrast sensitivity.[7] Corneal refractive surgery is known to increase corneal HOA.[12] Many studies have analyzed changes in corneal HOA following SMILE.[13,14] Sekundo et al.[13] performed SMILE in 10 myopic patients and evaluated corneal HOA occurring in the 5 mm pupillary zone over a 6-month follow-up period. Total HOA were 0.18 µm preoperatively and 0.21 µm postoperatively, which was not a statistically significant change.[13] Shah et al.[14] performed SMILE in 51 eyes of 41 patients and evaluated changes in ocular wavefront after 6 months. They found that total HOA increased significantly from 0.19 µm preoperatively to 0.32 µm at 6 months postoperatively (p=0.01). They also observed significant increases in coma (0.13 to 0.20 µm) and spherical aberrations (0.06 to 0.17 µm). In Pedersen et al.'s[7] evaluation of the 5 mm zone of high-myopic patients, they found a significant increase in corneal HOA postoperatively but showed that the amount of aberration decreased over the long term. They attributed this to corneal restructuring following SMILE. In the present study, we observed a significant increase in corneal HOA at postoperative 12 months. We believe the higher rate of HOA in our study compared to other studies may be related to our use of a 6 mm pupillary diameter.

Agca et al.[8] compared total corneal HOA between eyes in 20 patients who underwent SMILE in one eye and LASIK in the fellow eye. They found that total HOA, coma, spheric aberrations and trefoil aberrations were significantly increased in both groups at the end of follow-up. We also observed significantly higher total HOA, coma, trefoil and spheric aberrations at postoperative 12 months.

This increase in HOA may be a result of the composition of our study group, which included patients with high myopia, or the fact that treatment did not involve wavefront-based correction.

Many intra- and postoperative complications have been reported for the SMILE procedure.[6] These include abrasion at the incision site, tears, difficulty extracting the lenticule, cap perforation and foreign bodies in the interface. No sight-threatening complications occured in our study. In 1 eye of 1 patient, a 1 mm tear occured in the sidecut while removing the lenticule and metallic particles from the surgical spatula were later detected in the interface near the sidecut. None of the patients exhibited corneal ectasia in the 2-year follow-up period.

Some limitations of this study were the retrospective collection of data by chart review, a small patient population, not comparing the results of high-myopic patients to those with low or moderate myopia, and not comparing SMILE with other procedures (LASIK, phakic IOL, etc.) that can be applied in high myopia.

Conclusion

In this study we have demonstrated that correcting high myopia with SMILE is safe and effective in the long-term, but the procedure significantly increases corneal HOA.

Ethics

Ethics Committee Approval: The study were approved by the Beyoğlu Eye Training and Research Hospital Local Ethics Committee (retrospective study, protocol number: 15), Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ahmet Demirok, Alper Ağca, Concept: Yusuf Yıldırım, Cengiz Alagöz, Design: Yusuf Yıldırım, Engin Bilge Özgürhan, Data Collection or Processing: Abdülvahit Demir, Onur Ölçücü, Mehmet Özveren, Analysis or Interpretation: Alper Ağca, Cengiz Alagöz, Literature Search: Onur Ölçücü, Yusuf Yıldırım, Abdülvahit Demir, Writing: Yusuf Yıldırım.

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

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References

1. Soong HK, Malta JB. Femtosecond lasers in ophthalmology. Am J Ophthalmol. 2009;147:189-197.
2. Kim P, Sutton GL, Rootman DS. Applications of the femtosecond laser in corneal refractive surgery. Curr Opin Ophthalmol. 2011;22:238-244.
3. Vestergaard AH, Grauslund J, Ivarsen AR, Hjortdal JO. Efficacy, safety, predictability, contrast sensitivity, and aberrations after femtosecond laser lenticule extraction. J Cataract Refract Surg. 2014;40:403-411.
4. Lin F, Xu Y, Yang Y. Comparison of the visual results after SMILE and femtosecond laser-assisted LASIK for myopia. J Refract Surg. 2014;30:248-254.
5. Hashemi H, Miraftab M, Asgari S. Comparison of the visual outcomes between PRK-MMC and phakic IOL implantation in high myopic patients. Eye (Lond). 2014;28:1113-1118.
6. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology. 2014;121:822-828.
7. Pedersen IB, Ivarsen A, Hjortdal J. Three-Year Results of Small Incision Lenticule Extraction for High Myopia: Refractive Outcomes and Aberrations. J Refract Surg. 2015;31:719-724.
8. Agca A, Demirok A, Cankaya KI, Yasa D, Demircan A, Yildirim Y, Ozkaya A, Yilmaz OF. Comparison of visual acuity and higher-order aberrations after femtosecond lenticule extraction and small-incision lenticule extraction. Cont Lens Anterior Eye. 2014;37:292-296.
9. Lin F, Xu Y, Yang Y. Comparison of the visual results after SMILE and femtosecond laser-assisted LASIK for myopia. J Refract Surg. 2014;30:248-254.
10. Vestergaard AH, Grauslund J, Ivarsen AR, Hjortdal JO. Efficacy, safety, predictability, contrast sensitivity, and aberrations after femtosecond laser lenticule extraction. J Cataract Refract Surg. 2014;40:403-411.
11. Vestergaard A, Ivarsen AR, Asp S, Hjortdal JO. Small-incision lenticule extraction for moderate to high myopia: Predictability, safety, and patient satisfaction. J Cataract Refract Surg. 2012;38:2003-2010.
12. Moreno-Barriuso E, Lloves JM, Marcos S, Navarro R, Llorente L, Barbero S. Ocular aberrations before and after myopic corneal refractive surgery: LASIK-induced changes measured with laser ray tracing. Invest Ophthalmol Vis Sci. 2001;42:1396-1403.
13. Sekundo W, Kunert K, Russmann C, Gille A, Bissmann W, Stobrawa G, Sticker M, Bischoff M, Blum M. First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results. J Cataract Refract Surg. 2008;34:1513-1520.
14. Shah R, Shah S, Sengupta S. Results of small incision lenticule extraction: All-in-one femtosecond laser refractive surgery. J Cataract Refract Surg. 2011;37:127-137.

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Original Article

Posterior Capsular Opacification in Preschool- and School-Age Patients after Pediatric Cataract Surgery without Posterior Capsulotomy

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**Ondokuz Mayıs University Faculty of Medicine, Department of Ophthalmology, Samsun, Turkey

Summary

Objectives: We aimed to evaluate the development of posterior capsular opacification (PCO) in preschool- and school-age children with cataract who underwent cataract surgery without posterior capsulotomy and anterior vitrectomy.

Materials and Methods: The records of 30 eyes of 21 patients who underwent pediatric cataract surgery and intraocular lens (IOL) implantation were retrospectively reviewed. Patients' age, PCO status and duration, need for neodymium-doped yttrium aluminium garnet (Nd:YAG) laser treatment based on coverage of visual axis, and follow-up period were recorded.

Results: The mean age of the patients was 7.6±2.83 (4-12) years. Unilateral cataract surgery and IOL implantation were performed in 12 patients (57.14%) and bilateral cataract surgery and IOL implantation were performed in nine patients (42.86%). Average follow-up time was 17.7±22.67 (3-83) months. PCO developed in 21 eyes (70%) and covered the visual axis in 15 eyes (50%), which therefore required Nd:YAG laser posterior capsulotomy. The mean duration of postoperative PCO development was 8.91±18.7 months (1 week-71 months).

Conclusion: We believe that with adequately experienced surgeons, performing both cataract surgery and posterior capsulotomy with anterior vitrectomy in the same session is appropriate for selected preschool- and school-age children with cataract.

Keywords: Pediatric cataract, posterior capsular opacification, posterior capsulotomy

Introduction

Despite substantial improvements in cataract surgery techniques and intraocular lenses (IOLs), posterior capsular opacification (PCO) continues to be the most frequent postoperative complication of pediatric cataract surgery. Age is the main factor in PCO development, with the incidence increasing as age decreases. PCO development has been reported in up to 100% of infants after cataract surgery.[1]

Performing posterior capsulotomy and anterior vitrectomy in the same surgical session as cataract extraction is effective in preventing PCO obscuring the optical axis. However, in necessary cases and with cooperative patients, especially school-aged children whose posterior capsule is intact, neodymium-doped yttrium aluminium garnet (Nd:YAG) laser capsulotomy is another treatment option for PCO. In patients not suitable for laser therapy, anterior vitrectomy and posterior capsulotomy can be performed via the pars plana approach.[2,3,4]

Nd:YAG laser therapy has certain limitations, including transient intraocular pressure (IOP) elevation, high cost, limited access to the instruments, noncompliance with laser therapy in young children, need for general anesthesia and the high incidence of IOL damage. Furthermore, even in the absence of the posterior capsule, residual lens fibers may migrate to the intact vitreous surface and form secondary opaque membranes.[5]

Performing posterior capsulotomy and anterior vitrectomy in the same surgical session as cataract extraction also has some disadvantages. These include longer surgery time, requirement of more experience and skill on the part of the surgeon, vitreous loss, IOL dislocation, and higher rates of cystoid macular edema and retinal detachment.[2,3,4] As a result, surgeons face several questions. At what age should patients' posterior capsule be opened and when should it be left intact? At what age should posterior capsulotomy and anterior vitrectomy be performed together?

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In this study we aimed to evaluate PCO status and treatment required due to PCO obscuring the optical axis in patients 4-12 years of age who underwent pediatric cataract surgery without posterior capsulotomy or anterior vitrectomy.

Materials and Methods

The charts of pediatric patients who underwent cataract surgery and IOL implantation at Yüzüncü Yıl University Faculty of Medicine, Department of Ophthalmology (between 2006-2013, n=18) and Ondokuz Mayıs University Faculty of Medicine, Department of Ophthalmology (between 2012-2013, n=12) were analyzed retrospectively.

Patients whose operations did not include posterior capsulotomy and anterior vitrectomy, who were between 4 and 12 years old and had non-traumatic cataract were included in the study. Thirty eyes of 21 patients were included.

Retinoscopy, biomicroscopy and dilated fundus examinations were done preoperatively in some patients based on extent of cataract and postoperatively in all patients. Pre- and postoperative best corrected visual acuity (BCVA) of compliant patients was recorded (Snellen). The diopter, brand and implantation location was recorded for implanted IOLs. Cataract type was evaluated.

Surgical technique: The anterior chamber was accessed by clear corneal incision. After staining the anterior capsule with trypan blue, continuous anterior capsulotomy of 5-5.5 mm diameter was performed under viscoelastic. Two side ports were created. The lens material was aspirated using bimanual irrigation/aspiration handpieces. The IOL was implanted in the sulcus in 2 patients (6.67%) and in the capsule in the remaining patients. The corneal incision was widened in some patients to accommodate the implantation of polymethyl methacrylate (PMMA) IOLs. The viscoelastic in the anterior chamber and under the IOL was then aspirated using irrigation/aspiration and the corneal incision was sutured with 10-0 nylon. The procedure was concluded with diluted cefuroxime injection into the anterior chamber and subconjunctival dexamethasone injection.

After the procedure, patients used 1% prednisolone drops 8 times a day, ofloxacin drops 8 times a day, 1% cyclopentolate drops twice a day and systemic 1 mg/kg methylprednisolone for 3 days. Topical drops were tapered and discontinued within 1 month. Postoperative follow-up examinations were done at 1 day, 1 week, 1 month, and 3 months after the procedure, and thereafter at fixed intervals determined based on the patient's condition. PCO development, PCO duration, need for Nd:YAG laser therapy due to optical axis obscuration and follow-up time were recorded at follow-up visits.

Results

Mean age of the patients was 7.6±2.83 (4-12) years. Twelve (57.14%) of the patients had unilateral cataract surgery (6 right, 6 left eyes) and 9 patients (42.86%) had bilateral cataract surgery. Cataract types are given in Table 1.

Mean power of implanted IOLs was 24.67±6.11 (8-31) diopters.

PCO developed in 21 eyes (70%) and obscured the optic axis to an extent that required capsulotomy by Nd:YAG laser in 15 eyes (50%). IOL types and PCO status are shown in Table 2.

Mean follow-up time was 17.7±22.67 (3-83) months. Postoperative time to PCO development was 8.91±18.7 months (1 week-71 months).

Preoperative visual acuity could not be determined in 6 patients (20%). Pre- and postoperative BCVA values are shown in Table 3.

Discussion

Pediatric cataract is one of the leading causes of preventable blindness in children. As visual development is ongoing in children, pediatric cataracts do not only impact vision but also impair normal visual development, leading to amblyopia, strabismus or nystagmus.[6] Children are particularly susceptible to amblyopia in the first 2-3 years of life. There is a better chance of successfully treating amblyopia that develops after the age of 4. The critical period is considered to continue until 6-12 years of age, though this period may vary for different visual functions.[7]

There are several factors that affect the incidence of PCO development after pediatric cataract surgery. These factors include surgical age, accompanying ocular pathologies, extent of cortex clearance, surgical management of the posterior capsule and anterior vitreous, IOL parameters (design, material and location) and surgical trauma.[5]

Table 1. Distribution of cataract types [n, (%)]

Posterior polar	10 (33.34%)
Nuclear	7 (23.34%)
Lamellar	6 (20%)
Nuclear and cortical	5 (16.67%)
Posterior polar and punctate (blue dot)	2 (6.67%)

Table 2. Types of intraocular lens implanted and posterior capsular opacification status [n (%)]

IOL type	Number implanted	PCO status
Hydrophobic acrylic (AcrySof, Alcon)	15 (50%)	6 (40%)
Polymethyl methacrylate (BAL, Hanita)	5 (16.66%)	5 (100%)
Acrylic (Sensar, AMO)	5 (16.66%)	5 (100%)
Hydrophilic-coated hydrophobic (Acriva, VSY)	5 (16.66%)	5 (100%)

IOL: Intraocular lens, PCO: Posterior capsular opacification

Table 3. Pre- and postoperative best corrected visual acuity levels (Snellen)

	Preoperative BCVA [n (%)]	Postoperative BCVA [n (%)]
0.1 or lower	11 (36.67%)	4 (13.33%)
0.2-0.5	13 (43.33%)	14 (46.67%)
0.5-1.0	0	12 (40%)

BCVA: Best corrected visual acuity

Ensuring a clear visual axis after pediatric cataract surgery is crucial for good visual acuity results. In young children, the inflammatory response is very intense and the visual axis may be obscured by fibrous membranes proliferating on the intact anterior vitreous surface.[5] Opacification obscuring the visual axis is a common postoperative complication of pediatric cataract surgery. The rate of PCO development can reach 100% in children younger than 4 years old when the posterior capsule is intact.[1]

Various surgical procedures are utilized to prevent PCO. Opacity in the optic axis has been reported in up to 60% of patients who had primary posterior capsulotomy without anterior vitrectomy.[8,9] Some researchers have reported the lens epithelial cells and their remnants formed a basis for proliferation on the anterior hyaloid surface.[10] Opacity in the optic axis has been reported at rates less than 20% when anterior vitrectomy and posterior capsulotomy are performed together with cataract surgery.[4,11,12] Despite anterior vitrectomy, this opacity arose due to insufficient posterior capsule opening and anterior vitrectomy.[11]

Another technique used to prevent PCO is optic capture, in which the IOL haptics are positioned inside the capsule after the primary posterior capsulotomy (with or without anterior vitrectomy), thus fixing the optics posterior to the capsule. This prevents the proliferation of lens epithelial cells on the anterior vitreous surface. However, lens epithelial cells may migrate from the IOL haptic-optic junction and proliferate on the posterior of the capsule and the IOL surface. Therefore, this technique may also fail to completely prevent secondary membrane development.[5]

Gimbel et al.[13] expressed concerns that performing vitrectomy in the eyes of children negatively impacts ocular development. However, anterior vitrectomy should be performed with primary posterior capsulotomy in infants and young children due to the risk of amblyopia and high PCO incidence. For older children, Nd:YAG laser capsulotomy can be considered.[14]

There is no consensus on the age range within which posterior capsulotomy should be performed in the same surgical session as cataract extraction. Luo et al.[15] recommended up to the age of 5 years, Jensen et al.[2] recommended up to 6 years old, Vasavada et al.[5] up to 6 or 7 years old, and Guo et al.[16] up to 10 years old. Astle et al.[17] found that the PCO rate decreased with age from 70.8% in children less than 1 year old to 6.1% in children older than 7 years old. In practice, we generally perform posterior capsulotomy and anterior vitrectomy in our cataract surgeries for children younger than 6 years of age. However, in PCO cases we believe will cooperate with Nd:YAG laser treatment, we prefer performing cataract surgery without posterior capsulotomy.

In a study using acrylic IOLs (AcrySof) in children aged 2-16 years, PCO developed in 83.8% (27.7% requiring treatment) of patients that did not undergo posterior capsulotomy, 37.5% (7.5% requiring treatment) of patients that had posterior capsulotomy without vitrectomy, and 6.7% (treatment was not necessary) of patients that underwent both vitrectomy and posterior capsulotomy.[12] The authors also reported a significantly higher rate of PCO development in children 8 years old or younger compared with children over 8 years old (p=0.01).[12] In another study, 9 of 21 pediatric patients who underwent cataract surgery without posterior capsulotomy developed PCO and 7 of those patients required Nd:YAG laser therapy.[18]

Luo et al.[15] divided congenital cataract patients aged 2-5 years into 2 groups and determined PCO rate as 11.8% in the group that had posterior capsulotomy with vitrectomy versus 76.9% in the group that had cataract extraction. The rate of Nd:YAG laser capsulotomy was 2.9% and 57.7% in the groups, respectively.

Jafarinasap et al.[19] reported that of 9 patients aged 10-15 years who underwent lensectomy and posterior chamber IOL (Alcon AcrySof MA60 AC) implantation, 3 patients developed PCO but none required treatment, while none of the 8 patients that had anterior vitrectomy and posterior capsulotomy during lensectomy surgery developed PCO.

Aasuri et al.[20] implanted an acrylic IOL in one eye and a PMMA IOL in the fellow eye of bilateral cataract patients aged 5 years and older. Clinically significant PCO rates were reported in both the acrylic IOL group (21%) and the PMMA group (75%).

We consider the PCO rate determined in our study consistent with data from the published studies cited above. A limitation of our study was the lack of PCO development data from a group of patients that underwent posterior capsulotomy (and anterior vitrectomy) during their cataract surgery.

Although Nd:YAG laser capsulotomy is used to treat PCO safely and effectively, it is not without complications. There have been reports of serious complications such as retinal edema and retinal detachment as well as other complications like IOP elevation, vitreous prolapse, corneal damage, vitritis, pupil block, hyphema, and IOL damage and dislocation.[21]

Study Limitations

Limitations of Nd:YAG laser therapy include high cost, limited access to the instruments, noncompliance with laser therapy in young children, and the need for general anesthesia. Furthermore, even without the posterior capsule, residual lens fibers may migrate to the intact vitreous surface and form secondary opaque membranes. Hutcheson et al.[4] reported that visual axis obscuring opacity recurred at a rate of 57% after Nd:YAG laser capsulotomy and a third laser treatment was required in 17% of cases.

The inability to prevent PCO is the greatest difficulty faced by pediatric ophthalmologists worldwide. The development (for pediatric eyes) of medical antagonists against factors leading to PCO or capsule washing substances that reduce the speed and severity of lens epithelial cell proliferation would solve this problem.[14]

Conclusion

Young children have a high rate of PCO development, making cataract extraction with posterior capsulotomy (and anterior vitrectomy) appropriate for this age group. We believe that with adequately experienced surgeons, posterior capsulotomy and anterior vitrectomy should be performed in the same surgical session as cataract extraction in selected preschool- and school-age children.

Ethics

Ethics Committee Approval: The study were approved by the Van Yüzüncü Yıl University of Local Ethics Committee (protocol number: 10, date: 10.03.2015), Informed Consent: Not needed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tekin Yaşar, Muhammed Batur, Adem Gül, Concept: Muhammed Batur, Adem Gül, Design: Muhammed Batur, Adem Gül, Data Collection or Processing: Muhammed Batur, Adem Gül, Ertuğrul Can, Erbil Seven, Analysis or Interpretation: Tekin Yaşar, Muhammed Batur, Adem Gül, Literature Search: Muhammed Batur, Erbil Seven, Writing: Muhammed Batur.

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References

1. Spierer A, Desatnik H, Blumenthal M. Refractive status in children after long-term follow up of cataract surgery with intraocular lens implantation. J Pediatr Ophthalmol Strabismus. 1999;36:25-29.
2. Jensen AA, Basti S, Greenwald MJ, Mets MB. When may the posterior capsule be preserved in pediatric intraocular lens surgery? Ophthalmology. 2002;109:324-327.
3. Guo S, Wagner RS, Caputo A. Management of the anterior and posterior lens capsules and vitreous in pediatric cataract surgery. J Pediatr Ophthalmol Strabismus. 2004;41:330-337.
4. Hutcheson KA, Drack AV, Ellish NJ, Lambert SR. Anterior hyaloid face opacification after pediatric Nd:YAG laser capsulotomy. J AAPOS. 1999;3:303-307.
5. Vasavada AR, Praveen MR, Tassignon MJ, Shah SK, Vasavada VA, Vasavada VA, Van Looveren J, De Veuster I, Trivedi RH. Posterior capsule management in congenital cataract surgery. J Cataract Refract Surg. 2011;37:173-193.
6. Uzun A, Atilla H. Pediatrik katarakt kedeniyle opere edilen çocuklarda hayat kalitesi. Turk J Ophthalmol. 2013;43:156-160.
7. Koçak G, Duranoğlu Y. Ambliyopi ve tedavisi. Turk J Ophthalmol. 2014;44:228-236.
8. Morgan KS, Karcioglu ZA. Secondary cataracts in infants after lensectomies. J Pediatr Ophthalmol Strabismus. 1987;24:45-48.
9. Nishi O. Fibrinous membrane formation on the posterior chamber lens during the early postoperative period. J Cataract Refract Surg. 1988;14:73-77.
10. Jones NP, McLeod D, Boulton ME. Massive proliferation of lens epithelial remnants after Nd-YAG laser capsulotomy. Br J Ophthalmol. 1995;79:261-263.
11. Alexandrakis G, Peterseim MM, Wilson ME. Clinical outcomes of pars plana capsulotomy with anterior vitrectomy in pediatric cataract surgery. J AAPOS. 2002;6:163-167.
12. Vasavada AR, Trivedi RH, Nath VC. Visual axis opacification after AcrySof intraocular lens implantation in children. J Cataract Refract Surg. 2004;30:1073-1081.
13. Gimbel HV, Ferensowicz M, Raanan M, DeLuca M. Implantation in children. J Pediatr Ophthalmol Strabismus. 1993;30:69-79.
14. Medsinge A, Nischal KK. Pediatric cataract: challenges and future directions. Clin Ophthalmol. 2015;9:77-90.
15. Luo Y, Lu Y, Lu G, Wang M. Primary posterior capsulorhexis with anterior vitrectomy in preventing posterior capsule opacification in pediatric cataract microsurgery. Microsurgery. 2008;28:113-116.
16. Guo S, Wagner RS, Caputo A. Management of the anterior and posterior lens capsules and vitreous in pediatric cataract surgery. J Pediatr Ophthalmol Strabismus. 2004;41:330-337.
17. Astle WF, Alewenah O, Ingram AD, Paszuk A. Surgical outcomes of primary foldable intraocular lens implantation in children: understanding posterior opacification and the absence of glaucoma. J Cataract Refract Surg. 2009;35:1216-1222.
18. Er H, Doganay S, Evereklioglu C, Erten A, Cumurcu T, Bayramlar H. Retrospective comparison of surgical techniques to prevent secondary opacification in pediatric cataracts. J Pediatr Ophthalmol Strabismus. 2000;37:294-298.
19. Jafarinasab MR, Rabbanikhah Z, Karimian F, Javadi MA. Lensectomy and PCIOL Implantation with versus without posterior capsulotomy and anterior vitrectomy for pediatric cataracts. J Ophthalmic Vis Res. 2008;3:37-41.
20. Aasuri MK, Fernandes M, Pathan PP. Comparison of acrylic and polymethyl methacrylate lenses in a pediatric population. Indian J Ophthalmol. 2006;54:105-109.
21. Karahan E, Er D, Kaynak S. An Overview of Nd:YAG Laser Capsulotomy. Med Hypothesis Discov Innov Ophthalmol. 2014;3:45-50.

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Original Article

Bedside Diode Laser Photocoagulation Under Remifentanil Analgesia for Retinopathy of Prematurity: Early Structural Outcomes

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Summary

Objectives: To evaluate one-year structural outcomes of bedside diode laser photocoagulation with remifentanil analgesia for retinopathy of prematurity (ROP) and discuss clinical and demographic characteristics of infants and other possible risk factors that may affect the outcome.

Materials and Methods: The medical records of premature infants who were treated with bedside transpupillary diode laser photocoagulation under remifentanil analgesia for ROP were evaluated for clinical and demographic characteristics, accompanying systemic risk factors, laser parameters, complications of treatment, retreatment rate and one-year structural outcomes.

Results: One-hundred and ninety-five eyes of 99 infants (59 males, 40 females) were recruited for the study. The mean gestational age and birth weight were 27.4±2.3 weeks (23-34) and 1003.3±297.8 g (570-2250), respectively. Laser therapy was performed for high-risk prethreshold ROP in 66.2% of eyes, aggressive posterior ROP (APROP) in 15.4% and threshold ROP in 18.4%. The mean number of laser spots was 1510.4±842.1 per laser session. No adverse effects of laser photocoagulation were observed except small lens opacities in two eyes and corneal opacity in one eye. Retreatment was needed in only three eyes, and vitreoretinal surgery was needed in six eyes of six patients despite laser treatment. Anatomic outcome was favorable in 189 eyes (96.9%) at the end of a 1-year follow-up. Presence of dilated and tortuous iris vessels (p=0.002) and tunica vasculosa lentis (p=0.009) along with type of ROP (APROP and stage 4a ROP at initial presentation) (p=0.001) were associated with poor anatomical outcome.

Conclusion: Accurate and timely bedside transpupillary diode-laser photocoagulation under remifentanil analgesia is an effective and safe treatment modality for ROP, and may prevent vision-threatening retinal detachment and reduce the need for vitreoretinal surgery.

Keywords: Laser photocoagulation, remifentanil, retinopathy of prematurity

Introduction

Approximately 25,000 low birth weight babies are born each year in Turkey, and about 1,000 of these babies are at high risk of blindness.[1,2] Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy arising from the avascular retina in premature neonates. Low gestational age and low birth weight are known to be the main risk factors of ROP.[3] Previous studies have reported the effect of various factors in the development of ROP, including prolonged mechanical ventilation, excessive oxygen use, bronchopulmonary dysplasia, surfactant treatment, apnea, anemia, blood transfusion, sepsis, hyperbilirubinemia, intraventricular hemorrhage, candidemia, maternal preeclampsia, maternal diabetes, multiples pregnancy, and chorioamnionitis.[4,5] Whether these factors are truly independent risk factors leading to ROP or emerge secondarily to already existing prematurity remains controversial. With the increasing use of assisted conception techniques, multiples pregnancy and premature birth rates are rising. Advances in premature neonatal care have greatly

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increased survival rates among very low birth weight infants, but the high comorbidity rates in these infants has made ROP a serious health issue, particularly in developing nations. Despite improvements in diagnosis and treatment, ROP continues to be one of the leading causes of childhood blindness in developing countries.[6] The aim of ROP screening examinations is to prevent blindness through timely detection and appropriate treatment of high-risk patients.[7]

ROP treatment protocols are created based on the multi-center cryotherapy (CRYO)-ROP and Early Treatment for Retinopathy of Prematurity (ETROP) studies.[8,9] In the CRYO-ROP study, cryoablation of the entire avascular retina was recommended for patients with threshold disease.[8] It was later thought that treating threshold disease may be too late, and the ETROP study evaluated laser photocoagulation of the avascular retina in patients with high-risk prethreshold disease (zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; zone II, stage 2 or 3 ROP with plus disease).[9] The ETROP study reported treatment of prethreshold disease reduced unfavorable functional outcomes from 19.5% to 14.5% and unfavorable structural outcomes from 15.6% to 9.1%. Thus, laser photocoagulation of the entire retinal avascular field at the high-risk prethreshold stage is currently accepted as the safest and most effective approach. Laser photocoagulation is usually performed in operating room conditions under general anesthesia. However, in cases where general anesthesia cannot be used or the associated risks should be avoided, laser photocoagulation can be performed in the neonatal intensive care unit under alternative anesthesia methods.[10,11,12]

In the present study we analyzed the records of premature infants with ROP treated by transpupillary diode laser photocoagulation under remifentanil analgesia in the neonatal intensive care unit in order to present 1-year anatomic outcomes and discuss the probable impact of clinical and demographic characteristics on those outcomes.

Materials and Methods

After receiving approval from the ethics committee, the medical records of 99 premature babies who were diagnosed with ROP and underwent transpupillary 810 nm diode laser photocoagulation under remifentanil in the neonatal intensive care unit between October 2010 and September 2012 were analyzed retrospectively. The study group included both neonates born and followed in our hospital and neonates admitted to the neonatal intensive care unit of our hospital for treatment following ROP diagnosis at other centers. The following data were recorded for all patients: ROP stage before treatment; anterior segment findings such as tunica vasculosa lentis and iris vascular dilation and tortuosity, detected by a portable, handheld biomicroscope (XL-1, Shin-Nippon, Japan); timing of laser treatment and laser settings used; treatment response and retina examination findings at 1 year. Patients with attached retina and without optic disc shrinkage or tractional membranes were categorized as group 1; patients with retinal detachment, optic disc shrinkage and/or tractional membranes were categorized as group 2. Furthermore, the patients' records were analyzed for the presence of neonatal and maternal risk factors such as gestational age, birth weight, APGAR scores at 1 and 5 minutes, mode of delivery, gender, multiples pregnancy, preeclampsia, maternal diabetes, early membrane rupture, placenta ablatio, blood transfusion, clinical sepsis, respiratory distress syndrome, necrotizing enterocolitis, intracranial hemorrhage, hydrocephaly, and assisted conception techniques.

Prior to treatment, 2.5% phenylephrine (Mydfrin®, Alcon, USA) and 0.5% tropicamide (Tropamid®, Bilim İlaç, Turkey) eye drops were instilled 3 times at 10 minute intervals. The patients were sedated using 0.1 mg/kg midazolam administered by intravenous bolus by a neonatal specialist and intubated. Intravenous infusion of 0.2 to 0.6 µg/kg/min remifentanil was performed under the supervision of a neonatal specialist while monitoring life signs and level of analgesia. After achieving sufficient pupil dilation and sedoanalgesia, 0.5% proparacaine hydrochloride (Alcaine®, Alcon, USA) was instilled immediately before laser treatment as local anesthesia. Panretinal photocoagulation was applied with a 810 nm diode laser (Iridex, Oculight SL, USA) to the entire avascular zone leaving half-spot intervals (200-400 mW power; 0.2-0.3 second exposures). In eyes with stage 4a ROP, the laser was also applied twice to the vascular area posterior to the detachment. The laser photocoagulation procedure was performed while monitoring life parameters in the presence of a neonatal specialist. None of the patients developed any anesthesia-related problems which complicated the laser treatment.

SPSS for Windows version 21.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) software was used for statistical analyses. Student's t test, Mann-Whitney U test and Wilcoxon test were used in comparison of the variables. Normality of data distribution was determined by Kolmogorov-Smirnov test. Descriptive statistics were expressed as frequency and percent for qualitative data, as mean ± standard deviation for quantitative data with normal distributions and median (minimum-maximum) for non-normal distributions. Results with p values less than 0.05 were accepted as statistically significant.

Results

The medical records of 99 neonates were retrospectively analyzed. Fifty-nine (59.6%) patients were male and 40 (40.4%) were female. Mean gestational age was 27.4±2.3 (23-34) weeks and mean birth weight was 1,003.3±297.8 (570-2,250) g. Gestational age was 28 weeks or less for 74 patients (74.7%), 29-32 weeks for 20 (20.2%) and over 32 weeks for 5 (5.1%). The mean age was 26.17±1.50 weeks in the 18 neonates who underwent laser therapy for aggressive posterior ROP (APROP) and 27.69±2.40 weeks in the other neonates (p=0.001). Gestational age was 837.2±170.4 g in the neonates with APROP and 1040.2±308.1 g in the others (p=0.008).

A total of 195 eyes of 99 neonates were laser treated (bilaterally in 96 patients, unilaterally in three patients) at mean postmenstrual 36.9±2.3 (33-43) weeks, at a mean chronological age of 66.9±18.9 (20-110) days; a mean of 1,510.4±842.1 (381-5258) laser pulses were applied at half-spot intervals to the entire avascular retina. Laser therapy was applied in 129 eyes (66.2%) at the high-risk prethreshold disease stage as per the ETROP study, 30 eyes (15.4%) with threshold disease as per the CRYO-ROP study, and in 36 eyes (18.4%) with APROP. We observed that there were differences in treatment indications and that in some patients, treatment delay was a result of delayed referral to our clinic from other medical centers. In the 6 eyes that presented with stage 4a disease limited to 2-3 clock hours, an additional 2 laser applications were applied to the ridge tissue behind the vascular retina. Mean regression time of ROP after laser therapy was 4.5±1.8 (3-10) weeks. A second session of laser treatment was done a mean 9.0±5.3 days (5-15 days) later for 3 patients due to insufficient treatment response and/or untreated areas. Anterior segment complications occured in 3 eyes (small lens opacity in 2 eyes, corneal opacity in 1 eye) after laser therapy.

Retinal attachment was observed in 189 (96.9%) of the laser-treated eyes for the 1-year follow-up period (group 1). Six eyes (3.1%) were referred to another center for vitreoretinal surgery due to retinal detachment (group 2; 2 eyes with new detachment following APROP, 3 eyes with stage 4a disease detachment not resolved by laser therapy). Patients with unfavorable anatomic outcomes had lower average birth weights and gestational ages, higher chronologic and postmenstrual ages at time of laser application, and lower APGAR scores at 1 and 5 minutes, but these differences were statistically nonsignificant (Table 1). APROP, delayed laser treatment (stage 4a), tunica vasculosa lentis prior to treatment, and iris vascular dilation/tortuosity emerged as significant risk factors for unfavorable anatomic outcomes (p=0.001, p=0.001, p=0.009, p=0.002, respectively). APROP

Table 1. Comparison of selected clinical characteristics of patients in group 1 and group 2

	Group 1	Group 2	p value
Birth weight (g)	1005.5±294.0 (570-2250)	968.3±383.0 (650-1690)	0.768
Gestational age (weeks)	27.4±2.3 (23-34)	26.8± 3.2 (24-33)	0.532
Chronological age at laser treatment (days)	66.3±18.2 (20-110)	74.5±28.4 (50-110)	0.518
Postmenstrual age at laser treatment (weeks)	36.8±2.3 (33-43)	37.3±3.0 (34-40)	0.627
APGAR score at 1 min	4.3±1.1 (2-7)	4.2±1.2 (3-6)	0.777
APGAR score at 5 min	7.1±1.1 (5-10)	6.8±1.3 (5-9)	0.449

Table 2. Comparison of selected clinical and demographic characteristics of patients in group 1 and group 2

		Group 1	Group 2	p value
Gestational age (weeks)	≤28	69 (93.2%)	5 (6.8%)	0.249
	29-32	20 (100.0%)	0 (0.0%)	
	>32	4 (80.0%)	1 (20.0%)	
Birth weight (g)	≤ 1,000	53 (93.0%)	4 (7.0%)	0.380
	1,001-1,500	34 (97.1%)	1 (2.9%)	
	>1,500	6 (85.7%)	1 (14.3%)	
Retinopathy of prematurity before laser treatment	Comorbid disease*	12 (80.0%)	3 (20.0%)	**0.001****
	High-risk comorbid diseases	66 (100.0%)	0 (0.0%)	
	APROP	15 (83.3%)	3 (16.7%)	
Gender	Male	54 (91.5%)	5 (8.5%)	0.397
	Female	39 (97.5%)	1 (2.5%)	
Multiples pregnancy	Dizygotic	17 (100.0%)	0 (0.0%)	0.586
	Monozygotic	76 (92.7%)	6 (7.3%)	
Mode of birth	Cesarean section	61 (95.3%)	3 (4.7%)	0.663
	Normal vaginal	32 (91.4%)	3 (8.6%)	
Laser applications	1	91 (94.8%)	5 (5.2%)	0.173
	2	2 (66.7%)	1 (33.3%)	
Anterior segment complications after laser	(+)	3 (100.0%)	0 (0.0%)	1.000
	(-)	90 (93.8%)	6 (6.2)	

*Six patients had stage 4a disease prior to laser treatment, **p<0.005, APROP: Aggressive posterior retinopathy of prematurity

was observed in all 6 neonates with abnormal anterior segment findings like tunica vasculosa lentis and iris vascular dilation and tortuosity; of these, 3 eyes of 3 patients required vitreoretinal surgery due to new retinal detachment. The relationships between other neonatal and maternal risk factors and anatomic outcomes at 1-year follow-up are shown in detail in Tables 2 and 3.

Discussion

The method currently accepted as safest and most effective for the management of ROP is laser photocoagulation of the entire retinal avascular field at the high-risk prethreshold stage. The procedure is traditionally performed in an operating room under general anesthesia and yields favorable anatomic outcomes at high rates when applied appropriately and in a timely manner. In the present study, we found that anatomic success at 1 year was achieved in 96.9% of eyes that underwent laser photocoagulation of the avascular field performed in the neonatal intensive care unit under sedoanalgesia with remifentanil.

Table 3. Comparison of neonatal and maternal risk factors of patients in group 1 and group 2

		Group 1	Group 2	p value
Increased iris vascular dilation and tortuosity	(+)	3 (50.0%)	3 (50.0%)	**0.002***
	(-)	90 (96.8%)	3 (3.2%)	
Tunica vasculosa lentis	(+)	6 (66.7%)	3 (33.3%)	**0.009***
	(-)	87 (96.7%)	3 (3.3%)	
Assisted conception	(+)	9 (100.0%)	0 (0.0%)	1.000
	(-)	84 (93.3%)	6 (6.7%)	
Early membrane rupture	(+)	8 (88.9%)	1 (11.1%)	0.444
	(-)	85 (94.4%)	5 (5.6%)	
Placenta ablatio	(+)	2 (100.0%)	0 (0.0%)	1.000
	(-)	91 (93.8%)	6 (6.2%)	
Maternal preeclampsia	(+)	6 (100.0%)	0 (0.0%)	1.000
	(-)	87 (93.5%)	6 (6.5%)	
Maternal diabetes	(+)	1 (100.0%)	0 (0.0%)	1.000
	(-)	92 (93.9%)	6 (6.1%)	
Respiratory distress syndrome	(+)	80 (94.1%)	5 (5.9%)	1.000
	(-)	13 (92.9%)	1 (7.1%)	
Blood transfusion	(+)	53 (94.6%)	3 (5.4%)	1.000
	(-)	40 (93.0%)	3 (7.0%)	
Clinical sepsis	(+)	30 (93.7%)	2 (6.3%)	1.000
	(-)	63 (94.0%)	4 (6.0%)	
Intracranial hemorrhage	(+)	6 (100.0%)	0 (0.0%)	1.000
	(-)	87 (93.5%)	6 (6.5%)	
Necrotizing enterocolitis	(+)	9 (90.0%)	1 (10.0%)	0.481
	(-)	84 (94.4%)	5 (5.6%)	
Hydrocephaly	(+)	3 (100.0%)	0 (0.0%)	1.000
	(-)	90 (93.8%)	6 (6.2%)	

*p<0.005

The growing number of neonatal intensive care facilities have led to higher rates of various complications associated with prematurity, especially ROP.[6] Low birth weight and gestational age are the main risk factors for ROP.[5] For this reason, international screening guidelines generally recommend screening neonates born at a gestational age less than 32 weeks or birth weight under 1,500 g.[13] However, particularly in developing nations, older neonates have also been reported to develop ROP which may require treatment due to less than ideal neonatal intensive care conditions.[14,15,16,17] In our study, 5 neonates (3.9%) with gestational ages over 32 weeks required laser treatment, and 1 neonate born at 33 weeks developed retinal detachment despite laser treatment. Therefore, it is important that screening programs be designed according to local conditions and that screening also include neonates at gestational ages over 32 weeks who have additional risk factors or are indicated for screening by a neonatal specialist.

The conventional treatment for ROP is laser photocoagulation of the avascular retinal fields performed under general anesthesia in operating room conditions. In some cases, however, general anesthesia cannot be used or the associated risks should be avoided, such as in the absence of an anesthesiologist experienced in neonatal anesthesia or in patients with concomitant systemic conditions. In such cases, laser photocoagulation can be applied in the neonatal intensive care unit using alternative means of anesthesia.[10,11,12] Especially in developing countries, ROP screening examinations are usually performed in obstetric and gynecologic hospitals, which may not always have an anesthesiologist experienced in neonatal anesthesia. When general anesthesia is not applicable, patients are referred to other centers which are able to administer general anesthesia for urgent treatment of ROP. However, disease progression during the time required to transfer the patient decreases the chance of favorable treatment outcomes. Three of the infants that required vitreoretinal surgery due to retinal detachment were not able to receive treatment before the disease reached stage 4a. This demonstrates how serious the consequences of delaying treatment during the process of referring patients to other centers can be. Furthermore, 1 of these 3 infants was born at a gestational age of 33 weeks and a birth weight of 1,690 g, illustrating that delayed treatment can result in irreparable damage even in infants that are not considered high-risk. Even when institutional conditions permit the use of general anesthesia, an infant's general condition may deteriorate while being transferred from the neonatal intensive care unit to the operating room, and extubation takes time following general anesthesia. Laser therapy for ROP is generally performed between postnatal weeks 6 and 8; for a premature infant who has been very recently extubated, postsurgical extubation will also take time. As a result, laser therapy is increasingly performed under topical anesthesia and sedation as an alternative to general anesthesia. For all these reasons, we also conduct laser photocoagulation therapy in the neonatal intensive care unit under the guidance of a neonatal specialist, without giving general anesthesia. Although general anesthesia may be ideal in terms of keeping the infant

motionless and thus facilitating laser application, performing laser therapy under remifentanil analgesia provides anatomic success without causing any lasting systemic complications.

Remifentanil is an ultra short-acting synthetic opoid analgesic drug. Its rapid plasma clearance, rapid effect onset and cessation as soon as the infusion is stopped make it suitable for use in premature infants.[11,12] Sammartino et al.[11] reported that performing laser therapy under remifentanil infusion provided optimal surgery stress control with no side effects and found that premature infants were able to return quickly to preoperative respiratory function. A study analyzing premature infants' pain scales showed that the infants did not experience any severe pain during laser application under remifentanil anagesia.[12] The authors of that study reported transient hypotension and bradycardia in 2 of the 64 infants treated for ROP with laser therapy under remifentanil infusion; the remaining infants experienced no side effects associated with anesthesia. They concluded that this procedure is effective, reliable and practical in hospitals where access to pediatric anesthesiologists is limited. Our retrospective chart review of infants who underwent laser therapy under remifentanil analgesia did not include analysis of the effectiveness or side effects of this anesthesia method. However, there were no incidences of anesthesia-related difficulties with laser application.

In the present study, we found that anatomic success at 1 year was achieved in 96.9% of eyes that underwent laser photocoagulation of the avascular field performed in the neonatal intensive care unit under sedoanalgesia with remifentanil. However, due to possible refractive errors, anisometropia, strabismus, late-stage retinal tears and detachment as well as cortical causes, functional success rates may not be as high as anatomic success rates. In the current study we present only anatomic outcomes because other factors which may influence functional success, such as refractive errors and strabismus, were not analyzed. Another limitation of the study is the small number of patients requiring vitreoretinal surgery due to retinal detachment. A study including a larger patient group may reveal different risk factors statistically associated with retinal detachment.

APROP has poor prognosis and is more difficult to treat than classic ROP. The extreme vascular activity of this disease results in a very high rate of unfavorable anatomic and functional outcomes.[18] Therefore, some researchers recommend early vitrectomy.[19,20] However, early vitrectomy is not currently a widely accepted practice. It was reported that off-label use of intravitreal bevacizumab injections with or before laser therapy positively influences prognosis and resulted in better outcomes than laser photocoagulation alone in zone I disease.[21] Regardless, as the possible side effects and long-term safety of intravitreal therapies in premature infants still in early development are not known, they should be used with caution.

Conclusion

In conclusion, we achieved a high rate of anatomic success at postoperative 1 year by performing laser photocoagulation therapy in the neonatal intensive care unit under sedoanalgesia with midazolam and remifentanil. The main risk factors for unfavorable anatomic outcomes were APROP, delayed laser therapy (stage 4a) and abnormal anterior segment findings such as tunica vasculosa lentis or increased iris vascular dilation and tortuosity prior to treatment. Despite satisfactory anatomic outcomes at 1 year, desired functional outcomes may not be achievable due to various reasons including refractive errors, anisometropia, strabismus, cortical causes, and late-stage retinal tears and detachment.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Beyza Özcan, Ahmet Yağmur Baş, Nihal Demirel, Concept: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Design: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Data Collection or Processing: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Analysis or Interpretation: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Beyza Özcan, Ahmet Yağmur Baş, Nihal Demirel, Jale Karakaya, Literature Search: Mehmet Ali Şekeroğlu, Emre Hekimoğlu, Beyza Özcan, Writing: Mehmet Ali Şekeroğlu.

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References

1. Yurdakök M. Ülkemizde yenidoğan bebek sağlığı sorunu ve öneriler. Türk Neonatoloji Derneği Bülteni. 2008;18:5-9.
2. Ergenekon E, Turan Ö, Özdek Ş, Hirfanoğlu İ, Bozkaya D, Önal E, Türkyılmaz C, Koç E, Atalay Y. Türkiye'de prematüre retinopatisi sıklığının durumu. Çocuk Sağlığı ve Hastalıkları Dergisi. 2010;53:4-9.
3. Hartnett ME. Pathophysiology and mechanisms of severe retinopathy of prematurity. Ophthalmology. 2015;122:200-210.
4. Miller MM, Revenis ME, Lai MM, Meleth AD, Jeffress ES, Carrera A, Cheng YI, Sill AM, McCarter R. Risk and clinical course of retinopathy of prematurity in 78 infants of gestational age 22-25 weeks. J AAPOS. 2014;18:266-270.
5. Özcan E, Yenice Ö, Kozakoğlu H, Bavbek T, Toker E, Özek E. Prematüre Retinopatisi Gelişiminde Etkili Risk Faktörleri ve Tarama Sonuçları. Ret-Vit. 2006;14:127-132.
6. Sommer A, Taylor HR, Ravilla TD, West S, Lietman TM, Keenan JD, Chiang MF, Robin AL, Mills RP, Council of the American Ophthalmological S. Challenges of ophthalmic care in the developing world. JAMA Ophthalmol. 2014;132:640-644.
7. Quiram PA, Capone A, Jr. Current understanding and management of retinopathy of prematurity. Curr Opin Ophthalmol. 2007;18:228-234.
8. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Arch Ophthalmol. 1988;106:471-479.

9. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;123:991-999.
10. Sekeroglu MA, Hekimoglu E, Sekeroglu HT. Topical anesthesia for laser treatment of retinopathy of prematurity. Paediatr Anaesth. 2012;22:1224-1225.
11. Sammartino M, Bocci MG, Ferro G, Mercurio G, Papacci P, Conti G, Lepore D, Molle F. Efficacy and safety of continuous intravenous infusion of remifentanil in preterm infants undergoing laser therapy in retinopathy of prematurity: clinical experience. Paediatr Anaesth. 2003;13:596-602.
12. Demirel N, Bas AY, Kavurt S, Celik IH, Yucel H, Turkbay D, Hekimoglu E, Koc O. Remifentanil analgesia during laser treatment for retinopathy of prematurity: a practical approach in neonatal intensive care unit. Am J Perinatol. 2014;31:983-986.
13. Fierson WM, American Academy of Pediatrics Section on O, American Academy of O, American Association for Pediatric O, Strabismus, American Association of Certified O. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189-195.
14. Ugurbas SC, Gulcan H, Canan H, Ankarali H, Torer B, Akova YA. Comparison of UK and US screening criteria for detection of retinopathy of prematurity in a developing nation. J AAPOS. 2010;14:506-510.
15. Basmak H, Niyaz L, Sahin A, Erol N, Gursoy HH. Retinopathy of prematurity: screening guidelines need to be reevaluated for developing countries. Eur J Ophthalmol. 2010;20:752-755.
16. Sanghi G, Dogra MR, Katoch D, Gupta A. Aggressive posterior retinopathy of prematurity in infants >/= 1500 g birth weight. Indian J Ophthalmol. 2014;62:254-257.
17. Esen E, Erdem E, Yar K, Demircan N, Soylu M. Prematüre Retinopatisi Tarama Sonuçlarımız: İdeal Tarama Programı Nasıl Olmalı? Turk J Ophthalmol. 2014;44:42-46.
18. Kychenthal A, Dorta P, Katz X. Zone I retinopathy of prematurity: clinical characteristics and treatment outcomes. Retina. 2006;26:S11-15.
19. Azuma N, Ito M, Yokoi T, Nakayama Y, Nishina S. Visual outcomes after early vitreous surgery for aggressive posterior retinopathy of prematurity. JAMA Ophthalmol. 2013;131:1309-1313.
20. Nishina S, Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Azuma N. Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fundus fluorescein angiography. Ophthalmology. 2009;116:2442-2447.
21. Mintz-Hittner HA, Kennedy KA, Chuang AZ, Group B-RC. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603-615.

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Original Article

Clinical Features and Course of Patients with Peripheral Exudative Hemorrhagic Chorioretinopathy

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Summary

Objectives: To evaluate the clinical characteristics of patients who were followed in our clinic with the diagnosis of peripheral exudative hemorrhagic chorioretinopathy (PEHC).

Materials and Methods: Medical records of 12 patients who were diagnosed with PEHC in İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology between July 2006 and June 2014 were reviewed retrospectively.

Results: This study included 21 eyes of 12 patients. Four (33.3%) of the patients were male and 8 (66.7%) were female and ages ranged between 73 and 89 years. Eight (66.7%) of the patients were referred to us with the diagnosis of choroidal mass. Unilateral involvement was found in 3 and bilateral involvement in 9 patients. Temporal quadrants were involved in all eyes. Fifteen eyes (71.4%) had subretinal hemorrhage and hemorrhagic/serous retinal pigment epithelial detachment, 11 (52.4%) had lipid exudation, 5 (23.8%) had chronic retinal pigment epithelium alterations, 2 (9.5%) had subretinal fibrosis and 1 (4.8%) had vitreous hemorrhage. PEHC lesions were accompanied by drusen in 11 eyes (52.4%), geographic atrophy in 2 eyes (9.5%), and choroidal neovascularization scar in 2 eyes (9.5%). Treatment was done in both eyes of a patient for lesions which threatened the macula, in a patient with bilateral macular edema and in a patient with vitreous hemorrhage. The remaining eyes were followed-up without any treatment because the lesions did not threaten the macula and they showed no progression during follow-up.

Conclusion: PEHC is a degenerative disease of peripheral retina that is seen in older patients, and signs of age-related macular degeneration (AMD) may accompany this pathology. Especially in patients with AMD findings, the peripheral retina must be evaluated carefully for existing PEHC lesions.

Keywords: Hemorrhage, retinal pigment epithelial detachment, age-related macular degeneration

Introduction

Peripheral exudative hemorrhagic chorioretinopathy (PEHC) is a disease of the peripheral retina that emerges with advancing age. PEHC is characterized by exudation and hemorrhages and can often be mistaken for an intraocular mass.[1] In 1962, Reese and Jones[2] first reported patients who exhibited sub-retinal pigment epithelium (RPE) hematoma in the peripheral fundus and accompanying age-related macular degeneration (AMD). Silva and Brockhurst[3] described patients with a similar clinical picture and called the disease 'peripheral RPE hemorrhagic detachment'. In 1980, Annesley[4] named the condition of subRPE and/or subretinal hemorrhage with subretinal exudation as the term used today, 'PEHC'. PEHC is more common in older patients who are female and white.[5,6] Though the etiology of this pathology remains unclear, its defining features are peripheral subretinal and/or subRPE hemorrhage, exudation and retinal pigment epithelial detachment (PED), and the lesions are often located in the temporal quadrant.[5,6]

The disease is usually static or spontaneously regresses, leaving a fibrotic scar. However, lesions that progress from the periphery to the macula result in declines in visual acuity. Signs of AMD such as drusen, RPE alterations and choroidal neovascularization (CNV) may also accompany the disease.[5]

The aim of this study was to evaluate the clinical characteristics, follow-up and treatment outcomes of patients diagnosed with PEHC in our clinic.

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Materials and Methods

The medical records of patients diagnosed with PEHC between July 2006 and June 2014 in the İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology were analyzed retrospectively. PEHC diagnosis was based on the presence of subRPE and/or subretinal exudation or hemorrhage and/or the appearance of a mass in the extramacular peripheral retina. Patients with history of ocular trauma, intraocular inflammation or tumor and those with other systemic or ocular diseases which may cause retinal hemorrhage or exudation were not included in the study.

Data regarding age, gender, duration of symptoms, systemic diseases and medications used were recorded for all patients. Initial and final best corrected visual acuity (BCVA), anterior segment and fundus examinations, and intraocular pressure were evaluated. Patients with pronounced appearance of a mass were examined by ultrasonography (USG). Fundus photographs were taken. The presence of active PEHC lesions in both eyes was considered symmetric bilateral disease, while the presence of active disease in one eye and findings of RPE atrophy and sequelae in the peripheral retina of the fellow eye was considered asymmetric bilateral disease. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) were done in selected patients. The macula was evaluated by spectral domain optical coherence tomography (OCT).

The study was designed and conducted in accordance with the principles of the Declaration of Helsinki.

Data were analyzed by paired samples t-test using Statistics Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA) software. P values less than 0.05 were accepted as statistically significant.

Results

The patients' demographic and clinical characteristics are presented in Table 1. Of the 12 patients (21 eyes) included in the study, 4 (33.3%) were men and 8 (66.7%) were women. Mean age was 82.4 (range, 73-89) years. Mean follow-up time was 15.6 (range, 6-74) months. Eight patients (66.7%) were referred to our clinic with suspected choroidal mass. Mean duration of symptoms was 2.8 months (range, 1 week-12 months). The most common complaint at presentation (in 7 patients, 58.3%) was reduced vision. Four patients (33.3%) reported having metamorphopsia and 2 patients (16.7%) reported pain. Ten patients (83.3%) had systemic hypertension and 5 (41.7%) had diabetes mellitus. Eight patients (66.7%) had a history of using oral anticoagulants.

The right eye was involved in 1 patient, the left in 2 patients, and the remaining 9 patients had bilateral involvement. Of those with bilateral involvement, 4 (33.3%) had symmetric bilateral disease and 5 (45.7%) had asymmetric bilateral disease. Mean BCVA was 0.81±0.92 (0.00-2.6) logMAR at presentation and 0.73±0.84 (0.00-2.6) logMAR at final examination. The difference between initial and final BCVA was not statistically significant (p=0.39).

Lesions were observed in the temporal quadrant in all cases, and 2 patients (16.6%) also exhibited involvement in the nasal quadrant. Lesion involvement extended from the peripheral retina anteriorly to the midperipheral retina. Subretinal hemorrhage and/or hemorrhagic/serous PED was detected in 15 eyes (71.4%), lipid exudation in 11 eyes (52.4%), chronic RPE alterations in 5 eyes (23.8%), subretinal fibrosis in 2 eyes (9.5%) and intravitreal hemorrhage in 1 eye (4.8%) (Figures 1 and 2). The appearance of a mass was detected USG in 4 (19%) of the patients referred for further evaluation of a suspected choroidal mass.

Macular involvement was observed in 14 eyes (66.7%). Macular lesions were detected by ophthalmoscopic examination and OCT. Fifteen eyes (52.4%) had drusen, 3 (14.3%) had macular edema, 2 (9.5%) had geographic atrophy, 2 (9.5%) had CNV scar and 1 (4.8%) had epiretinal membrane. A patient with drusen in both eyes (patient #3) also exhibited macular edema in both eyes at presentation. This patient was treated for exudation extending to the macula in the left eye. In other eyes with drusen and geographic atrophy, the peripheral retinal hemorrhage or exudation had not reached the macula.

A patient whose vision level was hand motions and had intravitreal hemorrhage at presentation was treated with a single intravitreal bevacizumab (IVB) injection (1.25 mg/0.05 mL). The intravitreal hemorrhage resolved and the patient's vision improved to 20/20. A patient with bilateral involvement whose peripheral lesions threatened the macula in both eyes was treated with 3 IVB (1.25 mg/0.05 mL) injections in the right eye and 1 IVB injection in the left eye and with 2 sessions of photodynamic therapy (6 mg/m^2 verteporfin-50 J/cm^2) applied to midperipheral lesions in the left eye. A bilateral PEHC patient with macula edema in both eyes was treated with intravitreal 0.5 mg/0.1 mL ranibizumab in 3 injections to the right eye and 7 injections to the left eye. Treatment was not recommended for another patient with macular edema because the patient's vision level was counting fingers at 50 cm. Sixteen eyes (76.2%) were followed without treatment because the peripheral lesions did not threaten the macula or there were no active lesions.

Four patients underwent FFA and 3 patients underwent both FFA and ICGA. Areas of serous PED showed diffuse hyperfluorescence which became more pronounced in the late phase, while areas consistent with hemorrhages showed hypofluorescence in both phases. ICGA revealed polypoid lesions in the temporal quadrant in one patient, who was treated due to macular involvement (Figure 3).

Discussion

PEHC is a rare degenerative disease of the peripheral retina predominantly seen in elderly women and accompanied by hemorrhage and/or exudation.[4] In a study by Mantel et al.[5] including 45 patients, 68.9% were women and their ages ranged from 60 to 91. Another series of 143 PEHC patients determined that 67% were women and the average age was 80.[6] Consistent with the literature, 66.7% of the patients in

Table 1. Characteristics of patients with peripheral exudative hemorrhagic chorioretinopathy

Patient/ Age (years)/ Gender	Laterality	Location of lesions (quadrant)		Peripheral lesion characteristics		Macula		Initial visual acuity*		Treatment (#)		Final visual acuity*	
		Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
1/89/Male	OU	Temporal (I, S)	Temporal (I, S)	Hem, ex, fib	Hem, ex, fib	Normal	Normal	0.8	0.8	IVB (3)	IVB (1), PDT (2)	1.0	1.0
2/73/Female	OU	Temporal (I, S)	Temporal (I, S)	Hem, PED	RPE alt.	Drusen	Drusen	0.5	0.5	-	-	0.5	0.5
3/86/Female	OU	Temporal (I, S)	Temporal (I, S)	Hem, PED, ex	Hem, PED, ex, PCV	Drusen, CME	Drusen, CME	0.4	0.4	IVR (3)	IVR (7)	0.7	0.5
4/81/Female	OU	Temporal (I, S)	Temporal (I)	RPE alt.	Hem, ex	Drusen	Drusen, CME	0.5	CF 30 cm	-	-	0.5	CF 30 cm
5/86/Female	OU	Temporal (I)	Temporal (I)	Hem, ex	RPE alt.	Normal	Normal	0.3	0.3	-	-	0.3	0.3
6/77/Male	OD	Temporal (I, S)	-	IVH, hem, ex	-	Normal	-	HM	-	IVB	-	1.0	-
7/86/Male	OU	Temporal (I, S)	Temporal (I, S)	Hem, PED	Hem, PED	Drusen	CNV scar	0.3	CF 2 m	-	-	0.3	CF 2 m
8/81/Female	OS	-	Temporal (I)	-	Hem, ex	-	ERM	-	0.3	-	-	-	0.3
9/87/Female	OU	Temporal (I, S)	Temporal (I, S)	RPE alt.	PED	Drusen	Drusen	0.2	0.5	-	-	0.05	0.2
10/76/Male	OS	-	Temporal (S) Nasal (S)	-	Hem, ex	-	Normal	-	1.0	-	-	-	1.0
11/78/Female	OU	Temporal (I)	Temporal (I, S)	RPE alt.	Hem, ex	Drusen	Drusen, CNV scar	0.5	CF 3 m	-	-	0.5	CF 3 m
12/89/Female	OU	Temporal (I, S) Nasal (I)	Temporal (I) Nasal (I)	Hem, ex	Hem, PED	Geographic atrophy	Geographic atrophy	0.2	0.2	-	-	0.2	0.1

I: Inferior, S: Superior, CF: Counting fingers, HM: Hand motions, Ex: Exudation, PDT: Photodynamic therapy, Fib: Fibrosis, Hem: Hemorrhage, IVB: Intravitreal bevacizumab, IVR: Intravitreal ranibizumab, CME: Cystoid macular edema, CNV: Choroidal neovascularization, OD: Oculus dexter, OS: Oculus sinister, OU: Oculus uterque, PED: Retinal pigment epithelial detachment, PCV: Polypoidal choroidal vasculopathy, RPE alt.: Retina pigment epithelium alterations, IVH: Intravitreal hemorrhage

*According to Snellen chart, expressed in decimal

our study were women whose mean age was 82.4 years. Women have a longer life expectancy compared to men and thus they more often survive to the advanced age at which the disease becomes symptomatic, explaining the predominance of women in this pathology.[5]

Higher rates of systemic hypertension and systemic anticoagulant have been observed in PEHC patients.[1,6] We found that 83.3% of our patients had systemic hypertension and 66.7% used an anticoagulant agent. Fluctuations in systemic blood pressure and long-term use of anticoagulation are believed to be risk factors for hemorrhage, one of the main features of PEHC, and are suspected to have a role in recurrent hemorrhage.

PEHC lesions are usually located peripherally between the equator and the ora serrata in the temporal quadrant and anterior retina.[1,5,6] Nasal lesions often extend to the temporal quadrant as well, or may be present as separate lesions accompanying temporal lesions.[5] All of our patients exhibited temporal involvement of the peripheral retina. However, there is no evidence-based explanation for the predominance of lesions in the temporal quadrant.

Reduced visual acuity commonly occurs when peripheral subretinal hemorrhage, fluid or lipid exudation advances to the macula, or in the presence of intravitreal hemorrhage.[5] In addition to macular involvement of peripheral lesions, vision level may also be affected by macular edema and accompanying AMD-related findings such as drusen, CNV and geographic atrophy. Shields et al.[6] observed age-related macular changes in 17% of same eyes and 27% of contralateral eyes in PEHC patients. In a 2009 study, Mantel et al.[5] detected AMD in 31 of 56 eyes and macular edema in 4 eyes, and later reported in a 2012 study that 12 of 48 eyes had AMD findings and 6 had macular edema.[1] In the present study, we observed accompanying AMD findings in 15 of 21 eyes. One of the main features of PEHC is onset at advanced ages, which may explain the frequency of accompanying signs of AMD and the additional macular findings in these patients. Furthermore, checking the peripheral retina is often neglected during macular examination of AMD patients, leading to potential PEHC lesions being overlooked. Thorough peripheral examinations for additional pathologies should definitely be performed in AMD patients at every examination.

The natural course of the disease is generally stable, or spontaneous regression may occur with atrophy, fibrosis or hyperplasia.[6] Shields et al.[6] observed spontaneous regression in 89% of 173 eyes. Of the 76.2% of eyes in the current study that did not have active macular involvement and were followed without treatment, none showed lesions in new areas or clinical advancement or progression of existing lesions.

PEHC treatment options reported in the literature include monitoring, photocoagulation, photodynamic therapy, cryotherapy, intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection and vitrectomy.[7,8] Following without treatment is recommended for cases without affected central vision or macular involvement, and the disease may spontaneously regress in most of these cases.[9] Laser photocoagulation or photodynamic therapy may be applied in cases with macula-threatening findings or peripheral polyps.[10] Though rare, the development of vitreous hemorrhage or massive subretinal hemorrhage may require pars plana vitrectomy.[9] Alforja et al.[7] treated an eye with PEHC-related subretinal neovascularization and subfoveal fluid with a single IVB injection (1.25 mg/0.05 mL) and observed that the subfoveal fluid and lesion resolved,

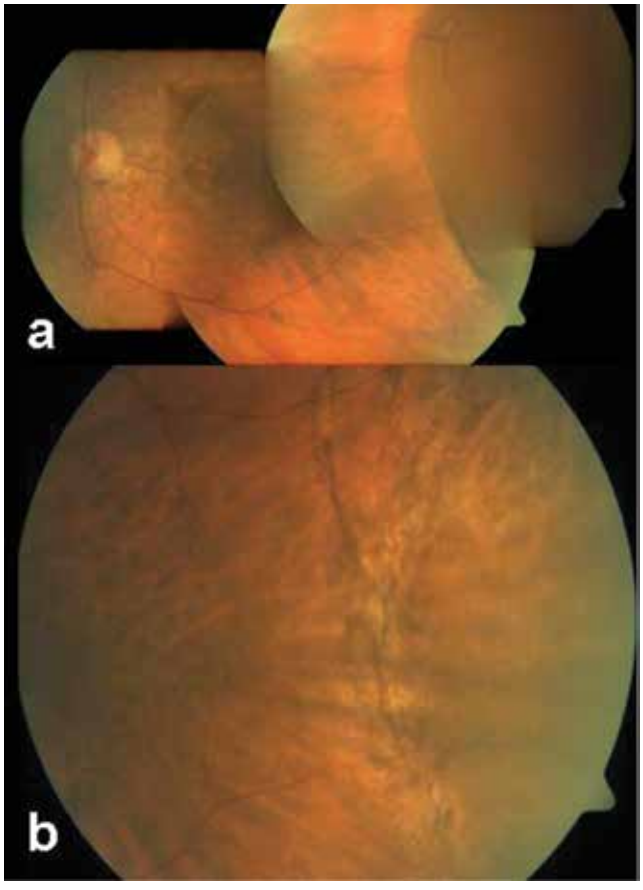

Figure 1. Images from an 87-year-old female patient referred for a choroidal mass in the left eye, a) macular drusen and serous retinal pigment epithelial detachment in the temporal periphery, b) appearance after spontaneous regression of pigment epithelial detachment during follow-up without treatment

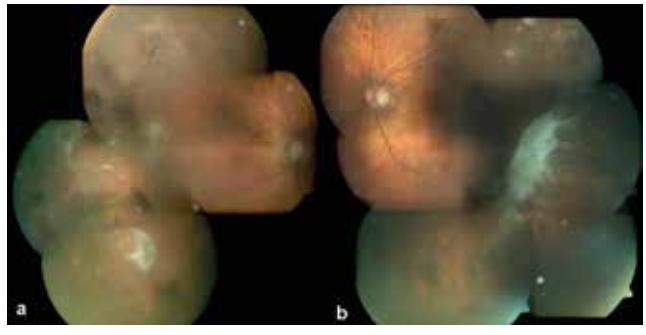

Figure 2. Color fundus photography of the eyes of an 89-year-old male patient, a) subretinal hemorrhage, exudation and subretinal fibrosis are visible in the temporal and inferior periphery of the right eye, b) subretinal fibrosis and hemorrhage are visible inferotemporally and exudation is apparent superotemporally in the left eye

leaving subretinal fibrosis. In a larger study, Pınarcı et al.[8] evaluated 23 eyes with PEHC of 15 patients and reported that lesions were stable or regressed in 11 patients (47.8%). They treated 12 patients with IVB injection, and 9 eyes (39.1%) showed lesion regression with atrophy and scarring after 2 or 3 injections. Visual acuity decreased in the other 3 patients due to macular involvement despite repeated injections.[8] The efficacy of intravitreal ranibizumab injection against PEHC-associated lesions has also been demonstrated.[11] We observed no reduction in vision during follow-up in our patients without macular involvement or macula-threatening lesions that we monitored without treatment. There was no significant change between initial and final visual acuities in our study. This may be due to the lack of PEHC-related macular involvement or CNV-like active macular pathology in patients who were followed without treatment and to the preservation of initial vision level in patients who underwent treatment. However, it is not possible to reach a definitive judgment regarding functional outcomes due to the small patient group and the low proportion of that group that underwent treatment.

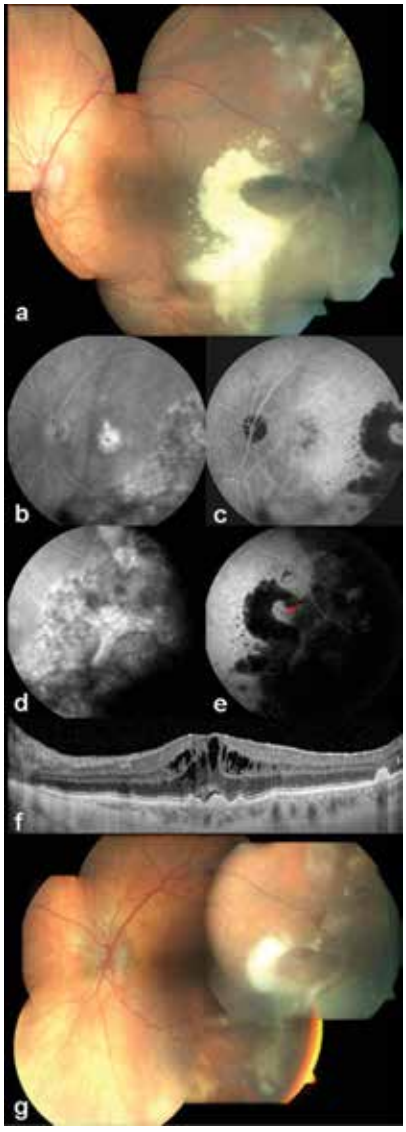

Figure 3. Images from an 86-year-old female patient who presented with reduced vision in the left eye, a) extensive exudation and subretinal hemorrhage in the temporal periphery, b) macular edema and hyperfluorescence due to temporal leakage are evident on fundus fluorescein angiography, c) temporal area of extensive exudation shows hypofluorescence on indocyanine green angiography, d) the temporal area shows hyperfluorescence on fundus fluorescein angiography, e) appearance of polyps (red arrow) in the center of the temporal hypofluorescent area on indocyanine green angiography, f) drusen and subretinal and intraretinal fluid are apparent on optical coherence tomography, g) exudation and hemorrhages partially regressed after seven intravitreal ranibizumab injections

In addition to diagnosing PEHC based on patient history and ophthalmoscopy, FFA and ICGA can assist in diagnosis. FFA can reveal hypofluorescence consistent with hemorrhage in lesion areas, and irregular hyperfluorescence shown by CNV and homogenous hyperfluorescence typical of serous PED in the periphery. In their 2009 study in which 20 eyes were examined by ICGA, Mantel et al.[5] did not find polypoidal choroidal vasculopathy (PCV) in any of the eyes but detected pathologic choroidal vascular networks in 6 eyes. However, in their 2012 study using ultra-wide angle ICGA in 48 eyes, they found polypoid formations in 69% of the eyes and abnormal choroidal vasculature in 50%.[1] As in PCV, choroidal vascular disorders may also play a role in PEHC. Like the serous or hemorrhagic PED and subretinal hemorrhage or exudation that may be seen in both pathologies, the presence of recurrent hemorrhage is another common factor that suggests a similar mechanism between the two conditions.[12] Therefore, it has been proposed that PCV and PEHC are actually two aspects of the same disease, or that PEHC may be a unique variation of type 1 neovascularization that results from PCV.[9,12]

Differential diagnosis of PEHC should include peripheral chorioretinal lesions such as retinal capillary hemangioma, retinal macroaneurysm, retinal telangiectasia, choroidal hemangioma, choroidal melanoma and choroidal detachment.[13] In a study evaluating 12,000 patients, PEHC was identified in 13% of patients referred with a diagnosis of uveal melanoma, and all 143 PEHC patients had been referred with an initial diagnosis of choroidal melanoma.[6,14] In Mantel et al.'s[5] series, 86.6% of 56 eyes presented with an initial diagnosis of choroidal malignancy. In the present study, 66.7% of our patients were referred to our clinic with an initial diagnosis of choroidal mass. Important features of PEHC that allow its differentiation from melanoma, the most common misdiagnosis, are retinal exudation, presence of diffuse macular and peripheral RPE alterations, absence of sentinel vessels on anterior segment examination, appearance of hypofluorescence on FFA, and absence of intrinsic vascular pulsation on USG.[6]

Limitations of our study include the small study population, retrospective analysis, and lack of FFA and ICGA data for all patients.

PEHC is a rare age-related disease of unknown etiology which can lead to reduced vision in patients with subfoveal exudation and/or hemorrhage accompanied by age-related degenerative changes. These patients should be examined regularly for sight-

threatening macular pathologies, and examinations should include a careful evaluation of the peripheral retina as well as the macula in patients with AMD findings. Studies with larger patient groups may elucidate the etiology of PEHC and facilitate the selection of appropriate treatment methods.

Ethics

Ethics Committee Approval: This study retrospective, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zafer Cebeci, Samuray Tuncer, Nur Kır, Concept: Zafer Cebeci, Şerife Bayraktar, Yasemin Dere, Samuray Tuncer, Nur Kır, Design: Zafer Cebeci, Şerife Bayraktar, Yasemin Dere, Samuray Tuncer, Nur Kır, Data Collection or Processing: Zafer Cebeci, Şerife Bayraktar, Analysis or Interpretation: Zafer Cebeci, Samuray Tuncer, Nur Kır, Literature Search: Zafer Cebeci, Şerife Bayraktar, Yasemin Dere, Writing: Zafer Cebeci, Şerife Bayraktar, Yasemin Dere, Samuray Tuncer, Nur Kır.

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References

1. Mantel I, Schalenbourg A, Zografos L. Peripheral exudative hemorrhagic chorioretinopathy: polypoidal choroidal vasculopathy and hemodynamic modifications. Am J Ophthalmol. 2012;153:910-922.
2. Reese AB, Jones IS. Hematomas under the retinal pigment epithelium. Am J Ophthalmol. 1962;53:897-910.
3. Silva VB, Brockhurst RJ. Hemorrhagic detachment of the peripheral retinal pigment epithelium. Arch Ophthalmol. 1976;94:1295-1300.
4. Annesley WH, Jr. Peripheral exudative hemorrhagic chorioretinopathy. Trans Am Ophthalmol Soc. 1980;78:321-364.
5. Mantel I, Uffer S, Zografos L. Peripheral exudative hemorrhagic chorioretinopathy: a clinical, angiographic, and histologic study. Am J Ophthalmol. 2009;148:932-938.
6. Shields CL, Salazar PF, Mashayekhi A, Shields JA. Peripheral exudative hemorrhagic chorioretinopathy simulating choroidal melanoma in 173 eyes. Ophthalmology. 2009;116:529-535.
7. Alforja MS, Sabater N, Giralt J, Adan A, Pelegrin L, Casaroli-Marano R. Intravitreal bevacizumab injection for peripheral exudative hemorrhagic chorioretinopathy. Jpn J Ophthalmol. 2011;55:425-427.
8. Pınarcı EY, Kılıç I, Bayar SA, Sızmaz S, Akkoyun I, Yılmaz G. Clinical characteristics of peripheral exudative hemorrhagic chorioretinopathy and its response to bevacizumab therapy. Eye (Lond). 2013;27:111-112.
9. Goldman DR, Freund KB, McCannel CA, Sarraf D. Peripheral polypoidal choroidal vasculopathy as a cause of peripheral exudative hemorrhagic chorioretinopathy: a report of 10 eyes. Retina. 2013;33:48-55.
10. Gomi F, Tano Y. Polypoidal choroidal vasculopathy and treatments. Curr Opin Ophthalmol. 2008;19:208-212.
11. Takayama K, Enoki T, Kojima T, Ishikawa S, Takeuchi M. Treatment of peripheral exudative hemorrhagic chorioretinopathy by intravitreal injections of ranibizumab. Clin Ophthalmol. 2012;6:865-869.
12. Mashayekhi A, Shields CL, Shields JA. Peripheral exudative hemorrhagic chorioretinopathy: a variant of polypoidal choroidal vasculopathy? J Ophthalmic Vis Res. 2013;8:264-267.
13. Collaer N, James C. Peripheral exudative and hemorrhagic chorio-retinopathy. the peripheral form of age-related macular degeneration? Report on 2 cases. Bull Soc Belge Ophtalmol. 2007:23-26.
14. Shields JA, Mashayekhi A, Ra S, Shields CL. Pseudomelanomas of the posterior uveal tract: the 2006 Taylor R. Smith Lecture. Retina. 2005;25:767-771.

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Original Article

The Efficacy of Intravitreal Bevacizumab in Vitreous Hemorrhage of Diabetic Subjects

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Summary

Objectives: To evaluate the efficacy of intravitreal bevacizumab (IVB) in the resolution of vitreous hemorrhage (VH) secondary to proliferative diabetic retinopathy (PDR).

Materials and Methods: Seventy eyes of 70 patients (43 male, mean age 55.6±12.2 years) diagnosed with VH secondary to PDR were evaluated retrospectively. Demographic characteristics of the patients, baseline and final clinical results, and the interventions the patients were subject to were recorded. The patients who received IVB injections (group 1, n=29) were compared to those who did not receive injections (group 2, n=41) in terms of VH clearance time and surgery rates.

Results: The mean follow-up time was 14.5±6.1 months in group 1 and 18.4±9.6 months in group 2 (p=0.185). The mean visual acuity was similar between the groups at baseline and at the last visit (for all p>0.05). Panretinal photocoagulation could be applied in 86% of subjects in group 1 and in 58% in group 2 2 within the first month (p=0.016). VH clearance time was not different between the groups (2.3±2.1 months in group 1 and 3.4±2.6 months in group 2, p=0.146). The number of subjects requiring surgery was 7 (24%) in group 1 and 20 (48.8%) in group 2 (p=0.048).

Conclusion: IVB was found effective in cases with VH secondary to PDR in terms of reducing the need for surgery and increasing the rate of subjects to whom panretinal photocoagulation could be applied in the early period, although there was no impact on final visual acuity.

Keywords: Proliferative diabetic retinopathy, vitreous hemorrhage, intravitreal bevacizumab

Introduction

Diabetic retinopathy (DR) is among the foremost causes of vision loss among working-age adults in developed countries.[1] The most common causes of vision loss in DR patients are macular edema, vitreous hemorrhage (VH) and tractional retinal detachment (TRD). In DR, angiogenic mediators such as insulin-like growth factor-1, erythropoietin, fibroblast growth factor and vascular endothelial growth factor (VEGF) are released secondary to retinal ischemia and lead to the formation of neovascular structures in the retina.[2,3,4] VH which arises due to these neovascular structures is an important clinical condition that prevents panretinal photocoagulation (PRP), the gold standard in proliferative (PDR) treatment. Half of PDR patients who do not receive timely treatment develop serious vision loss within 5 years.[5]

Bevacizumab is a humanized monoclonal recombinant anti-VEGF antibody that inhibits all isoforms of VEGF. VEGF has been reported at three times normal levels in the vitreous of advanced PDR patients and is believed to play a key role in neovascularization.[2,6] Intraocular injection of anti-VEGF drugs induces a rapid regression of retinal and iris neovascularization.[7,8,9,10] Although currently bevacizumab is usually used to treat macular edema in DR patients, it is also widely used to induce the regression of neovascularization in neovascular glaucoma and before pars plana vitrectomy (PPV).[11,12] Considering that anti-VEGF therapy accelerates the

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resolution of hemorrhage and facilitates PRP, it may also be a good choice for patients with VH.

The aim of this study was to evaluate the efficacy of intravitreal bevacizumab (IVB) therapy in patients with PDR-associated VH.

Materials and Methods

The medical records of consecutive patients who were diagnosed with VH due to PDR and showed no signs of TRD on ultrasonography in the retina clinic of our hospital between January 2011 and June 2012 were evaluated retrospectively. In accordance with the Declaration of Helsinki, all patients were informed about the surgical procedures and postoperative period, and written informed consent forms were obtained from all participants.

Vitrectomized eyes, patients with simultaneous bilateral VH, monocular patients, and patients with advanced glaucoma, rubeosis iridis or TRD were excluded from the study. We also excluded patients with any corneal or anterior segment pathology that would affect final visual acuity (VA) or interfere with fundus imaging. IVB was not administered to patients with uncontrolled systemic hypertension, a history of thromboembolism, or a known coagulation disorder, nor to patients with active ocular infection. Patients followed for at least 6 months were included in the study.

Patients' demographic data (age, gender, ocular and systemic diseases), initial corrected VA and lens status were recorded from their medical records. In addition, we also noted patients' VA during follow-up, intraocular pressure (IOP) measurements, whether or not PRP could be done, VH status, surgical interventions (injections and PPV), follow-up time and any systemic or local complications. VA was measured using Snellen's chart and converted to logMAR for statistical analysis. Goldmann applanation tonometer was used for all IOP measurements. Fundus examination was done using a +90 diopter lens.

VH clearance time was defined as the time until primary vessels in the posterior pole and the optic disc were clearly visible and at least 3 quadrants of the peripheral retina were clear enough to perform PRP. Recurrent hemorrhage was defined as hemorrhage developing after the complete resolution of previous hemorrhage and clearance of the fundus.

In our retina clinic, repeated IVB injections are applied to patients when initial IVB treatment does not result in VH clearance allowing PRP early in follow-up, or when VH recurs. Patients are followed for 4-6 months for spontaneous resolution except in cases with bilateral VH, monocular patients, and cases accompanied with rubeosis iridis or TRD. Surgery is indicated in eyes with hemorrhage that has not cleared by the end of this period. VH patients have monthly follow-up examinations and PRP is applied as soon as the fundus clears. When needed, PRP is repeated at subsequent visits. At all follow-up visits, patients without fundus clearing are evaluated for TRD by B-mode ultrasonography. Surgery is performed immediately in patients who develop TRD during follow-up.

Injection Technique

IVB (1.25 mg/0.05 mL, Altuzan®, Roche) injections were done in sterile conditions under topical anesthesia, into the vitreous in the superior temporal quadrant 3.5 mm posterior to the limbus. Light perception was checked after injection and paracentesis was performed when necessary. Topical antibiotic therapy (moxifloxacin eye drops, 4 times daily) was applied for 1 week after injection.

Surgical Technique

Vitrectomy was recommended for eyes that did not show hemorrhage clearance within the first 4-6 months or developed recurrent VH. Standard 23-gauge PPV was performed under local or general anesthesia. A trocar was placed in the inferotemporal quadrant for infusion. Additional trocars for the oculotome and vitrectomy probe were placed in the superotemporal and superonasal quadrants. After clearing the media of hemorrhage by core vitrectomy, the posterior hyaloid was removed using suction if still attached. Hemostasis was maintained by increasing the infusion pressure or applying laser directly to the extramacular neovascularization. After clearing the peripheral vitreous, endolaser was applied to any areas that could not be adequately cleared. Tamponade was not used in cases without any intraoperative complications; 20% sulfur hexafluoride (SF_6) gas was applied as a tamponade in cases that developed intraoperative hemorrhage and iatrogenic tear. After removing the trocars the scleral entries were assessed for leakage and any leaking incisions were sutured.

Statistical Analysis

SPSS version 20.0 (SPSS, Chicago, IL, USA) package software was used in the statistical analysis of all data. Numerical variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequency and percentage (%). The Wilcoxon test was used for dependent intergroup comparisons of numerical variables; the Mann Whitney U test was used for independent comparisons of the two groups. Fisher's Exact test was used for categorical variables. Results with P values less than 0.05 were accepted as statistically significant.

Patients who were treated by IVB injection and those who were followed without IVB therapy were compared in terms of VA change and final VA, VH clearance time, rate of early PRP application and rate of surgical intervention.

Results

Demographic Characteristics

Seventy eyes of 70 patients (43 male, 27 female) who met the inclusion criteria were included in the study. Study subjects were divided into two groups, eyes treated with IVB (group 1, n=29) and eyes not treated with IVB (group 2, n=41). Mean age was 56.2±9.6 years in group 1 and 57.4±10.1 in group 2 (p=0.441). The patients' preoperative characteristics are summarized in Table 1. Mean follow-up

time was 14.5±6.1 months in group 1 and 18.4±9.6 months in group 2 (p=0.185).

Anatomic Results

IVB therapy was administered to 29 eyes (group 1) at time of diagnosis. Thirteen (44.8%) of these eyes had a repeated IVB injection at an average of 4.1±3.1 months.

PRP could be performed within the first month in 25 eyes in group 1 (86.2%) and in 24 eyes in group 2 (58.5%) that showed partial or complete hemorrhage clearance (p=0.016) (Table 2).

VH clearance time was 2.3±2.1 months in group 1 and 3.4±2.6 months in group 2. Although VH clearance time was shorter in group 1, the different was not statistically significant (p=0.146).

Recurrent hemorrhage developed during follow-up in 4 eyes from group 1 and 4 eyes from group 2. Of the eyes with recurrent hemorrhage from group 1, PPV was performed in 3 of the eyes and IVB injection was repeated in the other. Of the group 2 eyes with recurrent hemorrhage, 2 underwent PPV and 2 were followed.

Seven patients (24.1%) from group 1 and 20 (48.8%) from group 2 underwent PPV due to persistent or recurrent VH (p=0.048) (Table 2). The proportion of patients that underwent PPV was significantly higher in group 2.

Functional Results

Initial VA was 1.83±1.0 logMAR in group 1 and 2.15±0.9 logMAR in group 2 (p=0.08). VA at final examination was 0.78±0.7 logMAR in group 1 and 0.69±0.5 logMAR in group 2 (p=0.925). Difference between initial and final VA was 1.05±1.0 logMAR in group 1 and 1.45±0.9 in group 2 (p=0.118) (Table 3).

Complications

During follow-up, 2 eyes (6.9%) from group 1 developed epiretinal membrane (ERM) and 4 (13.7%) developed cataract; in group 2, ERM formed in 1 eye (2.4%) and cataract in 3 eyes (7.3%) (p=0.299). None of the patients developed neovascular glaucoma due to iris or angle neovascularization. No systemic complications associated with IVB injection were observed during follow-up.

Table 1. Patients' demographic characteristics and preoperative findings

		IVB (+) (n=29)	IVB (-) (n=41)	p
Number of eyes, n (%)				0.311
	Right	17 (58.6)	19 (46.3)	
	Left	12 (41.4)	22 (53.7)	
Gender, n (%)				0.004
	Male	12 (58.6)	31 (75.6)	
	Female	17 (41.4)	10 (24.4)	
Age (years), mean ± standard deviation		56.2±9.6	57.4±10.1	0.441
HT, n (%)		6 (20.7)	8 (19.5)	1.000
Follow-up time (months), mean ± standard deviation		14.5±6.1	18.4±9.6	0.185
Previous PRP, n (%)				0.565
	Completed	2 (6.9)	1 (2.4)	
	Partial	27 (93.1)	40 (97.6)	

IVB: Intravitreal bevacizumab, HT: Systemic hypertension, PRP: Panretinal photocoagulation

Discussion

Retinal ischemia underlies the pathophysiology of PDR. Hypoxia-inducible factor released secondary to retinal hypoxia and ischemia increases expression of angiogenic factors such

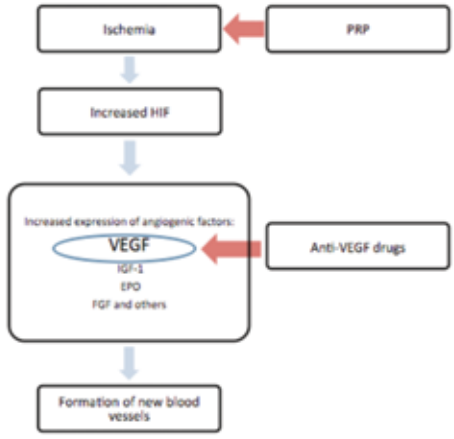

Figure 1. Pathophysiology of proliferative diabetic retinopathy
HIF: Hypoxia-inducible factor, VEGF: Vascular endothelial growth factor, IGF-1: Insulin-like growth factor-1, EPO: Erythropoietin, FGF: Fibroblast growth factor, PRP: Panretinal photocoagulation

Table 2. Clinical findings in eyes treated with intravitreal bevacizumab and eyes not treated with intravitreal bevacizumab

	Group 1, IVB (+) (n=29)	Group 2, IVB (-) (n=41)	p
Clearance time (months), mean ± standard deviation	2.3±2.1	3.4±2.6	0.146
PRP in first month, n (%)	25 (86.2)	24 (58.5)	0.016
PPV, n (%)	7 (24.1)	20 (48.8)	0.048
Recurrent hemorrhage, n (%)	4 (13.8)	4 (9.8)	0.709

IVB: Intravitreal bevacizumab, PRP: Panretinal photocoagulation, PPV: Pars plana vitrectomy

Table 3. Visual acuity changes in the study groups

	Group 1, IVB (+) (n=29)	Group 2, IVB (-) (n=41)	p^1
Initial VA	1.83±1.0	2.15±0.9	0.08
Final VA	0.78±0.7	0.69±0.5	0.925
Change in VA	1.05±1.0	1.45±0.9	0.118
p^2	0.002	<0.001	

IVB: Intravitreal bevacizumab, VA: Visual acuity (logMAR), Change in VA: the difference in visual acuity between initial and final values, p^1: Comparison of groups 1 and 2 (Mann-Whitney U test), p^2: Comparison of initial and final visual acuity values (Wilcoxon test)

as VEGF, insulin-like growth factor-1 and erythropoietin,[2,3,4] thereby leading to the formation of new vessels and fibrovascular structures (Figure 1). Contraction of the fibrous component can increase the tendency of neovascular structures to bleed and, in advanced cases, lead to TRD. PRP is currently accepted as the gold standard in PDR treatment.[13,14] However, photocoagulation therapy may not be possible in eyes with intravitreal opacity such as VH. This condition leads to the progression of neovascular tissue and may result in persistent VH, recurrent VH, or development of TRD. Currently, in patients whose hemorrhage does not clear spontaneously, PRP is performing after clearing the media by vitrectomy.

In recent years, intravitreal anti-VEGF agents have been used in DR treatment for diabetic macular edema, preretinal hemorrhage, active neovascularization and as preoperative adjuvant therapy in PDR cases.[9,10,11,12,15,16,17] Anti-VEGF drugs prevent the formation of new vasculature by directly affecting VEGF, but reducing retinal ischemia is not among their functions (Figure 1). It has been reported that the efficacy of anti-VEGF agents is transitory when used alone to treat PDR, and effective long-term results were only attainable when these drugs are used in addition to PRP.[18]

With the present study, we aimed to evaluate the effects of IVB on hemorrhage clearance time, need for surgery and final VA results in diabetic patients with VH. Our results indicate that IVB therapy does not significantly impact clearance time (2.3 months in group 1 and 3.4 months in group 2, p=0.146), but decreases the number of cases requiring surgery (24% in group 1 and 49% in group 2, p=0.048). Reports in the literature regarding the effect of anti-VEGF drugs in VH are equivocal.[19,20,21] Huang et al.[19] found that bevacizumab therapy reduced both clearance time and the surgery rate in VH patients. In a study by the Diabetic Retinopathy Clinical Research Network (DRCRnet), researchers applied intravitreal ranibizumab to 125 eyes and intravitreal saline to 136 eyes of diabetic patients with VH that precluded PRP. At 16 weeks after injection, eyes injected with ranibizumab showed a greater improvement in VA, lower rate of recurrent hemorrhage and significantly higher rate of PRP completion compared to the saline-injected group.[20] However, in a later report of results at 1 year, they reported no significant differences in VA outcomes or surgery rates.[21]

Intravitreal anti-VEGF drugs are known to have a half-life of 7-10 days in the eye[22,23] and their clinical efficacy is as short as 4 weeks.[23,24] As anti-VEGF agents block new vessel formation and also induce regression of existing vessels,[9,10,25] they can theoretically prevent new hemorrhages from preexisting or new loci in VH patients. Thus, injection of anti-VEGF drugs facilitates clearing of the media and should allow the application of PRP in more patients in the early phase. Consistent with the results reported in the DRCRnet study, in the present study we observed a higher rate of PRP completion in the first month in patients treated with IVB. Because of the drug's short half-life, it is expected that IVB is not effective against recurrent hemorrhage in the long term. The completion of laser photocoagulation, the current gold standard therapy for PDR, remains important for the long-term prevention of recurrent hemorrhage.[13,14] In our study, the rates of recurrent hemorrhage during follow-up were comparable in the two groups (13.8% in group 1 and 9.8% in group 2). However, in group 2 PRP could be completed in a larger proportion of patients after vitrectomy and media clearance.

The ideal interval for repeated IVB injections in cases of PDR-associated VH has not been clearly established. Huang et al.[19] applied a second injection in eyes not exhibiting signs of hemorrhage clearance 4-6 weeks after the first injection. Although the injection interval could not be standardized due to the retrospective nature of our study, repeated IVB injections were administered to eyes that did not show reduced hemorrhage or developed recurrent hemorrhage in early follow-up. Prospective, controlled studies are needed to determine the efficacy and frequency of repeated injections for the treatment of VH associated with PDR.

In general, the VA of PDR patients can be expected to return to pre-hemorrhage levels after the VH is completely resorbed. Huang et al.[19] found that eyes injected with IVB and those not injected showed similar improvements in VA in PDR-associated VH patients followed for at least 12 months. DRCRnet reported that VA improved more in the ranibizumab-injected group in the short term, but found no difference between the two groups in the long term.[20,21] Similarly, in our case series we observed comparable results in VA improvement and final VA levels between the two groups. Our findings that bevacizumab injection does not result in a significant difference in final VA support results obtained by other researchers. It has been demonstrated in previous studies that VA loss secondary to PRP is attenuated when anti-VEGF therapy is applied in combination to PRP in diabetic patients.[26,27,28] However, both the present study and previous ones[20,22] could not demonstrate any positive effect of anti-VEGF drugs on visual function in VH patients.

Conclusion

IVB was found effective in cases with VH secondary to PDR in terms of reducing the need for surgery and increasing the rate of PRP completion in the early period, but it did not impact final VA.

Ethics

Ethics Committee Approval: Retrospective study, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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References

1. Klein R. Retinopathy in a population-based study. Trans Am Ophthalmol Soc. 1992;90:561-594.
2. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480-1487.
3. Sivalingam A, Kenney J, Brown GC, Benson WE, Donoso L. Basic fibroblast growth factor levels in the vitreous of patients with proliferative diabetic retinopathy. Arch Ophthalmol. 1990;108:869-872.
4. Meyer-Schwickerath R, Pfeiffer A, Blum WF, Freyberger H, Klein M, Losche C, Rollmann R, Schatz H. Vitreous levels of the insulin-like growth factors I and II, and the insulin-like growth factor binding proteins 2 and 3, increase in neovascular eye disease. Studies in nondiabetic and diabetic subjects. J Clin Invest. 1993;92:2620-2625.
5. Chew EY. Major clinical trials of vitreoretinal diseases. In: Regillo CD, Brown GC, Flyn HW, eds. Vitreoretinal Disease: The Essentials. New York, Theme Medical Publishers Inc; 1999:667-677.
6. Malik RA, Li C, Aziz W, Olson JA, Vohra A, McHardy KC, Forrester JV, Boulton AJ, Wilson PB, Liu D, McLeod D, Kumar S. Elevated plasma CD105 and vitreous VEGF levels in diabetic retinopathy. J Cell Mol Med. 2005;9:692-697.
7. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ, Wendel R, Patel A. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113:1695.
8. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study). Retina. 2006;26:1006-1013.
9. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. Retina. 2006;26:352-354.
10. Isaacs TW, Barry C. Rapid resolution of severe disc new vessels in proliferative diabetic retinopathy following a single intravitreal injection of bevacizumab (Avastin). Clin Exp Ophthalmol. 2006;34:802-803.
11. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, Gandorfer A, Ulbig M, Kampik A. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina. 2006;26:999-1005.
12. Ishikawa K, Honda S, Tsukahara Y, Negi A. Preferable use of intravitreal bevacizumab as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy. Eye (Lond). 2009;23:108-111.
13. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:766-785.
14. Kapran Z, Acar N. Proliferatif Diyabetik Retinopati Tedavisi. Ret-Vit. 2008;16:85-90.
15. Shih CW, Yang CM, Chen MS, Wang TJ. Intravitreal injection of bevacizumab and gas for diabetic premacular hemorrhage with active fibrovascular proliferation. Graefes Arch Clin Exp Ophthalmol. 2008;246:1547-1551.
16. Alakuş MF, Taş M ÖV, İşcan Y, Türkçü FM, Şimşek A, Ünlü MK. Diabetik Maküla Ödeminde İntravitreal Bevacizumab Etkinliğininin Değerlendirilmesi. Ret-Vit. 2012;20:35-40.
17. Yüksel K, Baz Ö, Çelik U, Herdem U, Alagoz C, Özgürhan EB, Yazıcı AT, Demirok A. Diyabetik traksiyonel retina dekolmanlı olgularda 23-gauge pars plana vitrektomi cerrahisi sonuçları. Journal of Clinical and Experimental Investigations. 2015;6:27-32.
18. Arevalo JF. Intravitreal bevacizumab as anti-vascular endothelial growth factor in the management of complications of proliferative diabetic retinopathy. Med Hypothesis Discov Innov Ophthalmol. 2013;2:20-24.
19. Huang YH, Yeh PT, Chen MS, Yang CH, Yang CM. Intravitreal bevacizumab and panretinal photocoagulation for proliferative diabetic retinopathy associated with vitreous hemorrhage. Retina. 2009;29:1134-1140.
20. Diabetic Retinopathy Clinical Research N. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. JAMA Ophthalmol. 2013;131:283-293.
21. Bhavsar AR, Torres K, Glassman AR, Jampol LM, Kinyoun JL, Diabetic Retinopathy Clinical Research N. Evaluation of results 1 year following short-term use of ranibizumab for vitreous hemorrhage due to proliferative diabetic retinopathy. JAMA Ophthalmol. 2014;132:889-890.
22. Krohne TU, Liu Z, Holz FG, Meyer CH. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. Am J Ophthalmol. 2012;154:682-686.
23. Stewart MW. Pharmacokinetics, pharmacodynamics and pre-clinical characteristics of ophthalmic drugs that bind VEGF. Expert Rev Clin Pharmacol. 2014;7:167-180.
24. Miyake T, Sawada O, Kakinoki M, Sawada T, Kawamura H, Ogasawara K, Ohji M. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. Invest Ophthalmol Vis Sci. 2010;51:1606-1608.
25. Arevalo JF, Wu L, Sanchez JG, Maia M, Saravia MJ, Fernandez CF, Evans T. Intravitreal bevacizumab (Avastin) for proliferative diabetic retinopathy: 6-months follow-up. Eye (Lond). 2009;23:117-123.
26. Filho JA, Messias A, Almeida FP, Ribeiro JA, Costa RA, Scott IU, Jorge R. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. Acta Ophthalmol. 2011;89:e567-572.
27. Cho WB, Oh SB, Moon JW, Kim HC. Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy. Retina. 2009;29:516-522.
28. Mason JO, 3rd, Yunker JJ, Vail R, McGwin G, Jr. Intravitreal bevacizumab (Avastin) prevention of panretinal photocoagulation-induced complications in patients with severe proliferative diabetic retinopathy. Retina. 2008;28:1319-1324.

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Original Article

Evaluation of Follow-Up and Treatment Results in Coats' Disease

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Summary

Objectives: The aim of this study was to evaluate the clinical features, follow-up and treatment results of patients diagnosed with Coats' disease.

Materials and Methods: Medical records of 27 patients diagnosed with Coats' disease in our clinic were reviewed retrospectively. All patients underwent complete ophthalmological examination and fundus photography was taken. Disease stage and treatment methods used were recorded.

Results: Twenty-seven eyes of 27 patients were included in the study. Mean age was 9.03 years; 21 patients were male and 6 were female. Three patients were older than 18 years old. Based on the Shields classification, 1 (3.7%) eye was stage 2A, 4 (14.8%) eyes were stage 2B, 6 (22.2%) were stage 3A1, 3 (11.1%) were stage 3A2, 1 (3.7%) was stage 3B, 4 (14.8%) were stage 4 and 8 (29.6%) were stage 5. Fourteen patients underwent treatment, 12 of whom had combined therapy. The most common treatment modalities were laser photocoagulation and cryotherapy. Encircling band was done in one patient and pars plana vitrectomy in 3 patients. Enucleation was done in 5 patients.

Conclusion: Coats' disease is a chronic disease and main goal of treatment is to eliminate the vascular anomalies and their complications using repetitive combination therapies. Treatment in the early stages can lead to functional success, and in advanced stages can result in a salvageable eye.

Keywords: Coats' disease, laser photocoagulation, cryotherapy, pars plana vitrectomy

Introduction

Coats' disease is a nonhereditary condition characterized by retinal capillary telangiectasia, arterial aneurism, exudation and exudative retinal detachment.[1] Coats[2] first described the disease in a 1908 report of a patient group with retinal telangiectasia with massive intra- and subretinal exudation. In 1912, Leber[3] reported a condition involving retinal vascular anomalies but without exudation or serous retinal detachment and proposed the pathology may be an early or milder form of Coats' disease.

Coats' disease predominantly affects males and is usually unilateral.[1,4] The condition is often detected in early childhood, but may occasionally appear in adults and shows slower progression with later onset.[4,5] Shields et al.[6] divided Coats' disease into 5 stages ranging from mild disease with retinal telangiectasia only to severe, advanced disease with a blind, painless eye and possible cataract and phthisis bulbi (Table 1).

Treatments such as laser photocoagulation, cryotherapy and intravitreal corticosteroid or anti-vascular endothelial growth factor (anti-VEGF) injection may be effective against telangiectatic vasculature in the early stages of the disease.[1,7] More advanced disease with extensive exudative retinal detachment may also require additional surgical interventions such as vitrectomy, scleral buckling, and external drainage.[1,7]

The aim of this study was to examine the clinical characteristics and follow-up and treatment outcomes of patients diagnosed with Coats' disease in our clinic.

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Materials and Methods

We retrospectively analyzed the charts of patients diagnosed with Coats' disease in our clinic. Diagnosis of Coats' disease was based on idiopathic telangiectasia, aneurysms, intraretinal and/or subretinal exudation or exudative retinal detachment in the absence of any other ocular disease. Patients with idiopathic juxtafoveal telangiectasia, other pathologies which lead to retinal exudation, or intraocular inflammation were excluded from the study.

Patients' age, gender, complaints at presentation, disease laterality, and follow-up time were recorded. Best corrected visual acuity, intraocular pressure, and slit-lamp and fundoscopic examination findings at initial and final examinations were also recorded. Fundus photography was performed in suitable patients; images were acquired with a RetCam system (Clarity Medical Systems, Pleasanton, CA, USA) for children examined under general anesthesia, and with a Zeiss FF450 plus (Carl Zeiss, Meditec, Dublin, CA, USA) in other patients. Fundus fluorescein angiography (FFA) was performed when possible. Treatments applied during follow-up were recorded in detail. The study was designed and conducted in accordance with the principles of the Declaration of Helsinki.

Results

The study included 27 eyes of 27 patients diagnosed with Coats' disease; 21 patients (77.8%) were male, 6 (22.2%) were female. Mean age at presentation was 9.03 years (range, 18 months-44 years). Three patients (11.1%) were over the age of 18 at presentation. Mean follow-up time was 69.5 months (range, 6-324 months). All patients had unilateral involvement, 15 (55.6%) in the right eye and 12 (44.4%) in the left eye. Of the 18 patients referred to our clinic for advanced testing and treatment, referral diagnosis was intraocular tumor in 10 (55.6%), Coats' disease in 2 (11.1%), uveitis in 2 (11.1%), cataract in 1 (5.6%), retinal detachment in 1 (5.6%) and strabismus in 1 (5.6%). None of the patients had a family history of similar ocular pathology. Fourteen patients (51.8%) had low vision, 14 (51.8%) strabismus, 8 (29.6%) leukocoria and 1 (11.1%) eye pain. Mean age was 13.5 years in patients presenting with low vision, 5.5 years in patients presenting with strabismus and 3.7 years in patients with leukocoria.

Table 1. Staging of Coats' disease
Stage 1. Retinal telangiectasia only
Stage 2. Telangiectasia and exudation
a) Extrafoveal exudation
b) Foveal exudation
Stage 3. Exudative retinal detachment
a) Subtotal detachment
1. Extrafoveal
2. Foveal
b) Total retinal detachment
Stage 4. Total retinal detachment and glaucoma
Stage 5. Advanced end-stage disease

At initial presentation, disease severity was stage 2A in 1 eye (3.7%), stage 2B in 4 eyes (14.8%), stage 3A1 in 6 eyes (22.2%), stage 3A2 in 3 eyes (11.1%), stage 3B in 1 eye (3.7%), stage 4 in 4 eyes (14.8%) and stage 5 in 8 eyes (29.6%) (Figure 1).

FFA was done in 13 patients and showed filling of telangiectatic vessels, bulb-like hyperfluorescence and avascular regions in the early phase and diffuse hyperfluorescence due to leakage from telangiectatic vasculature in the late phase.

Patient characteristics and treatments administered are shown in Table 2. Coats' disease was treated with combined therapy in 12 patients and with a single treatment modality in 2 patients. In 13 patients, aneurysms and telangiectases were treated with laser photocoagulation therapy repeated at specific intervals. Nine patients were treated with cryotherapy (Figures 3a and b), 3 with intravitreal bevacizumab injection, 2 with intravitreal triamcinolone acetonide injection and 1 with intravitreal dexamethasone implant. One patient was treated surgically with scleral buckle and 3 patients underwent pars plana vitrectomy (PPV) (Figures 3c, 3d). PPV with internal tamponade was performed in 2 patients (#8 and 13) due to the development of total retinal detachment during follow-up and in the other patient due to subtotal retinal detachment with macular involvement at initial presentation. None of the patients treated for Coats' disease required enucleation during follow-up. Enucleation was performed in 3 patients due to neovascular glaucoma and painful eye and in 2 patients because of phthisis. Follow-up without treatment was recommended in the remaining 8 eyes due to lack of light perception or pain.

Discussion

Coats' disease is a disorder of unknown etiology that typically features idiopathic retinal telangiectases, aneurysms and retinal exudation leading to vision loss.[1] Although some cases of Coats' disease are asymptomatic, most patients diagnosed in childhood present with leukocoria, strabismus or low vision.[6] Shields et al.[4] evaluated a series of 150 cases and determined that 34% presented with low vision, 23% with strabismus and 20% with leukocoria. In a study including 97 eyes, approximately half presented with low vision, followed by strabismus and leukocoria.[8] The most common complaints at presentation in our series (reported by about half of our patients) were low vision and strabismus. Low vision was particularly common in older Coats' patients, whereas

strabismus and leukocoria were the most common complaints at presentation in early childhood, likely due to children's inability to describe their vision problems or their families not recognizing them.

Coats' disease is usually seen in children, though there are cases with adult onset. Smithen et al.[5] reported Coats' disease in 13 patients with a mean age of 50 years. Although these patients exhibit symptoms similar to those in children, the authors stated that disease detected in older patients followed a slower progression than seen in children and that this may lead to a later diagnosis. A community-based study demonstrated that stage 3 or higher disease was more common at younger ages, while early stages were more common in older patients.[9] In the present study, 3 of 27 patients were over 18 years of age. Two of those patients were followed with repeated treatment and the other patient was followed without treatment because the eye was blind.

Telangiectatic and aneurysmal vessels, particularly in the periphery, may be accompanied by avascular areas which can

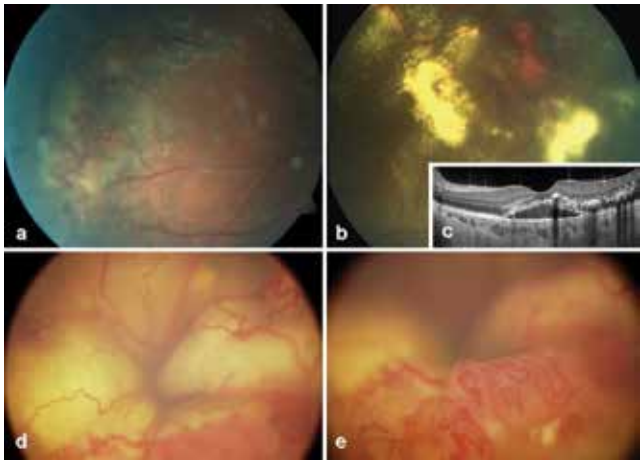

Figure 1. Images from various stages of Coats' disease, a) peripheral telangiectatic vessels and exudation in stage 2A disease, b) telangiectatic vessels and exudation in stage 2B, c) optical coherence tomography image from the patient in Figure 1b showing subretinal fluid and hyperreflective exudation at the macula, d) image from a patient referred for intraocular tumor, stage 4 disease with total retinal detachment, e) Inferior peripheral telangiectatic vessels of patient in Figure 1d

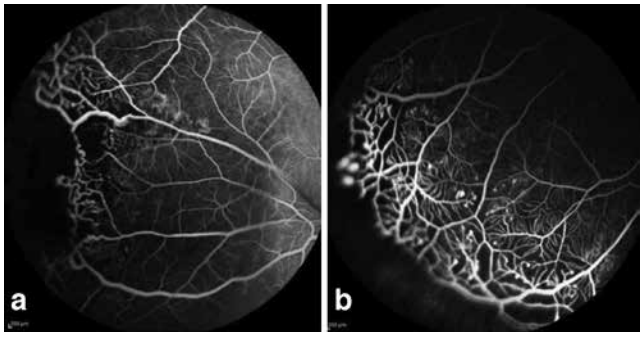

Figure 2. Fundus fluorescein angiography images of Coats' disease, a) Telangiectatic vessels and avascular areas in the temporal periphery, b) Inferior peripheral image from same patient

be visualized with FFA.[1,7] In one reported series of adult Coats' patients, areas of capillary nonperfusion were observed in regions of vascular abnormalities in 91.7% of cases.[5] Avascular fields and vascular anomalies may appear on FFA in fellow eyes without ophthalmoscopic findings as well as the involved eye.[10] It has been demonstrated that intraoperative FFA-guided laser photocoagulation may be more effective when applied in the early disease stages and that this may reduce the number of repeat treatments.[11] FFA is a particularly useful auxiliary imaging modality in terms of identifying areas of nonperfusion during treatment and monitoring the regression of vascular anomalies during follow-up.

The primary treatment for Coats' disease is ablation of the vascular anomalies that cause exudation, thus reducing intraretinal and subretinal exudation and protecting vision and the eye. In patients with stage 2 or 3 disease without severe detachment, laser photocoagulation and cryotherapy have been shown to be effective against telangiectases and aneurysms.[6,12,13,14] Repeated laser photocoagulation or cryotherapy applications may be required at certain intervals during follow-up. In a study evaluating 17 patients ranging from stage 2A to 4, at the end of follow-up with repeated laser photocoagulation therapy, the globe was conserved in 94% of patients and about half had a final visual acuity of 0.4 or better.[12]

Applying laser photocoagulation and cryotherapy is difficult in the presence of dense exudation. Intravitreal triamcinolone reduces subretinal fluid and exudates when administered as an initial treatment, even in cases of total bullous retinal detachment, and can therefore facilitate the application of other therapies for vascular pathologies.[15,16] Fifteen patients initially treated with intravitreal 4 mg/0.1 mL triamcinolone injection (with additional subretinal fluid drainage in some cases) all showed reduced size of telangiectatic

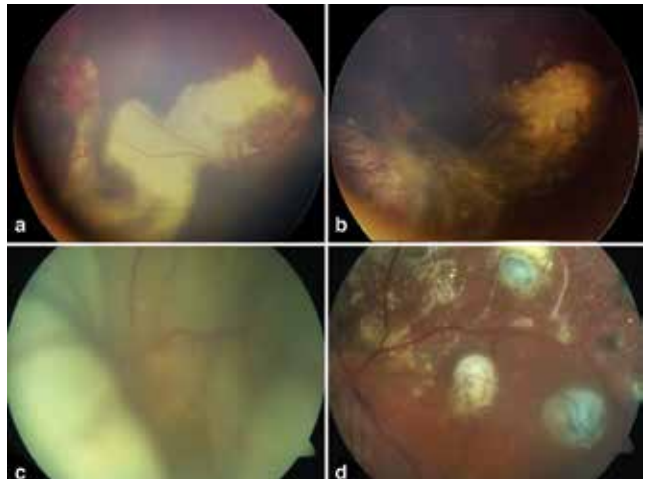

Figure 3. Fundus photographs taken before and after treatment, a) Telangiectatic vessels in the temporal periphery and exudation extending to the macula in a patient with stage 2B Coats' disease, b) Post-treatment image from the same patient showing cryo scars, fibrotic nodule at the macula and exudation following cryotherapy, c) Pre-treatment image from a patient with total retinal detachment, d) Image from the same patient following pars plana vitrectomy, internal drainage, endophotocoagulation and endocryotherapy

vessels at 1 month follow-up.[15] However, it must be kept in mind that intravitreal steroid injection can lead to cataract and glaucoma.[17]

Increasing use of anti-VEGF agents has led to their application in Coats' disease as well.[18,19,20] It has been shown that VEGF levels are elevated in the aqueous humour in Coats' disease and increase significantly as the disease progresses.[21] Histopathologic examinations have revealed macrophages in the subretinal space and increased vascular permeability caused by these cells, in addition to increased expression of VEGF, which leads to angiogenesis.[22] Administering 1.25 mg intravitreal bevacizumab before conventional treatments like laser coagulation and cryotherapy has been shown to positively influence visual outcomes.[18] Villegas et al.[19] applied intravitreal bevacizumab and laser photocoagulation to 24 advanced stage Coats' patients with exudative retinal detachment and observed regression of the exudative retinal detachment in all cases. Even in patients with stage 3B and 4 disease, adjuvant or neoadjuvant application of intravitreal ranibizumab may lead to partial visual recovery.[20] However, there remains the fact that combination therapy with intravitreal anti-VEGF injection may result in vitreoretinal fibrosis and tractional retinal detachment.[23] Laser photocoagulation and cryotherapy were also the most common treatment modalities in the current case series, especially in earlier stage disease. A subset of our patients received intravitreal corticosteroid or anti-VEGF injections, and all patients underwent repeated treatments. Intravitreal corticosteroid or anti-VEGF injections may be beneficial in reducing exudation in cases where a single treatment method does not yield satisfactory results or to facilitate additional procedures in selected patients.

Vitreoretinal surgery and scleral buckling are preferred for advanced Coats' disease (stage 3 and 4) patients with tractional bands or proliferative vitreoretinopathy.[1,24,25,26] Additional internal or external subretinal fluid drainage

Table 2. Demographic characteristics, treatments and visual outcomes of patients with Coats' disease

Patient no	Age (years)	Gender	Stage	Treatment (number of sessions)	Initial visual acuity (decimal)	Final visual acuity (decimal)	Follow-up time (years)
1	9	Male	2B	Laser PC (8)	HM (+)	CF 1.5 m	3.5
2	13	Male	2B	Laser PC (3)	0.05	0.05	2.5
3	44	Male	2A	Laser PC (3) Intravitreal bevacizumab injection (3) Intravitreal dexamethasone implant (1)	0.5	0.6	3
4	14	Male	3A1	Laser PC (1) Cryo (2) Intravitreal bevacizumab injection (1)	0.05	0.2	2
5	9	Male	3A1	Laser PC (2) Cryo (1)	CF 3 m	CF 3 m	6
6	6	Male	3A1	Laser PC (1) Cryo (1)	CF 1.5 m	0.05	4
7	19	Male	3A1	Laser PC (2) Cryo (1) Intravitreal bevacizumab injection (1)	CF 50 cm	0.05	5
8	12	Male	3A2	Laser PC (2) Intravitreal TA injection (1) PPV(2), C3F8	0.05	HM (+)	4
9	3	Female	3A1	Cryo (2) Intravitreal TA injection (2)	No vision	No vision	1
10	5	Male	2B	Laser PC (4) Cryo (1)	CF 3 m	CF 1 m	13
11	6	Male	3A1	Laser PC (1) Scleral buckle	CF 50 cm	CF 2 m	1.5
12	7	Female	2B	Laser PC (1) Cryo (1)	CF 1 m	CF 1 m	5
13	14	Male	3A2	Laser PC (1) Cryo (1) PPV, endolaser, Si injection (1)	CF 1 m	HM (+)	1.5
14	2	Male	3A2	PPV, endolaser, endocryo, C3F8	No vision	No vision	0.5

C3F8: Perfluoropropane, PC: Photocoagulation, TA: Triamcinolone acetonide, Cryo: Cryotherapy, PPV: Pars plana vitrectomy, Si: Silicone, HM: Hand motions, CF: Counting fingers

also facilitates the application of laser photocoagulation or cryotherapy. Mutfuoglu ve Gulkilik[25] achieved positive anatomic and functional outcomes in 5 patients with PPV, internal subretinal fluid drainage and silicone oil tamponade. Despite postoperative anatomic success, functional success may be achieved in a small number of patients.[1] Although the operated patients in our study did not show functional improvement, anatomic success was achieved and maintained throughout follow-up.

Some patients present with advanced disease which does not benefit from treatment, while others show disease progression despite treatment. Approximately one in four patients require enucleation due to total retinal detachment and neovascular glaucoma.[6,27,28] Other than those who underwent enucleation for painful eye or phthisis, none of the patients treated in our study required enucleation during follow-up. However, some patients may have reduced level of vision despite treatment and conservation of the eye.

Other causes of exudative retinal detachment should be considered in the differential diagnosis of Coats' disease. Retinoblastoma, persistent hyperplastic primary vitreous, Norrie's disease, and familial exudative vitreoretinopathy in particular are more common in childhood and should definitely be considered.[1] Although rare in adults, the differential diagnosis should include Eales' disease, vasoproliferative tumor, idiopathic retinal vasculitis and neuroretinitis, and sickle-cell anemia. About half of the patients referred to our clinic had an initial diagnosis of intraocular tumor. All of these patients could have been correctly diagnosed using ophthalmoscopic examination and additional imaging methods like FFA and ultrasonography when needed. Features such as lack of family history, predominance in males and typically unilateral manifestation, absence of vitreous opacity, presence of telangiectases, and no apparent mass can also assist diagnosis. Computed tomography and magnetic resonance imaging techniques can help differentiate between an intraocular malignancy and advanced stage Coats' disease.[1]

Coats' disease is a chronic disease requiring long-term follow-up. Favorable visual outcomes can be achieved with early detection and treatment with combined therapies as required. Even when treatment is not able to restore sight, it is beneficial in saving the eye. It must be noted that new telangiectases and aneurysms can develop over the course of follow-up and may require retreatment.

Ethics

Ethics Committee Approval: Retrospective study, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zafer Cebeci, Samuray Tuncer, Nur Kır, Concept: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Samuray Tuncer, Nur Kır, Design: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Samuray Tuncer, Nur Kır, Data Collection or Processing: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Analysis or Interpretation: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Samuray Tuncer, Nur Kır, Literature Search: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Writing: Zafer Cebeci, Şerife Bayraktar, Yusuf Cem Yılmaz, Samuray Tuncer, Nur Kır.

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References

1. Sigler EJ, Randolph JC, Calzada JI, Wilson MW, Haik BG. Current management of Coats disease. Surv Ophthalmol. 2014;59:30-46.
2. Coats G. Forms of retinal diseases with massive exudation. Roy Lond Ophthalmol Hosp Rep. 1908;17:440-525.
3. Leber T. Verber ein durch yorkommen miltipler miliaraneurisi men characterisierte form von retinaldegeneration. Graefes Arch Clin Exp Ophthalmol. 1912;81:1-14.
4. Shields JA, Shields CL, Honavar SG, Demirci H. Clinical variations and complications of Coats disease in 150 cases: the 2000 Sanford Gifford Memorial Lecture. Am J Ophthalmol. 2001;131:561-571.
5. Smithen LM, Brown GC, Brucker AJ, Yannuzzi LA, Klais CM, Spaide RF. Coats' disease diagnosed in adulthood. Ophthalmology. 2005;112:1072-1078.
6. Shields JA, Shields CL, Honavar SG, Demirci H, Cater J. Classification and management of Coats disease: the 2000 Proctor Lecture. Am J Ophthalmol. 2001;131:572-583.
7. Durukan AH. Coats Hastalığı. Ret Vit. 2012;20(özel sayı):115-119.
8. Al-Qahtani AA, Almasaud JM, Ghazi NG. Clinical Characteristics and Treatment Outcomes of Coats Disease in a Saudi Arabian Population. Retina. 2015;5:2091-2099.
9. Morris B, Foot B, Mulvihill A. A population-based study of Coats disease in the United Kingdom I: epidemiology and clinical features at diagnosis. Eye (Lond). 2010;24:1797-1801.
10. Blair MP, Ulrich JN, Elizabeth Hartnett M, Shapiro MJ. Peripheral retinal nonperfusion in fellow eyes in coats disease. Retina. 2013;33:1694-1699.
11. Suzani M, Moore AT. Intraoperative fluorescein angiography-guided treatment in children with early Coats' disease. Ophthalmology. 2015;122:1195-1202.
12. Schefler AC, Berrocal AM, Murray TG. Advanced Coats' disease. Management with repetitive aggressive laser ablation therapy. Retina. 2008;28:S38-41.
13. Küçümen RB, Görgün E, Yenerel NM, Başar D. Coats Hastalığının Güncel Tedavisinde Argon Laser Fotokoagülasyon. T Oft Gaz. 2009;39:64-69.
14. Erol N, Topbaş S. Coats Hastalığında Kriyoterapi ve Lazer Fotokoagülasyon Tedavisinin Etkinliği. Ret-Vit. 2010;18:46-51.
15. Othman IS, Moussa M, Bouhaimed M. Management of lipid exudates in Coats disease by adjuvant intravitreal triamcinolone: effects and complications. Br J Ophthalmol. 2010;94:606-610.
16. Ghazi NG, Al Shamsi H, Larsson J, Abboud E. Intravitreal triamcinolone in Coats' disease. Ophthalmology. 2012;119:648-649.
17. Sallam A, Comer RM, Chang JH, Grigg JR, Andrews R, McCluskey PJ, Lightman S. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Arch Ophthalmol. 2008;126:200-205.
18. Zheng XX, Jiang YR. The effect of intravitreal bevacizumab injection as the initial treatment for Coats' disease. Graefes Arch Clin Exp Ophthalmol. 2014;252:35-42.

19. Villegas VM, Gold AS, Berrocal AM, Murray TG. Advanced Coats' disease treated with intravitreal bevacizumab combined with laser vascular ablation. Clin Ophthalmol. 2014;8:973-976.
20. Gaillard MC, Mataftsi A, Balmer A, Houghton S, Munier FL. ranibizumab in the management of advanced Coats disease Stages 3B and 4: long-term outcomes. Retina. 2014;34:2275-2281.
21. Zhao Q, Peng XY, Chen FH, Zhang YP, Wang L, You QS, Jonas JB. Vascular endothelial growth factor in Coats' disease. Acta Ophthalmol. 2014;92:e225-228.
22. Grosso A, Pellegrini M, Cereda MG, Panico C, Staurenghi G, Sigler EJ. Pearls and pitfalls in diagnosis and management of coats disease. Retina. 2015;35:614-623.
23. Ramasubramanian A, Shields CL. Bevacizumab for Coats' disease with exudative retinal detachment and risk of vitreoretinal traction. Br J Ophthalmol. 2012;96:356-359.
24. Kranias G, Krebs TP. Advanced Coats' disease successfully managed with vitreo-retinal surgery. Eye (Lond). 2002;16:500-501.
25. Muftuoglu G, Gulkilik G. Pars plana vitrectomy in advanced coats' disease. Case Rep Ophthalmol. 2011;2:15-22.
26. Suesskind D, Altpeter E, Schrader M, Bartz-Schmidt KU, Aisenbrey S. Pars plana vitrectomy for treatment of advanced Coats' disease--presentation of a modified surgical technique and long-term follow-up. Graefes Arch Clin Exp Ophthalmol. 2014;252:873-879.
27. Gomez Morales A. Coats' disease. Natural history and results of treatment. Am J Ophthalmol. 1965;60:855-865.
28. Kıratlı H, Eldem B. Management of moderate to advanced Coats' disease. Ophthalmologica. 1998;212:19-22.

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Review

Imaging Methods in the Diagnosis of Optic Disc Drusen

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Summary

Optic disc drusen (ODD) are benign congenital anomalies of the optic nerve characterized by calcified hyaline bodies. While superficial drusen can be diagnosed easily during fundus examination, detecting buried drusen requires the use of additional imaging methods such as B-scan ultrasonography (USG), fundus fluorescein angiography (FFA), computed tomography (CT) and fundus autofluorescence (FAF). ODD can be detected by USG with the presentation of highly reflective round structures. ODD appear as hyperautofluorescent areas on FAF and bright spots on CT scans. FFA can be helpful in differentiating ODD from true optic disc edema. Optic disc edema shows early hyperfluorescence due to diffuse leakage whereas ODD presents as well-defined hyperfluorescence in the late phase. In recent years, it has been reported that optical coherence tomography (OCT) examination has allowed more detailed evaluation of ODD and yielded useful findings for the differentiation of optic disc edema from ODD. In this review, the role of OCT in the diagnosis of ODD is discussed.

Keywords: Optic disc drusen, imaging methods, optical coherence tomography

Introduction

Optic disc drusen (ODD) are autofluorescent, calcified deposits found in the optic nerve head, and typically occur in small, crowded optic discs.[1] Their prevalence ranges from 3.4 to 24 per 1,000 according to clinical studies and 1-2.4% in histological studies.[2,3,4] The prevalence of ODD is higher in women and involvement is usually bilateral.[5,6]

Although the mechanism of drusen formation has not been fully determined, it is believed that congenitally small disc and scleral channels may cause axoplasmic flow stasis and ganglion cell axon death.[7] Furthermore, it has been proposed that drusen continue to grow and move toward the disc surface due to ongoing neural tissue loss. This is supported by the fact that visual field defects, which progress with age, are often detected in the second decade of life.[8] Ophthalmic and systemic diseases commonly associated with drusen are retinitis pigmentosa, angioid streaks, Usher syndrome, Noonan syndrome and Alagille syndrome.[2]

ODD is usually overlooked in clinical examinations because it does not cause any visual symptoms; visual functions are generally not affected early in life. Visual field anomalies arising due to ODD are often not noticed by patients. Visual field defects are reported to occur less often with buried ODD compared to those which are more superficial.[9] ODD-associated visual field defects arise in the inferonasal quadrant in particular, and may manifest as blind spot enlargement, concentric constriction, arcuate defects or peripheral vision loss.[10]

Rarely, ODD can lead to vision loss, usually in the form of a slight decline in visual acuity.[11] The most common cause of sudden vision loss associated with ODD is nonarteritic anterior ischemic optic neuropathy (NAION). Compared to the typical NAION patients, ODD patients are younger and have better visual prognosis.[12] Other rare vascular complications arising due to ODD that have been reported in the literature include subretinal neovascularization, central retinal artery and vein occlusion.[13,14,15] ODD may lead to hemorrhage in the retina and disc margin. Optic disc hemorrhages in particular are more common in children.[16,17,18]

In clinical practice, it can be extremely difficult in some cases to differentiate ODD from true optic disc edema, which is a critical distinction in terms of treatment approach. Superficial ODD can be easily identified as round deposits

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in ophthalmoscopic examination (Figure 1), whereas those located closer to the lamina cribrosa (Figure 2) may not be evident in this examination, requiring additional imaging modalities to confirm diagnosis.[19] One of these is B-scan ultrasonography (USG), which is an inexpensive, fast and practical method of reliably and effectively diagnosing ODD. ODD are easily diagnosed by B-scan USG due to their inherent high reflectivity (Figure 3). The major advantage of USG is the ability to show even the posterior borders of buried drusen, but its drawbacks are low resolution and inability to provide data on the neural retina.[20,21] Although fundus autofluorescence (FAF) is a convenient method of visualizing more superficial drusen, it is insufficient for detecting buried drusen. Superficial drusen appear on FAF as round or oval hyperautofluorescent structures with irregular edges (Figure 4). Drusen at different levels show different intensity of hyperautofluorescence. Deeply buried drusen do not appear on FAF because the overlying tissue prevents autofluorescence. Fundus fluorescein angiography (FFA) is a more difficult and invasive procedure than FAF, but can be utilized in selected cases when differentiation of deeper ODD from optic disc edema is challenging. On FFA, eyes with ODD exhibit mild hyperfluorescence with smooth margins in the peripapillary area in the early phase which becomes more pronounced in the late phase. In optic disc edema and papilledema, hyperfluorescence is evident in the early phase due to diffuse leakage (Figure 5a and 5b). The most distinctive difference between ODD and papilledema is the absence of telangiectatic vessels at the optic nerve head in ODD. Furthermore, unlike in ODD, leakage appears in the early phase as spots on the disc surface which later coalesce.[2]

Figure 1. Superficial drusen located in the inferior optic disc appear as smooth-edged, round deposits (arrows)

Figure 2. Appearance of buried drusen (arrows) located near the lamina cribrosa on ophthalmoscopic examination

Computed tomography (CT) can also be utilized to detect buried drusen. Drusen appear as bright white bodies on CT due to their calcium content (Figure 6). In routine clinical CT examinations, scans are done in 1.5 mm sections, but a thorough scan using thinner sections should be performed in order not to miss small drusen. Because CT is not as sensitive as USG and involves radiation exposure, it is only used in the rare instances that other imaging modalities are not adequate.[2] Furthermore, buried drusen which are not calcified may not appear on fundoscopy, USG or CT.[22]

ODD are usually located on the nasal side of the optic disc. In some cases, they can lead to extensive, severe optic disc swelling, simulating optic nerve tumors.[23] It can be extremely difficult to differentiate ODD from the shiny particles seen in chronic papilledema.[24] The coincidence of ODD and glaucoma may make evaluation of the optic disc and visual field challenging. Although drusen may not block the development

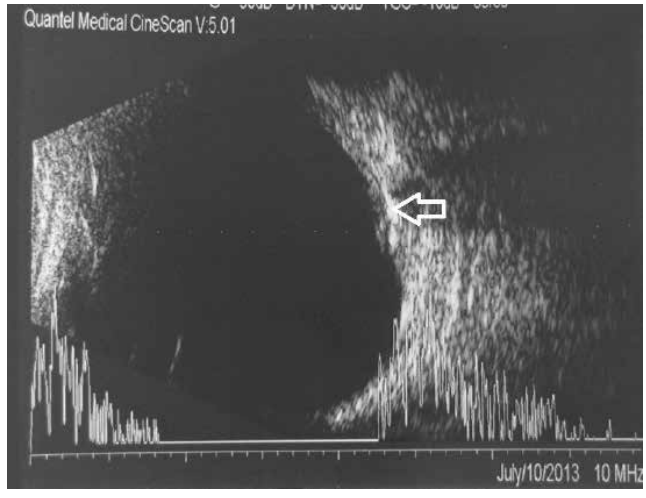

Figure 3. Buried drusen (arrows) have hyperechogenic appearance on B-scan ultrasonography

of glaucomatous cupping in such cases, the presence of a small, crowded disc may mask glaucomatous cupping.[25] Furthermore, it may not be possible with visual field testing to determine whether nerve fiber damage is a result of glaucoma or ODD. For this reason, objective evaluation of the nerve fiber layer by optical coherence tomography (OCT) is necessary, especially in patients without glaucomatous cupping.[26]

OCT allows the early detection of retinal nerve fiber layer (RNFL) thinning. Its advantages include the ability to quantitatively assess nerve fiber loss and its high degree of repeatability.[27] OCT provides more objective data in the evaluation of RNFL loss due to ODD compared to the subjective method of red-free photography.[28] OCT studies on this topic have demonstrated that RNFL thinning is most pronounced in the nasal peripapillary region, where ODD are most commonly found. RNFL values are often normal in cases of buried ODD, but RNFL thinning has been observed in all peripapillary quadrants in cases with superficial drusen.[2,29] In contrast, Gili et al.[30] did not find significant thinning in the temporal quadrant; they attributed this to the less common occurrence of drusen in the temporal disc. In the same study, they also observed a significant association between RNFL thinning and visual field defects. In a very recent report, macular ganglion cell layer (GCL) thickness and RNFL both decreased significantly with superficial drusen, while GCL thickness decreased more than RNFL thickness in buried drusen. The authors emphasized that GCL analysis was more sensitive than RNFL in the detection of axon damage seen with drusen.[31]

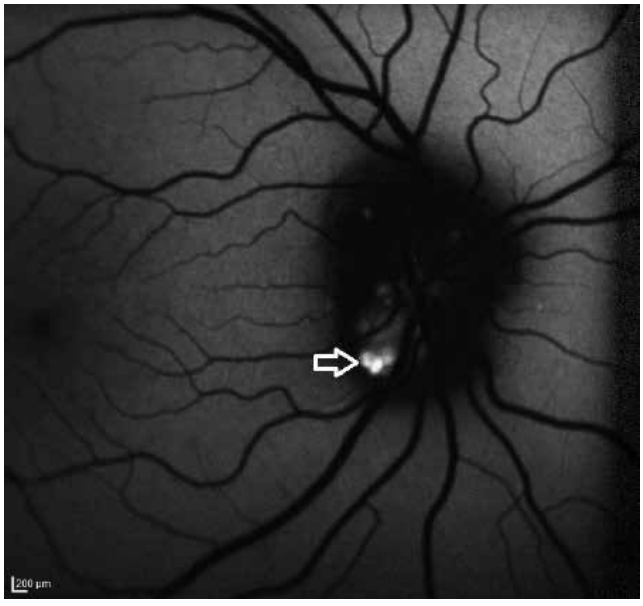

Figure 4. Superficial, round or oval drusen appear as hyperautofluorescent structures with irregular borders on fundus autofluorescence examination

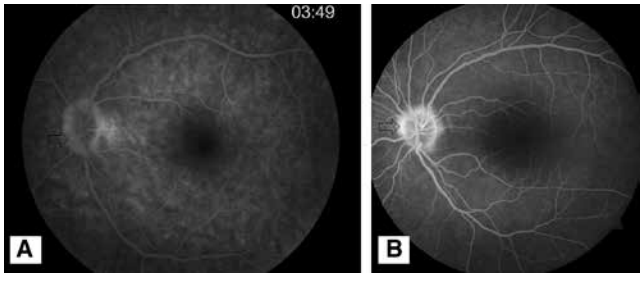

Figure 5. On fundus fluorescein angiography, drusen appear as smooth-bordered hyperfluorescence at late phase (A), whereas optic disc edema shows early diffuse leakage with irregular margins (B)

Because of the low resolution of time-domain OCT, detailed analysis of ODD have only been possible in clinical studies using high-resolution spectral-domain OCT (SD-OCT).[32,33] Substantially different results were reported in these studies regarding the shape, size, and reflective properties of ODD, which was proposed to be a result of variations in the anatomic position and composition of drusen.[33,34,35] Superficial drusen are reported to appear hyporeflective and have a shadow effect, whereas buried drusen appear hyperreflective on SD-OCT (Figure 7).[36] Despite the high resolution of SD-OCT, it may still be inadequate for the visualization of deeper ODD.[37] It is difficult to detect the posterior border of drusen on OCT because the resolution decreases as depth increases and the hyperreflective anterior surface of ODD causes a shadowing effect.[19] The biggest problem in evaluating optic disc lesions with OCT is the presence of nerve fibers and dense vasculature at the disc surface causing hyperreflectivity and shadowing. In some cases, it is not easy to distinguish calcified drusen and their shadows from large superficial blood vessels on OCT.[22]

Recent literature has provided new SD-OCT findings which may assist clinicians in differentiating optic disc edema from buried ODD in particular.[36,37,38,39,40,41,42] Optic nerve head elevation can be seen on OCT in both clinical conditions, but in disc edema the inner surface of the optic nerve has a smooth edge, whereas in ODD the surface is bumpy and has been termed 'lumpy-bumpy' in the literature. The triangular subretinal hyporeflective space (SHS) between

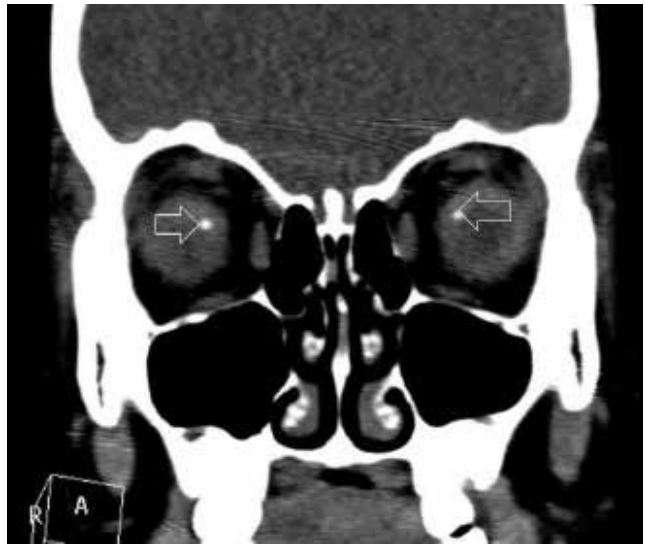

Figure 6. Bilateral optic disc drusen (arrows) appear white and shiny with smooth borders

the sensory retina and retinal pigment epithelium (RPE) has been reported to have a larger area and thickness in disc edema compared to ODD.[39,40,41] Furthermore, Johnson et al.[41] pointed out that the SHS gradually thins moving away from the optic disc in papilledema patients, whereas its thickness decreases suddenly and dramatically in patients with ODD. Kupersmith et al.[43] also demonstrated that in papilledema, the RPE and Bruch's membrane are deformed inward toward the vitreal space due to elevated pressure in the retrolaminar subarachnoid space. Another study determined that total retinal thickness, between the internal limiting membrane and the RPE, is a more sensitive and important parameter than RNFL in the differentiation of papilledema and ODD. In papilledema, a greater increase in total retinal thickness was observed compared to RNFL due to peripapillary subretinal fluid.[44]

New OCT technologies developed in recent years [enhanced depth imaging, (EDI)-OCT and swept source, (SS)-OCT] have improved our ability to examine the form and structure of drusen anatomically. EDI-OCT and SS-OCT allow the detailed examination of the area between the RPE and lamina cribrosa, which could not previously be visualized using SD-OCT. With its high-resolution capability, this new technology enables a closer evaluation of the internal structure of drusen and their relationship with the lamina cribrosa.[19] EDI-OCT allows the examination of structures 500-800 µm deeper than possible with conventional OCT. Furthermore, because the posterior margins of ODD can be better determined by EDI-OCT, their area and volume can also be calculated.[21] It has been reported that drusen have a central hyperreflective focus and an outer hyperreflective edge, with a hyporeflective area in between (Figure 8). A negative correlation between drusen diameter and RNFL thickness as well as greater RNFL loss in drusen located in the optic canal have been demonstrated. In addition, greater RNFL thinning was observed in the presence of drusen with internal hyperreflective foci. In recent years, it has been reported that EDI-OCT and SS-OCT are superior to USG in the detection of buried drusen.[38]

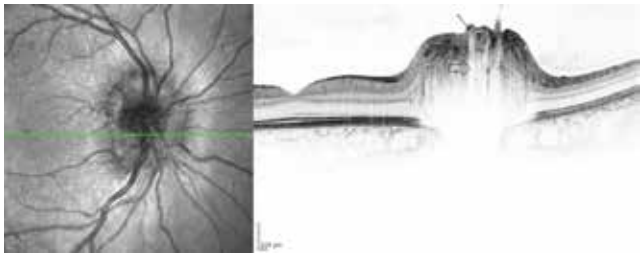

Figure 7. Appearance of superficial optic disk drusen on spectral-domain-optical coherence tomography (arrow indicates superficial drusen; bold arrow indicates hyporeflective shadow)

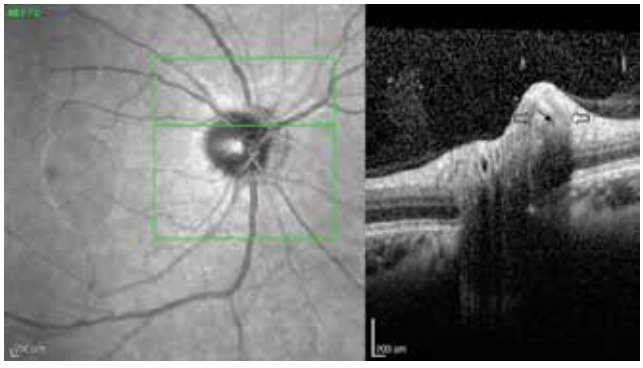

Figure 8. Enhanced depth imaging-optical coherence tomography image of drusen in the superonasal optic disc showing internal hyperreflective focus, external hyperreflective border and hyporeflective area in between (open arrows indicate the drusen borders; arrow shows hyporeflective area)

SS-OCT technology has enabled more detailed evaluation of ODD compared to standard SD-OCT.[45] The findings regarding ODD are similar to those of EDI-OCT studies. However, the SS-OCT studies are few and do not include enough patients. Although better penetration and resolution can be achieved using different wavelength lasers, this OCT technology has not yet become widely used in clinical practice.[19]

Even if followed without treatment, ODD patients should still be closely followed over the long term for possible complications. Detailed examination of ODD structure and location enabled by recent developments in OCT technology have bettered our understanding of the relationship between ODD, RNFL loss and visual field defects. Because the differential diagnosis of ODD includes papilledema and optic neuropathies causing disc edema, correctly diagnosing these patients is crucial to avoid unnecessary treatment and surgery. Although superficial drusen can sometimes be readily identified in a careful fundus examination, cases with buried drusen may require all of the methods described above to reach a definitive diagnosis. OCT technology has substantially facilitated differential diagnosis in these cases and with continuing improvements will undoubtedly have an even more important place in ODD diagnosis and follow-up in the future.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Betül Tuğcu, Hakan Özdemir, Concept: Betül Tuğcu, Hakan Özdemir, Design: Betül Tuğcu, Data Collection or Processing: Betül Tuğcu, Hakan Özdemir, Analysis or Interpretation: Betül Tuğcu, Hakan Özdemir, Literature Search: Betül Tuğcu, Writing: Betül Tuğcu.

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

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References

1. Lam BL, Morais CG, Jr., Pasol J. Drusen of the optic disc. Curr Neurol Neurosci Rep. 2008;8:404-408.
2. Auw-Haedrich C, Staubach F, Witschel H. Optic disk drusen. Surv Ophthalmol. 2002;47:515-532.
3. Friedman AH, Gartner S, Modi SS. Drusen of the optic disc. A retrospective study in cadaver eyes. Br J Ophthalmol. 1975;59:413-421.

4. Lorentzen SE. Drusen of the optic disk. A clinical and genetic study. Acta Ophthalmol (Copenh). 1966:90(Suppl):91-180.
5. Boldt HC, Byrne SF, DiBernardo C. Echographic evaluation of optic disc drusen. J Clin Neuroophthalmol. 1991;11:85-91.
6. Kiegler HR. [Comparison of functional findings with results of standardized echography of the optic nerve in optic disk drusen]. Wien Klin Wochenschr. 1995;107:651-653.
7. Spencer WH. Drusen of the optic disk and aberrant axoplasmic transport. The XXXIV Edward Jackson memorial lecture. Am J Ophthalmol. 1978;85:1-12.
8. Davis PL, Jay WM. Optic nerve head drusen. Semin Ophthalmol. 2003;18:222-242.
9. Wilkins JM, Pomeranz HD. Visual manifestations of visible and buried optic disc drusen. J Neuroophthalmol. 2004;24:125-129.
10. Savino PJ, Glaser JS, Rosenberg MA. A clinical analysis of pseudopapilledema. II. Visual field defects. Arch Ophthalmol. 1979;97:71-75.
11. Mustonen E. Pseudopapilloedema with and without verified optic disc drusen. A clinical analysis I. Acta Ophthalmol (Copenh). 1983;61:1037-1056.
12. Newman WD, Dorrell ED. Anterior ischemic optic neuropathy associated with disc drusen. J Neuroophthalmol. 1996;16:7-8.
13. Frohlich SJ, Ulbig MW, Klauss V. [Sudden loss of vision without previous symptoms. 58-year-old patient with sudden and painless loss of vision of the right eye]. Ophthalmologe. 1999;96:120-121.
14. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. Retina. 1981;1:27-55.
15. Harris MJ, Fine SL, Owens SL. Hemorrhagic complications of optic nerve drusen. Am J Ophthalmol. 1981;92:70-76.
16. Bozinovic MT, Jovanovic P, Zlatanovic G, Veselinovic D, Trenkic AA, Trenkic M. Retinal hemorrhages as one of complications of optic disc drusen during pregnancy. Med Pregl. 2014;67:185-189.
17. Söylev MF, Saatçi AO, Arsan AK, Kaynak S, Duman S, Ergin M. Optik Disk Druzeninin Komplikasyonları ve Birlikte Görüldüğü Oküler ve Sistemik Hastalıklar. Retina-Vitreus. 1996;4:457-462.
18. Neffendorf JE, Mulholland C, Quinlan M, Lyons CJ. Disc drusen complicated by optic disc hemorrhage in childhood. Can J Ophthalmol. 2010;45:537-538.
19. Sato T, Mrejen S, Spaide RF. Multimodal imaging of optic disc drusen. Am J Ophthalmol. 2013; 156:275-282.
20. Kurz-Levin MM, Landau K. A comparison of imaging techniques for diagnosing drusen of the optic nerve head. Arch Ophthalmol. 1999;117:1045-1049.
21. Silverman AL, Tatham AJ, Medeiros FA, Weinreb RN. Assessment of optic nerve head drusen using enhanced depth imaging and swept source optical coherence tomography. J Neuroophthalmol. 2014;34:198-205.
22. Kardon R. Optical coherence tomography in papilledema: what am I missing? J Neuroophthalmol. 2014;34(Suppl):S10-17.
23. Bronner A, Payeur G. [Papillary drusen with a tumoral aspect]. Bull Soc Ophtalmol Fr. 1970;70:136-140.
24. Sibony PA, Kennerdell JS, Slamovits TL, Lessell S, Krauss HR. Intrapapillary refractile bodies in optic nerve sheath meningioma. Arch Ophthalmol. 1985;103:383-385.
25. Samples JR, van Buskirk M, Shults WT, Van Dyk HJ. Optic nerve head drusen and glaucoma. Arch Ophthalmol. 1985;103:1678-1680.
26. Roh S, Noecker RJ, Schuman JS. Evaluation of coexisting optic nerve head drusen and glaucoma with optical coherence tomography. Ophthalmology. 1997;104:1138-1144.
27. Schuman JS, Pedut-Kloizman T, Hertzmark E, Hee MR, Wilkins JR, Coker JG, Puliafito CA, Fujimoto JG, Swanson EA. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. Ophthalmology. 1996;103:1889-1898.
28. Mustonen E, Nieminen H. Optic disc drusen--a photographic study. II. Retinal nerve fibre layer photography. Acta Ophthalmol (Copenh). 1982;60:859-872.
29. Pasol J. Neuro-ophthalmic disease and optical coherence tomography: glaucoma look-alikes. Curr Opin Ophthalmol. 2011;22:124-132.
30. Gili P, Flores-Rodriguez P, Martin-Rios MD, Carrasco Font C. Anatomical and functional impairment of the nerve fiber layer in patients with optic nerve head drusen. Graefes Arch Clin Exp Ophthalmol. 2013;251:2421-2428.
31. Casado A, Rebolleda G, Guerrero L, Leal M, Contreras I, Oblanca N, Munoz-Negrete FJ. Measurement of retinal nerve fiber layer and macular ganglion cell-inner plexiform layer with spectral-domain optical coherence tomography in patients with optic nerve head drusen. Graefes Arch Clin Exp Ophthalmol. 2014;252:1653-1660.
32. Patel NN, Shulman JP, Chin KJ, Finger PT. Optical coherence tomography/ scanning laser ophthalmoscopy imaging of optic nerve head drusen. Ophthalmic Surg Lasers Imaging. 2010;41:614-621.
33. Lee KM, Woo SJ, Hwang JM. Morphologic characteristics of optic nerve head drusen on spectral-domain optical coherence tomography. Am J Ophthalmol. 2013; 155:1139-1147.
34. Wester ST, Fantes FE, Lam BL, Anderson DR, McSoley JJ, Knighton RW. Characteristics of optic nerve head drusen on optical coherence tomography images. Ophthalmic Surg Lasers Imaging. 2010;41:83-90.
35. Slotnick S, Sherman J. Buried disc drusen have hypo-reflective appearance on SD-OCT. Optom Vis Sci. 2012;89:E704-708.
36. Kulkarni KM, Pasol J, Rosa PR, Lam BL. Differentiating mild papilledema and buried optic nerve head drusen using spectral domain opticalv coherence tomography. Ophthalmology. 2014;121:959-963.
37. Slotnick S, Sherman J. Disc drusen. Ophthalmology. 2012; 119:704-708.
38. Merchant KY, Su D, Park SC, Qayum S, Banik R, Liebmann JM, Ritch R. Enhanced depth imaging optical coherence tomography of optic nerve head drusen. Ophthalmology 2013;120:1409-14.
39. Karam EZ, Hedges TR. Optical coherence tomography of the retinal nerve fibre layer in mild papilloedema and pseudopapilloedema. Br J Ophthalmol. 2005;89:294-298.
40. Sarac O, Tasci YY, Gurdal C, Can I. Differentiation of optic disc edema from optic nerve head drusen with spectral-domain optical coherence tomography. J Neuroophthalmol. 2012;32:207-211.
41. Johnson LN, Diehl ML, Hamm CW, Sommerville DN, Petroski GF. Differentiating optic disc edema from optic nerve head drusen on optical coherence tomography. Arch Ophthalmol. 2009;127:45-49.
42. Savini G, Bellusci C, Carbonelli M, Zanini M, Carelli V, Sadun AA, Barboni P. Detection and quantification of retinal nerve fiber layer thickness in optic disc edema using stratus OCT. Arch Ophthalmol. 2006;124:1111-1117.
43. Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. Invest Ophthalmol Vis Sci. 2011;52:6558-6564.
44. Bassi ST, Mohana KP. Optical coherence tomography in papilledema and pseudopapilledema with and without optic nerve head drusen. Indian J Ophthalmol. 2014;62:1146-1151.
45. Nuyen B, Mansouri K, R NW. Imaging of the Lamina Cribrosa using Swept-Source Optical Coherence Tomography. J Curr Glaucoma Pract. 2012;6:113-119.

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Case Report

Isolated Microspherophakia Presenting with Angle-Closure Glaucoma

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Summary
We report a case of 13-year-old girl presenting to our clinic with blurred vision in both eyes. Ophthalmic examination revealed high myopia and angle-closure glaucoma due to pupillary block caused by small, spherical crystalline lenses. Treatment approaches to glaucoma in patients with microspherophakia are discussed in this case report.
Keywords: Microspherophakia, glaucoma, familial microspherophakia, lenticular myopia

Introduction

Microspherophakia is a rare entity in which there is a small, spherical crystalline lens with increased antero-posterior thickness.[1] The characteristic feature of microspherophakia is visibility of the lens equator on full mydriasis. The pathogenesis of this condition is thought to be related to defective development of the lens zonules.[2] Spherical lens may lead to pupillary block and secondary angle-closure glaucoma. Glaucoma is the most common sight-threatening complication of this condition. Lenticular myopia and lens dislocation are other common findings of microspherophakia.[3] Treatment of these patients is difficult and there is no consensus about the treatment approach, especially in patients presenting with secondary angle-closure glaucoma. We report a case with microspherophakia, whose brother also had microspherophakia, presenting as bilateral angle-closure glaucoma.

Case Report

A 13-year-old girl presented to the ophthalmology clinic for refractive eye examination. Her intraocular pressure (IOP) was 38 mmHg in the right eye (OD) and 36 mmHg in the left eye (OS). She had no pain, lacrimation or blepharospams in her eyes. Her visual acuity was 20/20 with -12.0 DS/-3.00 DC x140 degrees in OD and 20/20 with -13.0 DS /-2.75 DC x160 degrees in OS. Central corneal thickness was 560 µm OD and 555 µm OS. Slit-lamp biomicroscopy revealed a shallow anterior chamber in both eyes. Lenses were thicker and steeper than normal and appeared to bulge forward into the pupil (Figure 1). The lens edges and long, weak zonules were clearly visible on slit-lamp examination after pupillary dilation (Figure 2a, 2b). Lens thickness after pupillary dilation was 4.93 mm OD and 4.96 mm OS. Gonioscopic examination revealed completely closed angles and no anterior synechia was observed with indentation. Ultrasound biomicroscopy (UBM) showed anteriorly displaced small and spheric crystalline lenses and almost 360 degree closed angles (Figure 3). Anterior chamber depth was 2.00 mm OD and 2.02 mm OS. Axial length was 20.23 mm OD and 20.28 mm OS, suggesting lenticular myopia. A thorough family history could not be obtained; however, she had a positive family history of high myopia and poor vision on her mother's side.

Her brother also has myopia and microspherophakia. Her brother's IOP was normal but appositional angle closure was observed in both eyes. No systemic anomalies were found on detailed pediatric examination. Mental status was within normal limits for both siblings.

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Heidelberg retinal tomography was performed and both eyes were within normal limits. Standard automated perimetry revealed minimal visual field loss and Seidel's scotoma in both eyes.

We initiated medical treatment of 0.5% timolol maleate drops applied twice a day to both eyes. IOP was 29 mmHg OD and 26 mmHg OS after one month of timolol maleate treatment. We then added 2% dorzolamide hydrochloride twice a day to the therapy. At final examination, IOP was 32 mmHg OD and 33 mmHg OS. Because of uncontrolled IOP, we performed laser iridotomy in both eyes (Figure 4). Gonioscopic and UBM examinations revealed open angle in both eyes after laser iridotomy.

Figure 1. Slit-lamp biomicroscopic view of cornea and lens of the patient. Anterior chambers were shallow; lenses were thicker and steeper than normal and appeared to bulge forward into the pupil

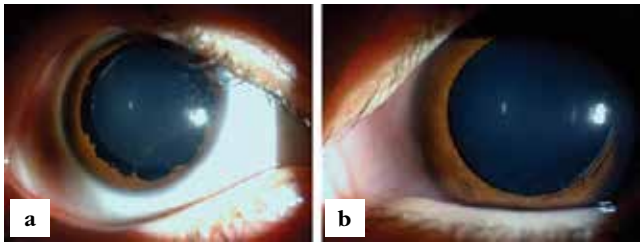

Figure 2. Slit-lamp biomicroscopic view of cornea and lens of the patient's right (a) and left (b) eye after pupil dilation; lens edges and zonules were clearly visible

After laser iridotomy, IOP was 21 mmHg OD and 23 mmHg OS. We prescribed 0.5% timolol maleate twice a day for both eyes. One month later, IOP was 15 mmHg OD and 16 mmHg OS. Her IOP levels were within normal limits at subsequent follow-up visits, but again increased to 38/24 mmHg OD/OS 15 months after laser iridotomy. The patient was given topical fixed-combination 0.5% timolol maleate 2% dorzolamide twice a day and 0.004% travoprost once a day. Following this treatment the IOP reduced to 32/19 mmHg OD/OS. Cyclopentolate 1% eye drops were administered three times a day to deepen the anterior chamber and correct appositional angle closure in order to reduce IOP. After this treatment her IOP values were 22/15 mmHg OD/OS. Although IOP was reduced to a safer level with cyclopentolate hydrochloride eye drops, the patient could not tolerate the treatment because of blurred vision. For this reason, clear lens extraction and intraocular lens implantation (IOL) was considered for the OD. The patient underwent phacoemulsification under general anesthesia, but an IOL could not be implanted because of small capsular bag and weak zonular support. Following lens extraction IOP reduced to 18 mmHg without antiglaucomatous medication. The patient began to use contact lens for refractive correction.

Discussion

Microspherophakia is usually associated with systemic disorders such as Weill-Marchesani syndrome (WMS), homocystinemia, Marfan syndrome, Alport syndrome and Klinefelter syndrome.[2,3,4,5,6,7,8,9,10] Less commonly, it has been reported with other disorders such as Lowe syndrome, Peter's anomaly, cri-du-chat syndrome, hyperlysinaemia, and rhizolemic form of chondrodysplasia punctata.[6,7,8,9]

Characteristic eye abnormalities of WMS are microspherophakia and ectopia lentis which causes high myopia (mostly dislocates either inferiorly or anteriorly). Other ocular associations are acute and/or chronic glaucoma, cataract and synechia. Glaucoma mostly develops due to the presence of the dislocated lens in the pupil or the anterior chamber. Progressive microspherophakia is responsible for severe and progressive myopia.[7,8,9]

Marfan syndrome is an autosomal dominantly inherited disorder. The main ocular features of Marfan syndrome, all of which can result in decreased vision, include bilateral lens dislocation, myopia and retinal detachment. About 80%

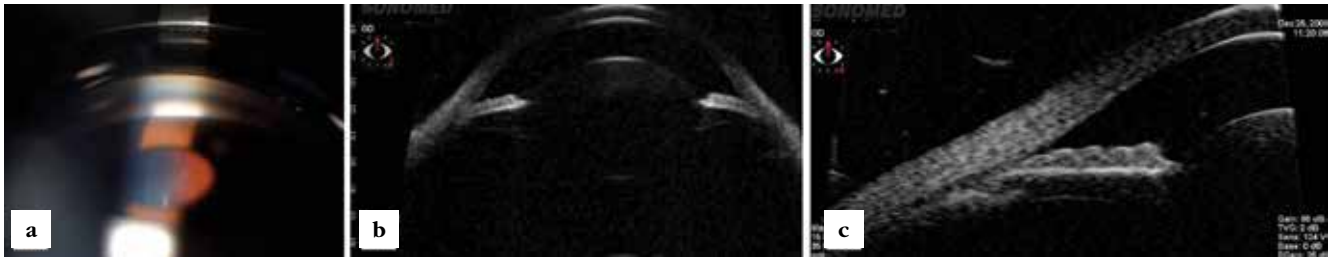

Figure 3. Gonioscopy (a) and ultrasound biomicroscopy showed an anteriorly displaced small and spheric crystalline lens (b) and almost 360 degree closed angles (c)

of patients have ectopia lentis, which is usually bilateral, symmetrical and upward. The most prominent angle anomalies are dense iris processes and thickened trabecular sheets.[3,10]

Our patient had no clinical features to suggest any of these syndromes. Her mental status and height were normal. She had no cardiac, skeletal or muscular anomalies. Also, there was no evidence to suggest Alport syndrome in her pediatric examination. Her condition might be familial in origin, because her brother also has microspherophakia. Genetic counseling could not be performed due to the patient's health insurance problem. Familial microspherophakia is not associated with any systemic defects. Although it is an autosomal recessive disorder, there is a case in the literature with autosomal dominant inheritance.[2] Other ocular features of familial microspherophakia are lenticular myopia, posterior staphyloma, myopic crescent, ectopic pupil, glaucoma and retinal detachment.[2]

Glaucoma in isolated microspherophakia is not common.[2,3] Several mechanisms can lead to glaucoma. Acute angle closure may result from pupillary block caused by the forward movement of the spherical lens or anterior chamber luxation of the lens due to weak and long zonules.[11] Peripheral anterior synechiae formation by unrelieved pupillary block can cause synechial angle closure and irreversible trabecular meshwork damage. Chronic pupillary block may also lead to crowding of the anterior chamber angle by the spherical lens.[3,11] Developmental anomaly of the anterior chamber angle may also contribute to the development of glaucoma in patients with microspherophakia.[3,11,12]

Our patient presented with bilateral angle-closure glaucoma. This resulted from pupillary block by the spherical lens. Peripheral iridectomy is the treatment of choice for these patients. Thus, uncontrolled IOP with medical therapy and resolution of her condition with laser iridotomy confirmed our diagnosis that microspherophakia induced pupillary-block glaucoma. However, these treatment modalities provided temporary improvement in the present case. For this reason, we suggest that more than one mechanism other than pupillary block might have led to the development of glaucoma in our case. As seen on UBM, the lens-iris diaphragm was persistently displaced anteriorally due to weak zonules and thus closed the iridocorneal angle. Therefore, IOP was not reduced permanently by laser iridotomy alone. Reduction of IOP after clear lens extraction confirms this observation. We did not consider lensectomy as a first choice therapy in our patient because of her age, risk of zonular defects, small capsular bag for standard IOL and postoperative visual problems such as accommodation and anisometropia. However, her IOP levels remained elevated despite patent peripheral iridotomy and maximum tolerated medical therapy, so we performed clear lens extraction. Indications for clear lens extraction in patients with microspherophakia are corneo-lenticular contact, unilateral high myopia, pupillary block and secondary intractable glaucoma.[12] However, there are higher rates of intraoperative complications, such as difficulties performing capsulorhexis and implanting the IOL, during clear lens extraction of these patients. In our case, small capsular bag led to difficulty implanting the IOL into the bag. We did not implant the IOL into the sulcus because of the weakness of the zonules as this may be a risky situation for uncontrolled glaucoma.

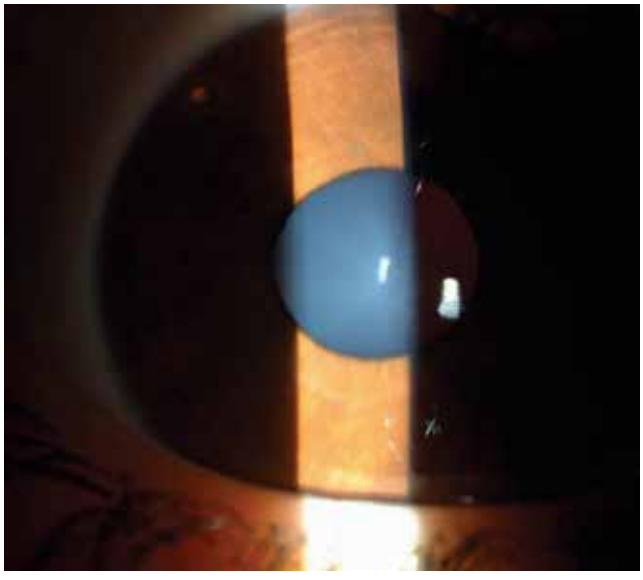

Figure 4. Anterior segment view of the patient after laser iridotomy

Management of microspherophakia is still debated. Medical and laser treatment fail in about 60% of eyes with this condition. Lensectomy is still the first choice if medical therapy and laser iridotomy fail. There are reports in the literature of treating microspherophakia with lensectomy. Khokhar et al.[13] reported a case that presented with superotemporally luxated microspherophakic lenses. They successfully treated this patient with clear lens extraction with IOL implantation. Kaushik et al.[12] described an adult patient who presented with bilateral acute angle-closure glaucoma with microspherophakia and whose IOP was successfully controlled with lensectomy and anterior vitrectomy. Willoughby and Wishart[14] described a case of spherophakia with glaucoma whose IOP was successfully controlled following lensectomy without additional medication. Kanamori et al.[15] also described a patient with microspherophakia and chronic angle-closure glaucoma whose IOP was controlled well with goniosynechiolysis and lensectomy. In contrast, Yasar[16] described a patient in whom IOP was not controlled with lensectomy in the short term and who subsequently required mitomycin-C augmented trabeculectomy in both eyes. Harasymowycz and Wilson[17] advised a combination of lensectomy, anterior vitrectomy, scleral-fixated IOL and Molteno tube shunt implantation to control IOP in patients with uncontrolled chronic angle-closure glaucoma caused by microspherophakia. They concluded that in early cases, prophylactic laser iridotomy should be performed. Senthil et al.[18] reported higher trabeculectomy success rates (86% at 6 months, 61% at 8 years) in patients with microspherophakia in their retrospective study with a long follow-up period. However, they observed significant complications, including shallow anterior

chamber and iridocorneal and iridolenticular contact, which required surgical intervention. A large proportion (45%) of the trabeculectomized eyes underwent lensectomy for IOP control in their study.

In our study, lensectomy effectively decreased IOP, but continued follow-up is necessary to determine whether lensectomy alone will be sufficient for IOP control over a longer time period. Based on available data, we suggest that a stepwise treatment protocol would be more safe and effective in the management of the patients with glaucoma secondary to microspherophakia. According to this treatment protocol, laser iridotomy should be performed first. If laser iridotomy is ineffective, clear lens extraction with or without goniosynechiolysis, filtering surgery and tube shunt surgery may be performed, in that order.

In conclusion, optimal management of glaucoma in microspherophakia is still uncertain. Multiple factors are responsible for the development of glaucoma in microspherophakia. For this reason, success may not be obtained with a single treatment modality, as with our patient. Microspherophakic patients should be monitored closely to determine the appropriate method for treating their glaucoma.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tülay Şimşek, Enver Şimşek, Faruk Öztürk, Concept: Tülay Şimşek, Enver Şimşek, Emrullah Beyazyıldız, Design: Tülay Şimşek, Emrullah Beyazyıldız, Faruk Öztürk, Data Collection or Processing: Tülay Şimşek, Enver Şimşek, Analysis or Interpretation: Tülay Şimşek, Faruk Öztürk, Literature Search: Tülay Şimşek, Enver Şimşek, Emrullah Beyazyıldız, Writing: Tülay Şimşek, Emrullah Beyazyıldız.

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References

1. Johnson VP, Grayson M, Christian JC. Dominant microspherophakia. Arch Ophthalmol. 1971;85:534-537.
2. Johnson GJ, Bosanquet RC. Spherophakia in a Newfoundland family: 8 years' experience. Can J Ophthalmol. 1983;18:159-164.
3. Nelson LB, Maumenee IH. Ectopia lentis. Surv Ophthalmol. 1982;27:143-160.
4. D T. Paediatric Ophthalmology. (2nd ed.) London; Blackwell Science; 1997;446-447.
5. Kitsiou-Tzeli S, Dellagrammaticas HD, Papas CB, Ladas ID, Bartsocas CS. Unusual ocular findings in an infant with cri-du-chat syndrome. J Med Genet. 1983;20:304-307.
6. Faivre L, Dollfus H, Lyonnet S, Alembik Y, Megarbane A, Samples J, Gorlin RJ, Alswaid A, Feingold J, Le Merrer M, Munnich A, Cormier-Daire V. Clinical homogeneity and genetic heterogeneity in Weill-Marchesani syndrome. Am J Med Genet A. 2003;123A:204-207.
7. Verloes A, Hermia JP, Galand A, Koulischer L, Dodinval P. Glaucoma-lens ectopia-microspherophakia-stiffness-shortness (GEMSS) syndrome: a dominant disease with manifestations of Weill-Marchesani syndromes. Am J Med Genet. 1992;44:48-51.
8. Dagoneau N, Benoist-Lasselin C, Huber C, Faivre L, Megarbane A, Alswaid A, Dollfus H, Alembik Y, Munnich A, Legeai-Mallet L, Cormier-Daire V. ADAMTS10 mutations in autosomal recessive Weill-Marchesani syndrome. Am J Hum Genet. 2004;75:801-806.
9. Nagata M, Takagi S, Yamasaki A, Tsunematsu S, Kumagami T, Itamochi C, Tamai A. Histopathological study of microspherophakia in the Weill-Marchesani syndrome. Jpn J Ophthalmol. 1995;39:89-95.
10. Probert LA. Spherophakia with brachydactyly; comparison with Marfan's syndrome. Am J Ophthalmol. 1953;36:1571-1574.
11. Chan RT, Collin HB. Microspherophakia. Clin Exp Optom. 2002;85:294-299.
12. Kaushik S, Sachdev N, Pandav SS, Gupta A, Ram J. Bilateral acute angle closure glaucoma as a presentation of isolated microspherophakia in an adult: case report. BMC Ophthalmol. 2006;6:29.
13. Khokhar S, Pangtey MS, Sony P, Panda A. Phacoemulsification in a case of microspherophakia. J Cataract Refract Surg. 2003;29:845-847.
14. Willoughby CE, Wishart PK. Lensectomy in the management of glaucoma in spherophakia. J Cataract Refract Surg. 2002;28:1061-1064.
15. Kanamori A, Nakamura M, Matsui N, Tomimori H, Tanase M, Seya R, Maeda H, Negi A. Goniosynechialysis with lens aspiration and posterior chamber intraocular lens implantation for glaucoma in spherophakia. J Cataract Refract Surg. 2004;30:513-516.
16. Yasar T. Lensectomy in the management of glaucoma in spherophakia: is it enough? J Cataract Refract Surg. 2003;29:1052-1053.
17. Harasymowycz P, Wilson R. Surgical treatment of advanced chronic angle closure glaucoma in Weill-Marchesani syndrome. J Pediatr Ophthalmol Strabismus. 2004;41:295-299.
18. Senthil S, Rao HL, Hoang NT, Jonnadula GB, Addepalli UK, Mandal AK, Garudadari CS. Glaucoma in microspherophakia: presenting features and treatment outcomes. J Glaucoma. 2014;23:262-267.

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Case Report

A Case of Lyme Disease Accompanied by Uveitis and White Dot Syndrome

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Summary
In this case report we aimed to present a case of Lyme disease presenting as peripheral retinal vasculitis, intermediate uveitis and multifocal white dots in the posterior pole. The patient exhibited vitritis and snowball opacities in both eyes. A diagnosis of Lyme disease was made based on clinical, angiographic and laboratory findings. Fundus fluorescein angiography revealed optic nerve and retinal venous leakage as well as multiple hyperfluorescent foci in both eyes. The patient's symptoms and ocular findings significant improved after treatment with a combination of systemic antibiotics and steroids. Ophthalmologists should bear in mind that conditions presenting with uveitis and multifocal white dots may be related to Lyme disease.
Keywords: Lyme disease, white dot syndromes, retinal vasculitis, uveitis

Introduction

Lyme disease is the most common arthropod-related infectious disease caused by a spirochete known as *Borrelia burgdorferi*.[1] Ocular involvement of Lyme disease is characterized by conjunctivitis, episcleritis, keratitis, uveitis, neuroretinitis, retinal vasculitis and cranial nerve palsies.[2] It is probably underdiagnosed by ophthalmologists due to difficulty in the serologic diagnosis of the disease, as well as its nonspecific symptoms.

In this case report, we present a case of Lyme borreliosis and aim to point out a possible association between Lyme disease and white dot syndromes.

Case Report

A 30-year-old male patient with arthralgia had a history of an erythema on his leg resembling erythema nodosum. His best-corrected visual acuity was 20/20 in both eyes and intraocular pressure was normal at presentation. On slit-lamp examination, there was mild anterior chamber reaction and 2+ vitreous cells in both eyes. Fundus examination revealed snowball opacities and vascular sheathing in the inferior quadrants of the retina in both eyes (Figure 1a). Fluorescein angiography showed optic disc and retinal vascular leakage, and hyperfluorescent foci (Figure 1b, 1c, 1d). Indocyanine green angiography also showed hyperfluorescent foci at the posterior pole and in the peripheral fundus (Figure 1e, 1f, 1g, 1h).

From the patient's history we learned that he was working as a map engineer and had a history of trip to an endemic area. During his trip, he had noted erythema with papules on his leg, but had not assigned importance to the lesions, which spontaneously resolved. The patient was referred to the department of rheumatology for uveitis-associated systemic vasculitis work-up. The laboratory tests for sarcoidosis, syphilis and toxoplasmosis were within normal limits, except for elevated serum level of Lyme immunoglobulin M (350, normal range: 40-230) and positive immunoblot analysis. The patient did not exhibit any signs of Behçet's disease. Given the findings and medical history, he was diagnosed with Lyme disease and a combination of topical prednisolone acetate therapy and intravenous ceftriaxone (10 days) was given, followed by a 4-week course of amoxicillin/clavulanate and oral corticosteroid

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therapy. After 3 months of therapy, no cells were observed in anterior chamber and vitreous, and leakage from retinal veins was reduced in fluorescein angiography at final visit (Figure 2). No recurrence was observed over a 1.5-year follow-up period.

Discussion

The clinical features and course of Lyme borreliosis in various systems are well described in the literature, but there has been little attention paid to its ocular involvement. Ocular presentations of Lyme disease include conjunctivitis, episcleritis, keratitis, uveitis, neuroretinitis, retinal vasculitis and cranial nerve palsies.[2,3] In 1991, Smith et al.[4] published the first report of retinal vasculitis in patients with seroreactivity to Lyme borreliosis. Their two patients' ocular findings resolved with a combination of systemic antibiotic and corticosteroid therapy. Recently, Mikkila et al.[5] reported the largest case series of 20 patients with ocular Lyme disease; eight patients had retinal vasculitis, while the other cases developed ocular adnexa inflammation and neuro-ophthalmological disorder in addition to branch central retinal vein occlusion. Two of these cases were accompanied by intermediate uveitis and one of two presented with multiple hypofluorescent foci at the level of the retinal pigment epithelium.[5] Our patient also had intermediate uveitis and multiple foci around the posterior pole.

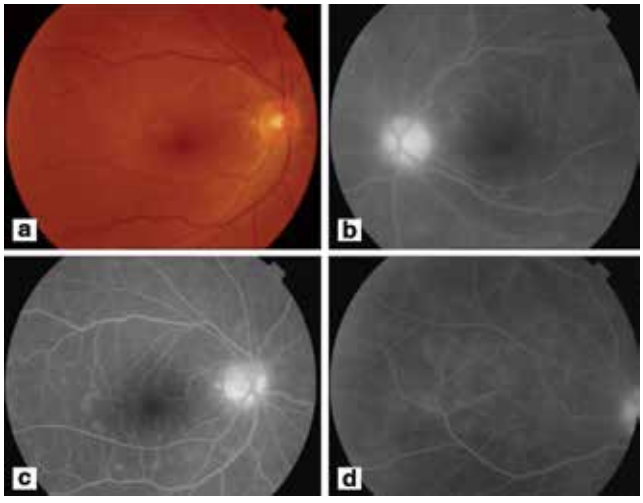

Figure 1a, b, c, d. The fundus photograph and fluorescein angiography findings of the patient. Fundus photographs showed normal disc, macula and vascular archs (a), fluorescein angiography revealed leakage of the optic nerve heads, retinal veins and hyperfluorescence around the macula (b, c, d)

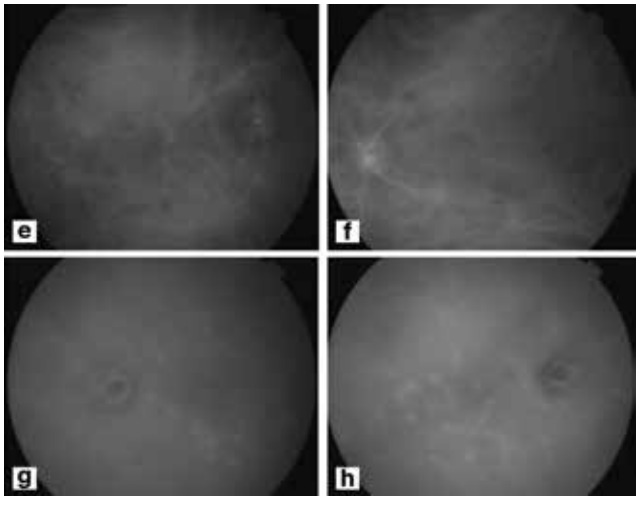

Figure 1e, f, g, h. Indocyanine green angiography revealed hyperfluorescent focuses around the macula

Ocular Lyme disease may affect either retinal arteries or veins to different degrees. Arterial involvement includes sheathing, cotton wool spots and obstruction, while venous involvement includes sheathing, retinal hemorrhage, edema and branch retinal vein occlusion.[6] Retinal vasculitis may occur around the macula as well as peripheral retina associated with anterior and/or posterior segment ocular inflammation. In our patient, we observed leakage from retinal veins only, which extended from mid-periphery to the far-periphery of the fundus with anterior chamber reaction in addition to snowball opacities in the inferior peripheral area.

Serologic tests are often used for the diagnosis of Lyme disease. The recommended protocol includes a 2-test approach: Enzyme-linked immunosorbent assay (ELISA) and Western blot (WB).[7] In this method, specimens are first tested by ELISA and then WB assay is used to confirm positive ELISA results. Because of limited sensitivity and specificity, these tests may be insufficient to diagnose current infection. Therefore the clinician should use both clinical findings and laboratory tests in order to diagnose Lyme disease, as in our case.

White dot syndromes have been associated with various diseases that are characterized by delayed hypersensitivity reaction such as sarcoidosis, tuberculosis, schistosomiasis and also Lyme disease.[8,9,10,11] Despite these reports, in a study with 18 patients who showed all characteristic fundus and angiographic signs of white dot syndromes and had elevated serum levels of *Borrelia burgdorferi*-specific antibodies, no patient demonstrated evidence of *Borrelia* using immunoblotting methods.[11]

Although the exact pathogenesis in white dot syndromes is controversial, we thought that the relationship between these two conditions may be a result of the common pathology, vasculitis, which is also responsible for complications in the late phase of Lyme disease.

We treated our patient with systemic antibiotics in combination with oral and topical steroids. Although some

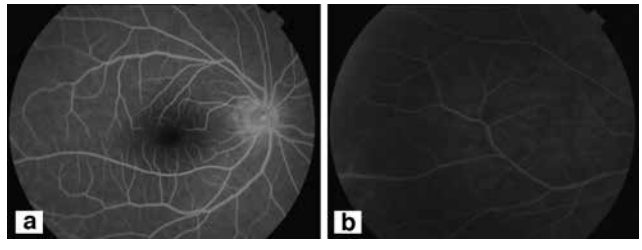

Figure 2a, b. Fundus fluorescein angiogram of the patient following medical treatment

manifestations of Lyme disease may resolve without antibiotic treatment; there is an increased risk of recurrence and progression to serious complications in the absence of antibiotic therapy.[12] No recurrence was observed in our case. Therefore, the recommended treatment is antibiotics therapy combined with systemic steroids in severe cases.[6]

In our study, we report a patient with retinal vasculitis, snowball opacities and multifocal dots. Lyme disease, although rarely encountered, should be considered in the differential diagnosis of white dot syndromes.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yonca Aydın Akova, Concept: Yonca Aydın Akova, Design: İlkay Kılıç Müftüoğlu, Yonca Aydın Akova, Sirel Gür Güngör, Data Collection or Processing: Yonca Aydın Akova, İlkay Kılıç Müftüoğlu, Analysis or Interpretation: Yonca Aydın Akova, İlkay Kılıç Müftüoğlu, Literature Search: İlkay Kılıç Müftüoğlu, Sirel Gür Güngör, Writing: İlkay Kılıç Müftüoğlu.

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

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

References

1. Stricker RB, Lautin A, Burrascano JJ. Lyme disease: point/counterpoint. Expert Rev Anti Infect Ther. 2005;3:155-165.
2. Mikkila HO, Seppala IJ, Viljanen MK, Peltomaa MP, Karma A. The expanding clinical spectrum of ocular lyme borreliosis. Ophthalmology. 2000;107:581-587.
3. Bozkurt MK, Saydam L, Ertürk Ö, B K. Lyme hastalığına bağlı bilateral fasiyal nöropati. Tıp Araştırmaları Dergisi. 2011;9:185-187.
4. Smith JL, Winward KE, Nicholson DF, Albert DW. Retinal vasculitis in Lyme borreliosis. J Clin Neuroophthalmol. 1991;11:7-15.
5. Mikkila HO, Seppala IJ, Viljanen MK, Peltomaa MP, Karma A. The expanding clinical spectrum of ocular lyme borreliosis. Ophthalmology. 2000;107:581-587.
6. Leys AM, Schonherr U, Lang GE, Naumann GO, Goubau P, Honore A, Valvekens F. Retinal vasculitis in Lyme borreliosis. Bull Soc Belge Ophtalmol. 1995;259:205-214.
7. Tugwell P, Dennis DT, Weinstein A, Wells G, Shea B, Nichol G, Hayward R, Lightfoot R, Baker P, Steere AC. Laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med. 1997;127:1109-1123.
8. Dick DJ, Newman PK, Richardson J, Wilkinson R, Morley AR. Acute posterior multifocal placoid pigment epitheliopathy and sarcoidosis. Br J Ophthalmol. 1988;72:74-77.
9. Wolf MD, Folk JC, Nelson JA, Peeples ME. Acute, posterior, multifocal, placoid, pigment epitheliopathy and Lyme disease. Arch Ophthalmol. 1992;110:750.
10. Framme C, Sachs HG, Gabler B, Roider J. Fundus autofluorescence in APMPPE in association with lyme disease. Retina. 2002;22:653-657.
11. Bodine SR, Marino J, Camisa TJ, Salvate AJ. Multifocal choroiditis with evidence of Lyme disease. Ann Ophthalmol. 1992;24:169-173.
12. Kauffmann DJ, Wormser GP. Ocular Lyme disease: case report and review of the literature. Br J Ophthalmol. 1990;74:325-327.

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Case Report

Idiopathic Isolated Cilioretinal Artery Occlusion Treated with Hyperbaric Oxygen Therapy

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Summary
Cilioretinal artery occlusion (CLRAO) is a rare event which has been reported in association with various systemic diseases. We report a case of idiopathic isolated CLRAO treated successfully with hyperbaric oxygen (HBO) therapy. A 26-year-old man presented with sudden, painless vision loss and an inferior hemivisual field defect in the left eye. Fundus fluorescein angiography revealed an occluded cilioretinal artery. After 2 weeks of HBO therapy, visual acuity improved from 20/200 to 20/20. The visual field defect improved.
Keywords: Cilioretinal artery occlusion, fundus fluorescein angiography, hyperbaric oxygen therapy, visual field

Introduction

Retinal artery occlusions (RAO) present with acute, painless loss of monocular vision. Central retinal artery occlusion (CRAO) is a rare event with an incidence of approximately 1 to 10 in 100,000.[1,2] Symptomatic cilioretinal artery occlusion (CLRAO) is even less common; comprising about 5.3%-7.1% of all RAOs.[3,4] To our knowledge, there have been few reports in the literature presenting isolated CLRAO treated with hyperbaric oxygen (HBO) therapy. In this study, we report a case of CLRAO treated with HBO therapy.

Case Report

A 26-year-old man came to our clinic with a complaint of painless sudden loss of vision in the left eye, which had started 20 hours earlier. On ophthalmic examination, best-corrected visual acuity was 20/200 in the left eye and 20/20 in the right eye (Snellen chart). Intraocular pressure was 12 mmHg in both eyes. Slit-lamp examinations of anterior chambers were normal in both eyes. Funduscopy of the left eye revealed well-demarcated retinal edema centered on a cilioretinal artery adjacent to the fovea (Figure 1). We diagnosed the disease as CLRAO. After application of topical timolol+dorzolamide+bimatoprost and oral 500 mg acetazolamide, ocular massage was performed. Fundus fluorescein angiography demonstrated an occluded cilioretinal artery (Figure 2).

HBO therapy was started 22 hours after the onset of symptoms. The patient underwent 5 HBO therapy sessions (2.5 atm, 2 hours). When he returned on the third day after treatment, his visual acuity was unchanged. Five additional HBO treatments were performed, and one week later the visual acuity of the left eye had improved to 20/30. Resolution of the retinal edema was also noted. HBO treatment was discontinued after 20 sessions (total 40 hours). When he returned on the second week after treatment his visual acuity had improved to 20/20. The retinal edema was further resolved. Fundus fluorescein angiography on the second week after the end of treatment demonstrated that the cilioretinal artery was recanalized (Figure 3a, 3b). Computerized visual field testing also demonstrated a significant decrease in the size of the visual field defect (Figure 4a, 4b). His blood laboratory findings, systemic physical examination, electrocardiogram, and chest

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x-ray were all unremarkable. Cryoglobulin, lupus anticoagulant, and anti-cardiolipin antibodies were all negative. Antithrombin III, protein C, and protein S activities were normal.

Discussion

The central retinal artery supplies the inner retina and the surface of the optic nerve. In some individuals, the cilioretinal artery, a branch of the ciliary circulation, may supply a portion of the retina including the macula. In our patient, the cilioretinal artery entered into the retina at the optic disc margin on the temporal side, supplying some part of the upper temporal quadrant of the retina (Figure 1).

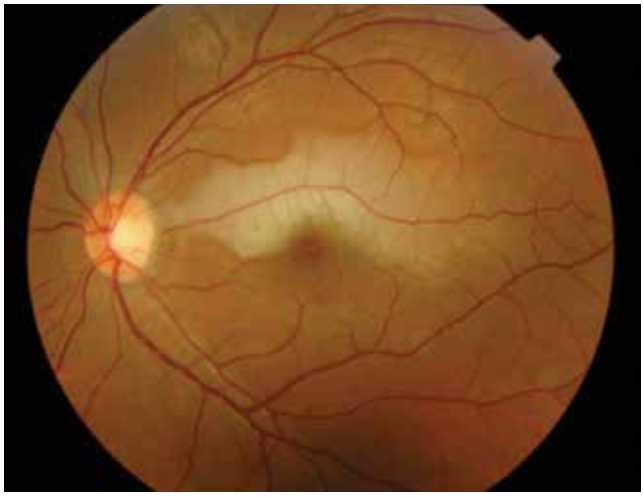

Figure 1. Fundus photograph at the first visit showing retinal edema adjacent to the fovea

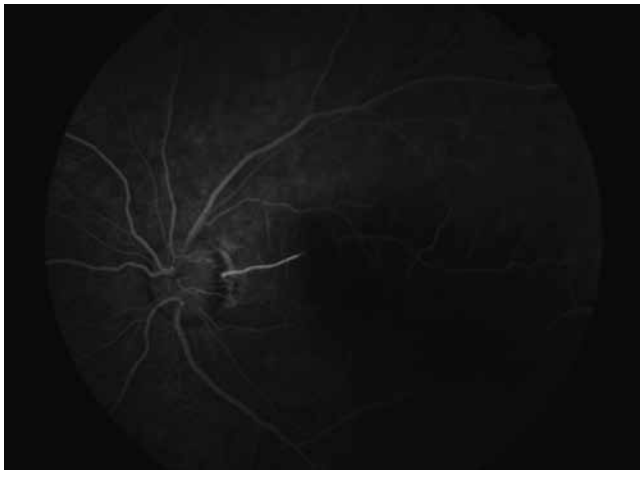

Figure 2. Fundus fluorescein angiography revealed an occluded cilioretinal artery

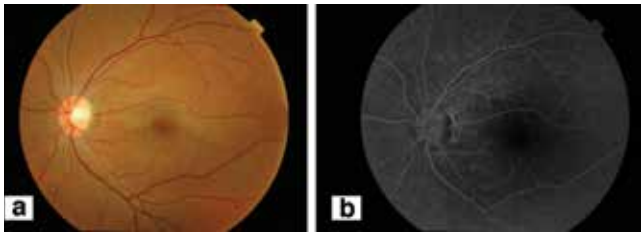

Figure 3. Fundus photograph (a) and fundus fluorescein angiography (b) in the second week after treatment showing recanalization of the cilioretinal artery

In CLRAO, vision loss results from cell death in the inner retinal layers (mainly ganglion cells) despite relative sparing of the outer layers. In order to prevent irreversible damage to the retina, HBO therapy must be provided as soon as possible after the onset of vision loss. According to the HBO treatment algorithm accepted at most centers, patients presenting within 24 hours of symptom onset should be considered for HBO therapy.[5] Our patient received HBO therapy 22 hours after the onset of vision loss. While there are a few case reports of patients presenting after this time interval who have had positive results when treated with HBO therapy, the majority of cases do not respond when treated beyond this point.[6,7,8,9] Hayreh et al.'s[10] animal model, in which a CRAO induced by clamping the artery for 4 hours or longer resulted in massive and irreversible retinal damage, may not be applicable to the human situation.[11] In the clinical setting, there are many variables, including the varying degrees and acuteness of the reduction in flow as well as the range, depending upon the patient, of differing perfusion pressures required to avoid retinal damage in different areas of the retina. In some cases of RAO, the retina, or at least a portion of the retina, may retain functional ability for a longer period of time than previously thought.[11] Weiss[11] reported an 81-year-old woman with mitral valve disease (on Coumadin) with a 12-day history of symptoms secondary to RAO. After 8 HBO sessions (1 hour, 1.5 atm), the visual acuity improved from counting fingers at 6 feet to 20/50 with improvement in the visual field.

There is no consensus with regard to the duration, pressure and the number of sessions of HBO treatment. Ophthalmology literature includes cases successfully treated with HBO at pressures ranging from 1.5 atm to 3 atm.[5,6,7,11] The retina has the highest rate of oxygen consumption of any organ in the body, at 13 ml/100 g/minute.[12] Therefore, it is very sensitive to ischemia, even more so at younger ages. Considering the young age of our patient, we preferred high pressure (2.5 atm) and long duration (2 hours) of HBO therapy. In order to be effective, the administration of supplemental oxygen must be continued until the obstructed retinal artery recanalizes, which typically occurs within the first 72 hours.[5,13] However, in our case, the occluded cilioretinal artery was not recanalized in the first 72 hours. On the third day, after 5 HBO therapy sessions, the visual acuity was unchanged. One week after the onset of CLRAO, following a total of 10 HBO treatments, the visual acuity of the left eye improved to 20/30. Resolution of the retinal edema was also noted. HBO treatment was stopped after 20 sessions (total 40 hours). When he returned in the second week after treatment, his visual acuity had improved to 20/20. Fundus fluorescein angiography on the second week after the treatment demonstrated that the cilioretinal artery was recanalized (Figure 3).

CLRAO has been reported in association with embolism, sildenafil, systemic lupus eryhematosus, Antiphospholipid

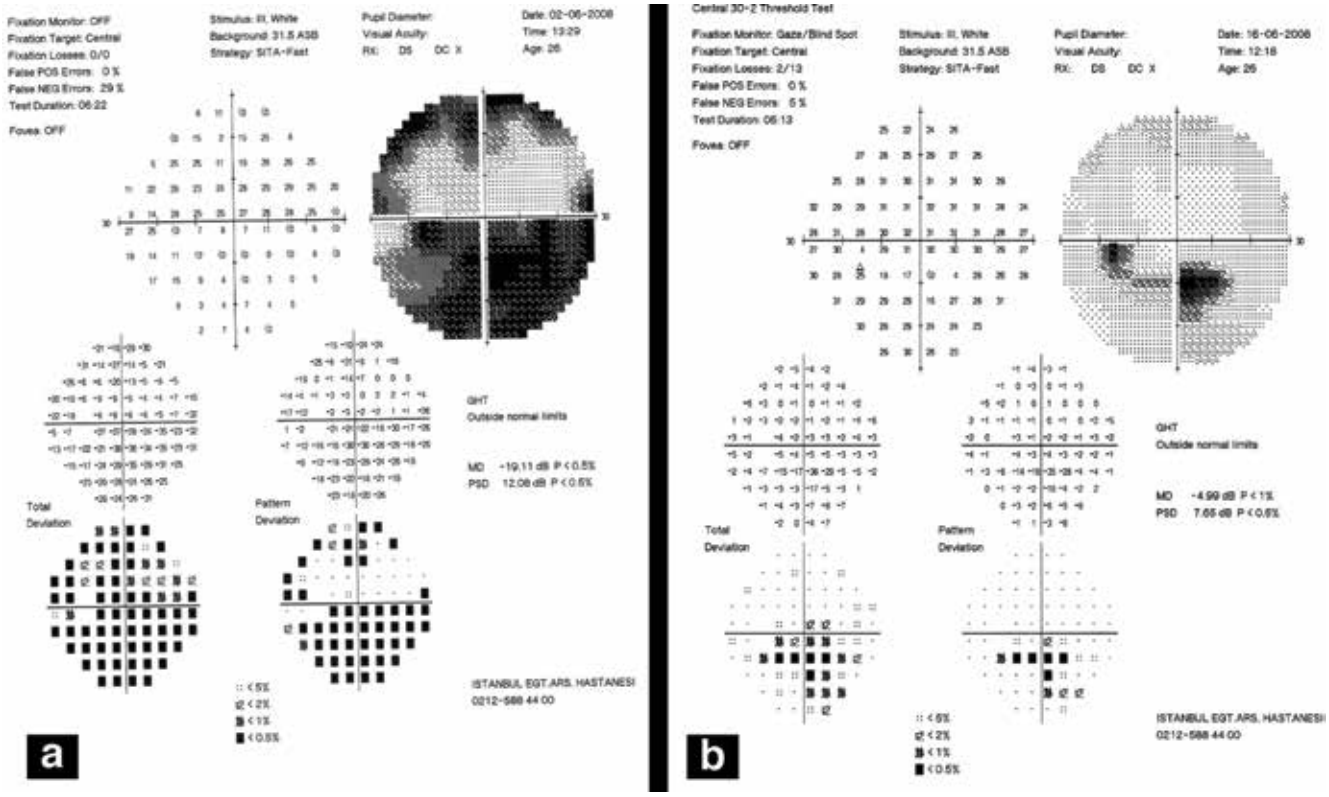

Figure 4. Computerized visual field testing revealed a significant decrease in the size of visual field defect after 5 sessions of hyperbaric oxygen treatment (a) and in the second week after discontinuation of treatment (b)

syndrome, migraine, pregnancy, systemic hypertension, and hyperhomocysteinemia.[14,15,16,17] In our case, there was no known associated risk factor for CLRAO. To our knowledge, our patient is the first case reported as idiopathic isolated CLRAO that was treated, successfully, with HBO therapy.

We believe that HBO therapy is safe and effective in the treatment of CLRAO and should be applied until the recanalisation of the retinal artery occurs. Further research is recommended to assess the effective pressure, duration and total number of sessions of HBO therapy.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Concept: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar, Design: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar, Data Collection or Processing: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar, Analysis or Interpretation: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar, Literature Search: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar, Writing: Serdar Aktaş, Osman Murat Uyar, Erol Özer, Hatice Aktaş, Kadir Eltutar.

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

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

References

1. Rumelt S, Dorenboim Y, Rehany U. Aggressive systematic treatment for central retinal artery occlusion. Am J Ophthalmol. 1999;128:733-738.
2. Leavitt JA, Larson TA, Hodge DO, Gullerud RE. The incidence of central retinal artery occlusion in Olmsted County, Minnesota. Am J Ophthalmol. 2011;152:820-823.
3. Brown GC, Shields JA. Cilioretinal arteries and retinal arterial occlusion. Arch Ophthalmol. 1979;97:84-92.
4. Schmidt D, Schumacher M, Feltgen N. Circadian incidence of non-inflammatory retinal artery occlusions. Graefes Arch Clin Exp Ophthalmol. 2009;247:491-494.
5. Murphy-Lavoie H, Butler F, Hagan C. Central retinal artery occlusion treated with oxygen: a literature review and treatment algorithm. Undersea Hyperb Med. 2012;39:943-953.
6. Hertzog LM, Meyer GW, Carson S, Strauss MB, Hart GB. Central retinal artery occlusion treated with hyperbaric oxygen. J Hyperbaric Medicine. 1992;7:33-42.
7. Anderson B, Jr., Saltzman HA, Heyman A. The Effects of Hyperbaric Oxygenation on Retinal Arterial Occlusion. Arch Ophthalmol. 1965;73:315-319.
8. Augsburger JJ, Magargal LE. Visual prognosis following treatment of acute central retinal artery obstruction. Br J Ophthalmol. 1980;64:913-917.
9. Yotsukura J, Adachi-Usami E. Correlation of electroretinographic changes with visual prognosis in central retinal artery occlusion. Ophthalmologica. 1993;207:13-18.

10. Hayreh SS, Zimmerman MB, Kimura A, Sanon A. Central retinal artery occlusion. Retinal survival time. Exp Eye Res. 2004; 8:723-736.
11. Weiss JN. Hyperbaric oxygen treatment of retinal artery occlusion. Undersea Hyperb Med. 2010;37:167-172.
12. KK J. Textbook of Hyperbaric Medicine, 4th ed. Hogrefe & Huber. 2004:383-392.
13. Weinberger AW, Siekmann UP, Wolf S, Rossaint R, Kirchhof B, Schrage NF. [Treatment of Acute Central Retinal Artery Occlusion (CRAO) by Hyperbaric Oxygenation Therapy (HBO)--Pilot study with 21 patients]. Klin Monbl Augenheilkd. 2002;219:728-734.
14. Hayreh SS. Acute retinal arterial occlusive disorders. Prog Retin Eye Res. 2011;30:359-394.
15. Park SU, Lee SJ, Kim M. Isolated cilioretinal artery occlusion in a patient with hypertensive crisis. BMJ Case Rep. 2014;2014:bcr2013202890.
16. Berkani Z, Kitouni Y, Belhadj A, Sifi K, Abbadi N, Bellatrache C, Hartani D, Kherroubi R. [Cilioretinal artery occlusion and central retinal vein occlusion complicating hyperhomocysteinemia: a case report]. J Fr Ophtalmol. 2013;36:e119-127.
17. Basu A, Eyong E. Cilioretinal arterial occlusion phenomenon: a rare cause of loss of vision in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2008;137:251-252.

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Turk J Ophthalmol 2016;46:248-250

Case Report

Tick Infestation of Eyelid: Two Case Reports

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Summary
Tick infestation of the eyelid is a rare but serious condition that can lead to Crimean-Congo hemorrhagic fever. In this report, we describe two cases who presented with tick infestation of the eyelid. Neither patient developed systemic disease or adverse sequelae after tick extraction. Complete mechanical removal of ticks located on the eyelid with blunt forceps is a safe and effective treatment method.
Keywords: Eyelid, tick, Crimean Congo hemorrhagic fever

Introduction

Ticks are ectoparasites which live by hematophagy of mammals, birds and reptiles, and consequently act as vectors of various diseases. Tick infestation has gained attention in recent years due to Crimean-Congo hemorrhagic fever (CCHF), a potentially fatal tickborne disease. Ticks have also been associated with localized lesions resembling erythema chronicum migrans, foreign body granuloma, lymphoid hyperplasia and tick-related alopecia.[1]

Tick infestation of ocular tissues is a rare occurrence. In this report, we describe two cases that were treated in our clinic just one week apart, one who presented complaining of a tick bite on the eyelid and another in which a tick was found on the eyelid during routine examination.

Case Reports

Case 1

Our clinic was consulted by emergency services regarding a 15-year-old female patient who presented complaining of a tick bite on her left upper eyelid. The patient's family reported that they had been in a hazelnut orchard the previous day and the patient had slept under a tree. That evening she had complained of itching on her left upper eyelid. Her family noticed a tick on her eyelid and took her to emergency services. The patient was referred to our clinic following unsuccessful attempts to remove the tick from the patient's eyelid in the emergency services department. On slit-lamp examination the tick was visible on the left superior eyelid just anterior to the eyelash line (Figure 1). We also noted edema and hyperemia of the eyelid, and mild hemorrhage and ecchymosis resulting from tissue damage incurred during attempts to remove the tick. The body of the tick had also been severed during these attempts; we carefully removed the remaining tick parts using toothless forceps with curved, blunt medium tips. Complete removal of the tick was confirmed by slit-lamp examination and 10% povidone iodine was applied to the area. At time of presentation, the patient's white blood cell count was at the upper limit of the reference range ($10.7x10^3$/µl) and eosinophil level was elevated ($1.03x10^3$/µl). The patient was prescribed topical tobramycin/loteprednol etabonate eye drops (instilled four times a day) and fusidic acid eye drops (twice a day). Hemogram, biochemical and serologic tests were ordered to determine the presence of CCHF, Lyme disease, tularemia or Q fever. The patient's whole blood, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) and other biochemical parameters were within reference ranges. The following day, her eyelid edema and hyperemia had regressed and no additional pathologic findings had developed. The patient was called for follow-up one week later due to the risk of CCHF, but no

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pathology was detected in her PT, PTT, INR tests or the results of the other serologic tests ordered for CCHF. After one week the patient's edema and hyperemia had resolved and the site of the tick bite had healed with no scarring.

Case 2

A 66-year-old female patient presented to our clinic with complaints of itching and stinging in her right eye. During routine examination a tick infestation was discovered incidentally on the patient's left lower eyelid (Figure 2). However, no accompanying findings were apparent in the eyelid or eye. It was learned that the patient lived in a rural area, but she reported no contact with any animals. The tick was carefully removed using toothless forceps with curved, blunt medium tips. Complete removal of the tick was confirmed by slit-lamp examination, and 10% povidone iodine was applied to the area. The patient was prescribed topical tobramycin/loteprednol etabonate eye drops (instilled four times a day) and fusidic acid eye drops (twice a day). Hemogram, biochemical and serologic tests were ordered to determine the presence of CCHF, Lyme's disease, tularemia or Q fever. The patient's whole blood, PT, PTT, and other biochemical parameters were within reference ranges. The patient was invited for follow-up one week later due to the risk of CCHF; the site of the tick bite had healed without scarring or sequelae. No pathology was detected in the PT, PTT, INR tests or the results of the other serologic tests ordered for CCHF.

Figure 1. Tick infestation of the left superior eyelid of a 15-year-old female patient. Mild hemorrhage and ecchymosis of the eyelid are apparent. The tick's body was severed due to inappropriate extraction method

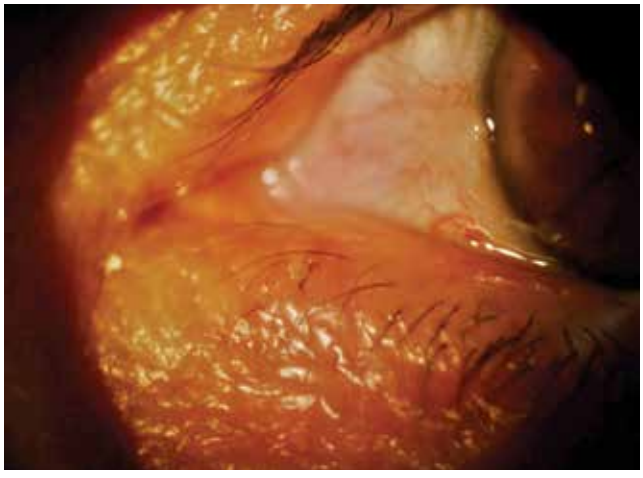

Figure 2. Tick infestation of the left inferior eyelid of a 66-year-old female patient

Discussion

Ticks are ectoparasitic vectors of serious, potentially life-threatening diseases such as CCHF, Lyme disease, tularemia, and Q fever.[2] The subtropical climate of Turkey provides a suitable environment for a wide variety of ticks. In addition to the climate, the breeding of livestock and uncontrolled application of pesticides create ideal conditions for ticks.[3] Ticks may mimic a mass on the eyelid, especially if located at the meibomian gland orifices. Previous reports of ocular tick infestation have documented cases with ticks located on the eyelid or conjunctiva.[3,4]

Removing ticks whole from the affected tissue is of utmost importance in the prevention of tickborne diseases and possible abscess, granuloma, or other local lesions. Therefore, ticks should be removed immediately and carefully from affected tissue. Human and animal studies have demonstrated that the risk of disease transmission and infection increases after the first 24 hours of tick infestation and is especially high after 48 hours.[5,6] After removal of the tick and all its body parts, the patient should undergo all necessary blood and serologic tests and be monitored closely for local and systemic complications.

Various chemical and mechanical techniques have been recommended for the removal of ticks, and even surgical excision of the tick with surrounding tissue has been proposed. Ether, lindane shampoo, deodorized kerosene, and iodine solutions have been used to prevent the disintegration of the tick and facilitate whole removal. However, experimental studies have shown that it is not possible to remove ticks whole using chemical substances and also that the use of chemicals stimulates ticks' salivation and increases the risk of disease transmission.[7] Furthermore, the chemicals used irritate the eyes.

The careful, mechanical extraction of ticks using blunt, curved, medium point forceps is recommended as safe and effective.[6] There is controversy concerning the administration of systemic antibiotic prophylaxis administration after tick bites. The Infectious Diseases Society of America does not recommend systemic antibiotic prophylaxis following a tick bite. According to the literature, however, local and topical antibiotics are used.

Both of our cases were exposed to ticks in rural areas. Using forceps with curved, blunt medium tips, we were able to safely remove the tick parts remaining after a failed removal attempt in emergency services in the first case and the intact tick in the second case. Blood and serologic tests necessary for diagnosis and follow-up of CCHF, Lyme's disease, tularemia and Q fever were performed in both cases. We did not administer systemic antibiotics to our patients. Both the local tissue reaction of

the 15-year-old girl and our 66-year-old female patient were successfully treated with combined topical steroid and antibiotic treatment after mechanical extraction of the tick. No signs of local or systemic disease were observed in either patient during follow-up.

In conclusion, ophthalmologists should be aware of possible local and systemic diseases that may arise after tick infestation of the eye and adjacent structures. Mechanical extraction of the whole tick using blunt forceps is a safe and effective treatment option. Patients should undergo blood and serologic tests for tickborne diseases and be monitored with clinical observation and follow-up.

Ethics

Informed Consent: Informed consent was obtained from patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Aslıhan Uzun, Murat Doğan İşcanlı, Concept: Aslıhan Uzun, Mustafa Gök, Murat Doğan İşcanlı, Design: Aslıhan Uzun, Mustafa Gök, Murat Doğan İşcanlı, Data Collection or Processing: Aslıhan Uzun, Analysis or Interpretation: Aslıhan Uzun, Mustafa Gök, Literature Search: Mustafa Gök, Writing: Aslıhan Uzun, Mustafa Gök, Murat Doğan İşcanlı.

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

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

References

1. Castelli E, Caputo V, Morello V, Tomasino RM. Local reactions to tick bites. Am J Dermatopathol. 2008;30:241-248.
2. Singh M, Gopalakrishnakone P, Yeoh RL. Ixodes tick infestation of the eyelid of a child. Can J Ophthalmol. 2006;41:783-784.
3. Aydin L, Bakirci S. Geographical distribution of ticks in Turkey. Parasitol Res. 2007;101(Suppl 2):S163-166.
4. Celik E, Turkoglu EB, Boz AA, Alagoz G. Conjunctival attachment of a tick: case report. Semin Ophthalmol. 2014;29:186-188.
5. Gammons M, Salam G. Tick removal. Am Fam Physician. 2002;66:643-645.
6. Keklikci U, Unlu K, Cakmak A, Akdeniz S, Akpolat N. Tick infestation of the eyelid: a case report in a child. Turk J Pediatr. 2009;51:172-173.
7. Pitches DW. Removal of ticks: a review of the literature. Euro Surveill. 2006;11:E060817.

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Case Report

Orbital Eccrine Hidrocystoma

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Summary
A 29-year-old female patient presented with a painless mass on her upper eyelid medially. She noticed the mass 4 years earlier and it had increased in size over time. She had no diplopia, eyelid swelling, skin lesion overlying the mass, or visual disturbances. On ocular examination, eye movements and funduscopy were normal. The mass was movable and painless with palpation. Magnetic resonance imaging with contrast showed a 12x8x7 mm well-circumscribed cystic lesion with no contrast dye appearance. Surgical removal was performed delicately and no capsular rupture occured. Pathological examination revealed an eccrine hidrocystoma. Our aim is to underline that eccrine hidrocystoma should be included in differential diagnosis of orbital masses.
Keywords: Eccrine gland, hidrocystoma, orbital cystic mass

Introduction

Hidrocystoma is a rare benign cutaneous cystic lesion originating from sweat glands (eccrine or apocrine). Hidrocystoma occurs predominantly in the head and neck region. Solitary lesions occur with equal frequency in both genders, while multiple lesions are more common in women.

Eccrine hidrocystomas may manifest as single or multiple small (1-6 mm in diameter), thin-walled cysts.[1] Lesions in the head/neck region are most often located in the periorbital/malar area.[2] Apocrine hidrocystomas are usually solitary and 3-15 mm in size.[1] In this case report we aimed to highlight that orbital eccrine hidrocystoma, though rare, should be included in the differential diagnosis of orbital lesions.

Case Report

A 29-year-old female patient presented to our clinic with complaints of a mass located medially on her left upper eyelid which had increased in size over the previous 4 years (Figure 1). The mass was movable and painless on palpation. The patient had no diplopia, and there was no erythema or warmth in the skin overlying the mass. Visual acuity was 20/20 in both eyes on Snellen chart, and intraocular pressure as measured by noncontact tonometry was within normal limits. The patient's eye movements were unrestricted. Direct and indirect light reflexes were normal. No pathology was detected on the skin over the mass on slit-lamp examination. Anterior segment structures and fundus examination were normal in both eyes.

The patient first noticed the mass 4 years earlier and since then its growth was documented by annual follow-up with orbital magnetic resonance imaging (MRI) with contrast (Figure 2 shows orbital MRI of the cystic mass from January 2014). It was documented as a dense cystic mass lesion with smooth borders, approximately 12x8x7 mm in size, located anteromedially to the left eye. It appeared mildly hyperintense on T1-weighted images and markedly hyperintense on T2-weighted images, and showed no enhancement pattern.

To surgically excise the mass, a cutaneous incision was made medially in the fold of the left upper eyelid and the mass was exposed by blunt dissection through the orbicular muscle and septum. Excision was continued by careful blunt dissection in order to avoid capsule rupture and the cystic mass was removed from the surrounding tissues. Following the total excision of the mass (Figure 3), it was sent for pathologic analysis.

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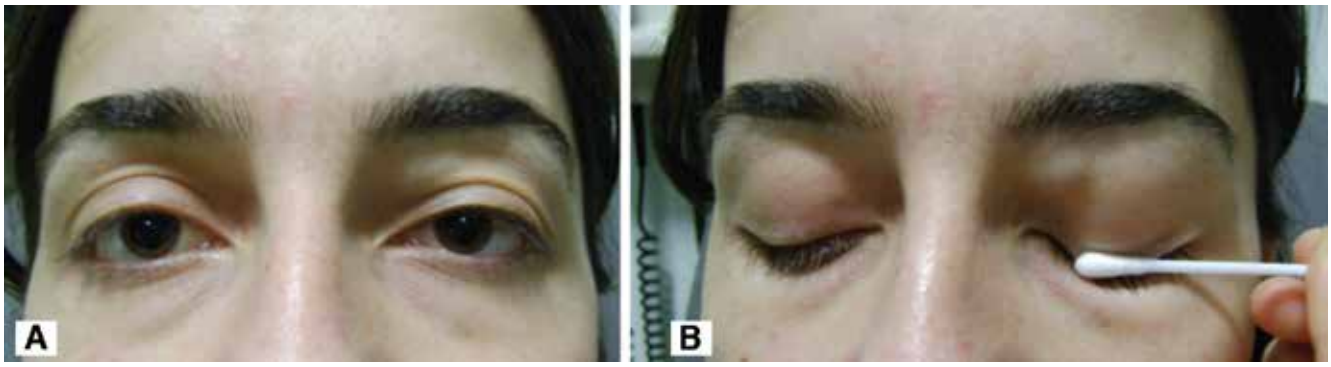

Figure 1. A and B. External photograph showing mass in the medial left upper eyelid

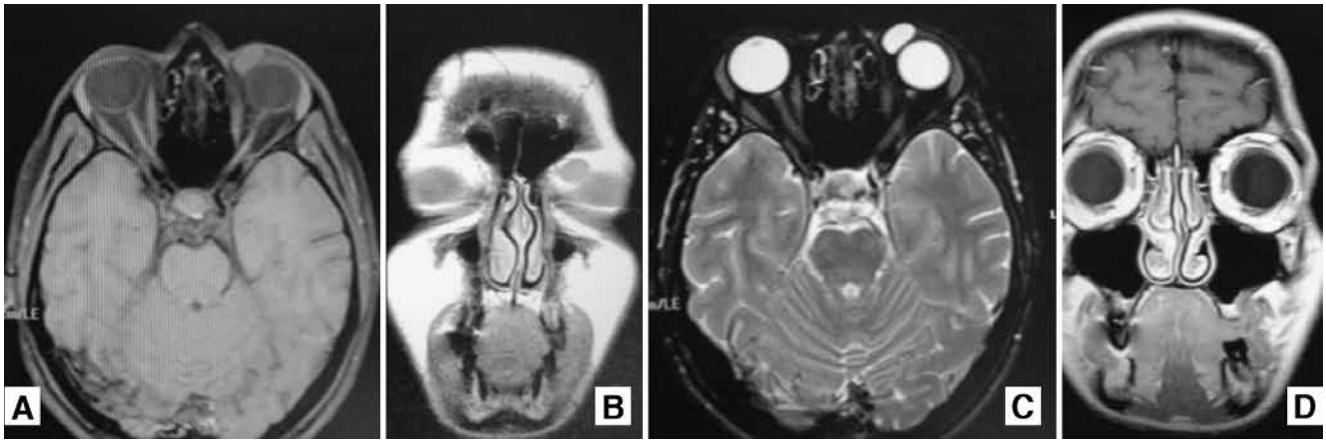

Figure 2. Magnetic resonance imaging of the mass: A Mild hyperintensity on T1-weighted horizontal section; B. Marked hyperintensity on T2-weighted horizontal section; C and D. In coronal section the mass is visible superomedially adjacent to the left globe

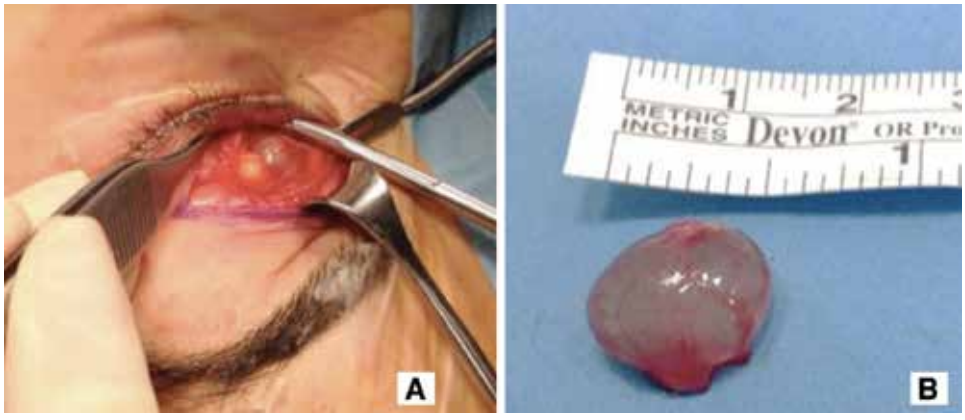

Figure 3. Surgical removal of the mass. A. The cystic mass, located behind the septum, was exposed by cutaneous incision in the medial upper eyelid and blunt dissection; B. The cystic mass excised as a whole with capsule intact

Macroscopically the mass was 15x15x6 mm in size and whitish-pink in color with translucent margins; microscopically the mass was determined to be a benign cystic formation lined with a single layer of columnar epithelium. Immunohistochemically, the mass did not exhibit ki-67 staining, while histochemical staining with Alcian blue revealed the presence of sporadic goblet cells in the mass epithelium (Figure 4). The results of the pathologic analysis reported that the mass was consistent with eccrine hidrocystoma.

Discussion

Hidrocystomas in the periorbital region are often located in the eyelid and inner canthus.[3]

Apocrine sweat glands are limited to specific regions like the

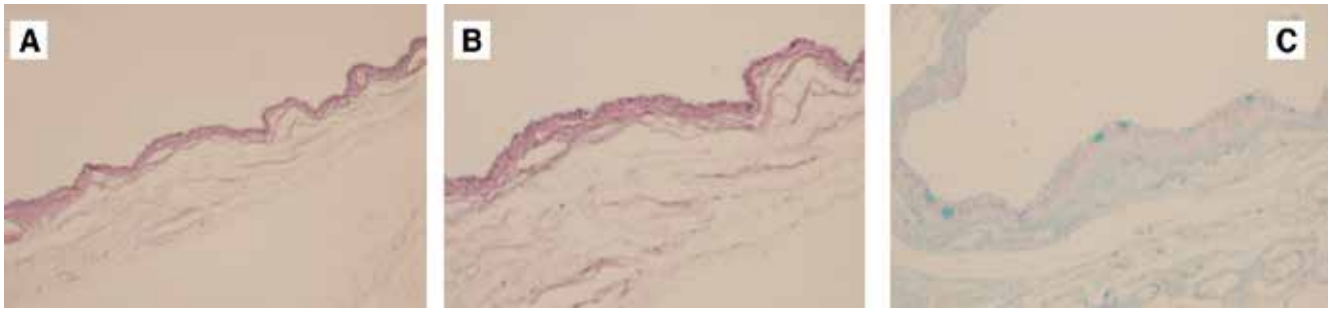

Figure 4. Histopathological examination of the mass. A. Single-layer cuboidal epithelium, hematoxylin&eosin (H&E) x100; B. H&E x200; C. Positive cytoplasmic staining of the sporadic goblet cells in the lining epithelium

axilla, nipple, external ear, external genitalia and eyelids, while eccrine sweat glands are widely distributed across the body.[4]

Eccrine hidrocystoma was first described by Robinson[5] and was classified according to lesion number as Robinson (multiple) or Smith (solitary) type. Eccrine hidrocystomas generally expand in summer and spontaneously regress in cooler weather.[1]

Hidrocystomas do not recur if total excision is achieved. Because eccrine hidrocystomas are usually subcutaneous, they are obvious and can be diagnosed even at very small sizes (1-6 mm).[1] Our patient had a mass with a maximum diameter of 15 mm; it was likely able to reach this size because it developed over 4 years within the orbit.

Other cystic lesions included in the differential diagnosis of eccrine hidrocystomas are follicular cysts, epidermal inclusion cysts, hemangioma, lymphangioma, apocrine hidrocystoma and eccrine acrospiroma.

Cases of 'orbital apocrine hidrocystoma' have been reported in the literature by Valenzuela and Heathcote[6], Ssi-Yan-Kai and Pearson[7], Vignes et al.[8] and Mehta et al.[9]

Valenzuela and Heathcote[6] described a 47-year-old male patient with a 3-month history of a painless mass in the superomedial aspect of his left upper eyelid which was impinging on his peripheral visual field. Orbital computed tomography (CT) imaging revealed a 13x8 mm extraconal cystic mass in close proximity to the globe. Mass excision by anterior orbitotomy was planned, but due to the attachments of the mass to the superomedial orbit, the brown contents of the cyst were first removed, then the excised cyst wall was sent for histopathologic examination. The inner walls of the cyst were lined with columnar epithelium and the cells contained PAS (Periodic Acid Schiff)-positive material in the apical cytoplasm. The mass was determined to be consistent with orbital apocrine hidrocystoma.

In a case reported by Ssi-Yan-Kai and Pearson[7] a 46-year-old woman had soft mass growing on the medial aspect of her right lower eyelid for several months. The mass had displaced the globe superolaterally, but the patient's eye movements appeared normal. Orbital CT revealed an 18 mm mass. However, the cyst ruptured during surgical excision and was determined insufficient for histopathological examination. Two years later, orbital MRI performed due to recurrence revealed another 17.5 mm cystic mass, also located in the inferomedial aspect of the orbit, which was surgically excised with cyst capsule intact. On histopathological examination, the mass was reported as 'benign apocrine hidrocystoma'.

Vignes et al.[8] reported the case of a 33-year-old male with an 18-month history of progressive swelling of his right eyelid. There was no pathology apparent in the eyelid other than edema. Visual acuity and eye movements were normal. An intraorbital extraconal cystic lesion was detected on orbital MRI. The mass was surgically excised and diagnosed as 'apocrine hidrocystoma' based on histopathological examination.

Mehta et al.[9] described a 65-year-old woman who presented complaining of ptosis starting 10 days earlier and a mass in her left upper eyelid. The patient had undergone eyelid repair 7 years earlier due to traumatic ptosis, but no ptosis or mass had been reported in an ocular examination 2 months earlier. Eye movements were restricted on upward gaze and levator function was 14 mm on the right and 5 mm on the left. A soft mass 1.5 mm in diameter could be palpated at the medial aspect of the left supraorbital margin. Orbital CT and ultrasonography were performed and the cystic mass was completely excised after dissecting its adhesions to the levator aponeurosis. Histopathologic examination was consistent 'apocrine hidrocystoma (sudoriferous cyst)'. The authors attributed cyst development in this patient to one of two mechanisms: either superficial sweat gland cells were implanted in deeper tissues at the time of the injury, or some epithelial cells were implanted into deeper tissues during the eyelid surgery following the trauma, where they gradually proliferated to form a cyst.

To our knowledge, there are no reports of orbital eccrine hidrocystoma in the literature other than the case of a 14-year-old patient with giant eccrine hidrocystoma reported by Eslami et al.[10] That case involved a 3-month history of a painless mass in the right upper eyelid. The patient presented with diplopia, proptosis and ptosis. Orbital CT revealed a 1.5x1 cm oval mass in the superomedial aspect displacing the right globe inferolaterally. Total excision was performed by cutaneous incision. The mass was a giant eccrine hidrocystoma, 1x1x2.5 cm in size, encapsulated in fibrous connective tissue.

Our aim in this study was to emphasize that eccrine hidrocystomas, although rare, should be considered during differential diagnosis of orbital masses.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Concept: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Design: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Data Collection or Processing: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Analysis or Interpretation: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Literature Search: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi, Writing: Deniz Marangoz, Işın Doğan Ekici, Ferda Çiftçi.

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References

1. Alfadley A, Al Aboud K, Tulba A, Mourad MM. Multiple eccrine hidrocystomas of the face. Int J Dermatol. 2001;40:125-129.
2. Sarabi K, Khachemoune A. Hidrocystomas--a brief review. Med Gen Med. 2006;8:57.
3. Golden BA, Zide MF. Cutaneous cysts of the head and neck. J Oral Maxillofac Surg. 2005;63:1613-1619.
4. Warwick R, Williams PL. Gray's Anatomy. (35th Ed.) Longman Group Ltd: Edinburgh; 1973;1168-1169.
5. Robinson AR. Hidrocystoma. J Cutan Genitourin Dis. 1893;11:293-303.
6. Valenzuela AA, Heathcote JG. Apocrine hidrocystoma of the orbit. Orbit. 2011;30:316-317.
7. Ssi-Yan-Kai IC, Pearson AR. Recurrent giant orbital apocrine hidrocystoma. Eye (Lond). 2012;26:895-896.
8. Vignes JR, Franco-Vidal V, Eimer S, Liguoro D. Intraorbital apocrine hidrocystoma. Clin Neurol Neurosurg. 2007;109:631-633.
9. Mehta A, Rao A, Khanna A. Sudoriferous cyst of the orbit of adult origin after trauma. Indian J Ophthalmol. 2008;56:235-237.
10. Eslami F, Fazel F, Ghasemibasir H, Beni AN. Giant eccrine hidrocystoma of orbit. JRMS. 2007;12:150-152.

2016 INTERNATIONAL CONGRESSES

16th European Society of Retina Specialists (EURETINA) Congress
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http://www.euretina.org/copenhagen2016/default.asp

34th European Society of Cataract and Refractive Surgeons (ESCRS) Congress
10-14 September 2016 - Copenhagen, Denmark
http://www.escrs.org/

American Association for Pediatric Ophthalmology and Strabismus (AAPOS)/Strabismus and Pediatric Ophthalmological Society of India (SPOSI) Joint Conference: An Intercontinental Perspective of Pediatric Ophthalmology & Strabismus
2-4 December 2016 - Jaipur, India
http://www.aapos.org/meeting/2016_joint_meeting_jaipur_india_/

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

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

Equations of conversions for Microsoft Excel:
- Log10 (Decimal Acuity)= LogMAR Equivalent
Power (10; -Logmar Equivalent)= Decimal Acuity (for English version of Microsoft Excel)
Kuvvet (10; -Logmar Equivalent)= Decimal Acutiy (for Turkish version of Microsoft Excel)
Reference
Eğrilmez S, Akkın C, Erakgün T, Yağcı A. Standardization in evaluation of visual acuity and a comprehensive table of equivalent. Turk J Ophtalmol. 2002;32:132-136.