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Hüban ATİLLA
Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

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AT A GLANCE

2024 Issue 2 at a Glance:

Esteemed colleagues,

This issue of our journal features 4 original research articles, 2 reviews, and 4 case reports regarding different branches of ophthalmology that we think you will read with interest.

Although retinoscopy is the gold standard for refractive measurements in the pediatric age group, this method requires time and experience and is performed by ophthalmologists. The Welch-Allyn Spot Vision Screener (SVS) is a new handheld infrared photorefractometer that was designed to measure pupil size, interpupillary distance, ocular alignment, and refractive errors and can easily be used by healthcare professionals other than ophthalmologists. In their study titled "Comparison of Spot Vision Screener and Tabletop Autorefractometer with Retinoscopy in the Pediatric Population", Arslantürk Eren et al. obtained cycloplegic retinoscopy, SVS, and benchtop autorefractometer measurements from 44 patients between 6 months and 17 years of age and evaluated the correlation of spherical and cylindrical values, spherical equivalent, and Jackson cross-cylinder values at axes of 0° (J0) and 45° (J45) between methods using intraclass correlation coefficient (ICC) and Bland-Altman analysis. They observed moderate-to-good agreement between SVS and retinoscopy, with a stronger correlation between spherical measurements than cylindrical measurements (ICC 0.924 and 0.686, respectively). The authors concluded that although SVS was designed to be used in screening programs, it would also be useful for measuring spherical refractive errors in uncooperative pediatric patients (See pages 56-62).

Today, the aim of cataract surgery is not only to remove the cataractous lens, but also to improve the patient's quality of life by providing good refractive outcomes and restoring vision to the pre-presbyopia level, and maintaining this level for the rest of the patient's life with no need for repeat intervention. Multifocal intraocular lenses (IOLs), which improve both distance and near visual acuity (VA), are still not ideal because although they provide a reasonable degree of spectacle-independence, they can lead to halo and glare, loss of contrast sensitivity, and poor visual results for intermediate-distance tasks. In their study titled "Comparison of Two Presbyopia-Correcting Trifocal Intraocular Lenses: A Prospective Study", Bayhan et al. compared the Acriva Trinova IOL (VSY) and Acrysof IQ PanOptix IOL (Alcon) in a total of 79 patients and found no difference between the groups in terms of postoperative monocular and binocular corrected/uncorrected VA at intermediate (60 cm) or near distances. However, the Trinova group was shown to have statistically significantly better VA at 80 cm compared to the PanOptix group ($p<0.05$). In the Trinova group, the incidence of photic phenomena was found to be lower 1 month after surgery ($p<0.05$), but the difference disappeared at 3 months. Nearly all patients (97.9% of those in the Trinova group and 96.7% of those in the PanOptix group) said they would recommend the same IOL to others (See pages 63-68).

Graves' disease (GD) is an autoimmune disease in which thyroid-specific autoantibody levels are elevated, causing diffuse enlargement of the thyroid gland and hyperthyroidism. The immune system is primarily controlled by regulatory T-cells (Tregs). The Forkhead box P3 (*FOXP3*) gene is located on the X chromosome and its protein product, FoxP3, is predominantly expressed as a transcription factor in Tregs. FoxP3 deficiency can lead to autoimmune diseases by impairing the immunosuppressive effect of Tregs. In their study titled "The Role of *FOXP3* Polymorphisms in Graves' Disease with or without Ophthalmopathy in a Turkish Population", Yaylacıoğlu Tuncay et al. evaluated the frequency of the *FOXP3* single nucleotide polymorphisms (SNPs) rs3761547 (-3499 A/G), rs3761548 (-3279 C/A), and rs3761549 (-2383 C/T) in a Turkish sample of 100 GD patients with ophthalmopathy, 74 GD patients without ophthalmopathy, and 100 age- and sex-matched healthy individuals using the polymerase chain reaction-restriction fragment length polymorphism method. The rs3761548 AC and AA genotypes and the rs3761549 CT genotype were significantly more frequent in GD patients compared to the control group (all $p<0.05$), while no difference was observed in terms of rs3761547 ($p>0.05$ for all). However, none of the three SNPs was shown to be associated with the development of ophthalmopathy (See pages 69-75).

Although the pathogenesis of retinal vein occlusion (RVO) is still uncertain, it is known from comprehensive studies to be more common in patients with cardiovascular diseases such as arterial hypertension, hypercholesterolemia, atherosclerosis, and diabetes mellitus. In their study titled "Assessment of Serum Atherogenic Indices and Insulin Resistance in Retinal Vein Occlusion", Gönül and Eker compared plasma lipid profile (low-density lipo-protein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC] and triglycerides) and insulin resistance between 57 RVO patients and 63 healthy individuals. Although they were unable to demonstrate any differences in these parameters between the two groups, they found that atherogenic index values (TC/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C ratios) were higher in RVO patients ($p=0.015$, $p=0.036$, and $p=0.015$, respectively). In addition, fasting insulin, plasma insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) were found to be higher in RVO patients compared to the control group ($p=0.003$, $p=0.001$, and $p=0.001$, respectively) (See pages 76-82).

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AT A GLANCE

In their systematic review and meta-analysis study titled "Is Glaucoma a Two-Pressure-Related Optic Neuropathy?", Hoang et al. reviewed the literature published between 01/01/2010 and 31/12/2022 using the PubMed, Cochrane Eyes and Vision, and Google Scholar databases to examine the relationship between translaminar pressure difference (TLPD) and glaucoma. According to 8 articles selected from 471 results, it was shown that intraocular pressure was higher, cerebrospinal fluid pressure was lower, and TLPD was higher in the high-pressure and normal-pressure glaucoma groups compared to healthy groups (See pages 83-89).

The review by Şengör and Gençağa Atakan titled "Management of Contact Lenses and Visual Development in Pediatric Aphakia" discusses the types of contact lenses (CLs) used in pediatric aphakia after congenital cataract surgery, their application features, comparison with other optical systems, the features of amblyopia treatment in the presence of CLs, the results obtained with family compliance to CL wear and occlusion therapy in light of current studies (See pages 90-102).

Approximately 20% of facial burns involve periorbital and ocular involvement. Özbek and Kefeli present the management of a patient who underwent facial transplantation due to burns and subsequently developed cicatricial ectropion, lagophthalmos, and exposure keratopathy. The patient was started on a fortified topical antibiotic with a preliminary diagnosis of infectious keratitis. However, when culture yielded *Aspergillus fumigatus*, treatment was switched to topical and systemic amphotericin. Intracorneal voriconazole and amphotericin injections and lateral tarsorrhaphy and amniotic membrane transplantation were also performed. Due to a problem with epithelial healing in the inferior quadrant of the cornea after penetrating keratoplasty, the patient was fitted with a scleral contact lens for both therapeutic and visual rehabilitation purposes. She had perfect visual acuity and no complications in long-term follow-up (See pages 103-107).

Vasoproliferative tumors (VPT) are rare retinal lesions that can be primary or develop secondary to ocular diseases. In a case report by Abdel Jalil et al., a 55-year-old woman who presented with sarcoidosis-related intermediate uveitis, VPT, and exudative retinal detachment (ERD) was started on systemic and intravitreal steroid and systemic cyclosporine treatment and showed complete regression of the ERD. However, pars plana vitrectomy, cryotherapy, and laser photocoagulation were performed due to persistent severe vitreous opacities, low visual acuity, and ERD recurrence after 7 months. Two months after surgery, visual acuity in the left eye increased to 6/10, there was a significant regression of the VPT, and the ERD completely resolved (See pages 108-111).

Tumor necrosis factor-α antagonists (anti-TNFα) have been used in recent years for the treatment of dermatological, rheumatological, and gastroenterological diseases, as well as noninfectious uveitis. Değirmenci and Yalçındağ administered topical and sub-Tenon steroid therapy for intermediate uveitis to a 34-year-old man who presented with blurred vision and floaters in the right eye, but systemic cyclosporine was initiated when the inflammatory findings did not regress. Due to adverse effects, the cyclosporine was discontinued and adalimumab was started. The patient developed vitiligo in the lower jaw area in the 5th month of treatment and was evaluated for Vogt-Koyanagi-Harada syndrome, but no additional pathology was detected. The patient received tacrolimus (0.1%) pomade for the treatment of vitiligo, and no progression of the vitiligo lesion was observed at 3-month follow-up (See pages 112-115).

Merkel cells are deep epidermal cells that act as mechanoreceptors. They are necessary for light touch sensation and can exhibit malignant transformation. Merkel cell carcinoma (MCC) is a rare skin tumor that causes distant and local metastases and has a high mortality rate. It is usually seen on sun-exposed skin areas of older white people, presenting as painless, bluish-red, expanding nodules. Primary MCC of the eyelid is known to usually occur on the upper eyelid. In a case report by Özdemir et al., a patient who was diagnosed with MCC on the right thigh and received medical treatment three years earlier presented with numerous distant metastases and a firm, purplish, vascularized lesion on the upper eyelid, which was confirmed to be MCC by histopathological examination and imaging methods (See pages 116-119).

We hope that you read this issue with pleasure and benefit from it in clinical practice.

Respectfully on behalf of the Editorial Board,

Banu Bozkurt, MD

Editor-in-Chief

Original Article

Comparison of Spot Vision Screener and Tabletop Autorefractometer with Retinoscopy in the Pediatric Population

Mehtap Arslantürk Eren*, Hilal Nalcı Baytaroğlu**, Huban Atilla***

*Trabzon Kanuni Training and Research Hospital, Clinic of Ophthalmology, Trabzon, Türkiye
**University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
***Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: Determining the accuracy of cycloplegic refractive error measurements made with the Spot Vision Screener (SVS, Welch Allyn Inc, Skaneateles Falls, NY, USA) is important for refractive assessment of uncooperative patients during optometric examinations. This study compared cycloplegic refractive errors measured by SVS and tabletop autorefractometer to cycloplegic retinoscopy in children.

Materials and Methods: Eighty-eight eyes of 44 subjects were examined in the study. Refractive error measurements were obtained under cycloplegia using retinoscopy, SVS, and Nidek ARK-530 tabletop autorefractometer (ARK-530, Nidek, Japan). Spherical and cylindrical values, spherical equivalents (SE), and Jackson cross-cylinder values at axes of 0° (J0) and 45° (J45) were recorded. Correlations between methods were analyzed using intraclass correlation coefficient (ICC) and Bland-Altman analysis.

Results: The mean age was 7 years (range: 6 months-17 years). Sixteen (36%) of the subjects were female and 28 (64%) were male. For SE there was excellent agreement between retinoscopy and SVS (ICC: 0.924) and between retinoscopy and tabletop autorefractometer (ICC: 0.995). While there was a moderate correlation between retinoscopy and SVS for cylindrical values (ICC: 0.686), excellent correlation was detected between retinoscopy and autorefractometer (ICC: 0.966). J0 and J45 cross-cylinder power values were not correlated between retinoscopy and SVS (ICC: 0.472) or retinoscopy and tabletop autorefractometer (ICC: 0.442). Retinoscopy was correlated with both SVS and tabletop autorefractometer for all parameters within ±1.96 standard deviations in Bland-Altman analysis.

Conclusion: Cycloplegic retinoscopy is the gold standard for refractive error measurement in the pediatric population. However, it requires time and experienced professionals. This study revealed moderate to good agreement between SVS and retinoscopy, with better agreement in spherical errors than cylindrical errors. Although the SVS is intended for screening programs, it may also be useful in the pediatric eye office to estimate spherical refractive error in uncooperative patients.

Keywords: Autorefractometry, photoscreening, refraction, retinoscopy, Spot Vision Screener

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Address for Correspondence: Mehtap Arslantürk Eren, Trabzon Kanuni Training and Research Hospital, Clinic of Ophthalmology, Trabzon, Türkiye
E-mail: arslanturkmehtap@gmail.com **ORCID-ID:** orcid.org/0000-0002-3639-2961
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Introduction

Visual system maturation continues throughout childhood, a period in which untreated ocular pathologies can lead to amblyopia at a prevalence of up to 2%.[1] A recent study on visually impaired children revealed that almost one-third of cases were due to avoidable reasons.[2] Detection and treatment of refractive errors is one of the most important tasks in ophthalmologic examination of the pediatric age group, especially in preschool age, to prevent amblyopia.[3] The gold-standard method for measurement of refractive errors in children is cycloplegic retinoscopy, which is a basic necessary skill for every ophthalmologist. In addition, various handheld autorefractometers and screeners that can make approximations of refractive errors in a few seconds have been developed in recent years. In clinical practice, these devices are used by non-ophthalmologist healthcare professionals to detect children who have risk factors of amblyopia. However, the ability of these devices to measure refractive errors correctly remains a subject of investigation.[4,5,6]

The Welch-Allyn Spot Vision Screener (SVS) is a new handheld infrared photoscreener designed to detect refractive errors along with pupil size, interpupillary distance, and ocular alignments.[7] It is already shown to be an effective device for community screening of amblyopia risk factors. In several studies performed with various age groups, it was reported to

have a sensitivity of 60.9-89.8% and specificity of 70.4-94.9%, with a tendency to overlook hyperopia.[8,9,10,11] To compare, the sensitivity and specificity of a handheld autorefractometer was reported as 95% and 94%, respectively.[12] The purpose of this study was to compare the cycloplegic refractive measurements of the SVS with those of a tabletop autorefractometer and retinoscope, and determine if the SVS used with cycloplegia would provide measurements that have acceptable agreement with cycloplegic retinoscopy in the pediatric age group.

Materials and Methods

In this cross-sectional study, 88 eyes of 44 children were examined for refractive errors in the ophthalmology department of a tertiary level hospital. Patients with strabismus and any ocular pathology that prevented reliable measurement (e.g., corneal scars and cataracts) were excluded from study. The study was performed in compliance with the ethical principles of the Declaration of Helsinki and was approved by the Ankara University Clinical Research Ethics Comittee (registration number: 2023/415, decision no: İ06-430-23, date: 27.07.2023). A written informed consent form was obtained from the parents or guardians of all subjects before examination. After a complete ophthalmologic examination, 1% cyclopentolate hydrochloride eye drops (Sikloplejin, Abdi İbrahim, Türkiye) were applied to all eyes twice with a 5-minute interval. After adequate cycloplegia (waiting period of 45 minutes on average), measurements were obtained consecutively with a retinoscope, SVS (Welch Allyn, Skaneateles Falls, NY, USA), and tabletop autorefractometer (ARK-530, Nidek, Japan). Retinoscopy was performed and recorded before the autorefractometer and SVS measurements to avoid bias. For SVS measurements, the device was held approximately 1 meter away from the patient. While the patient focused on the display of twinkling lights and sounds of the device, the measurement was obtained in approximately 2 seconds. As a screening device, the SVS is not designed to be used with cycloplegia. However, in this study assessments were performed after cycloplegia to compare its efficacy to that of the tabletop autorefractometer and retinoscopy under cycloplegia. Patients with adequate cooperation (children aged 4 years and older) were placed with their forehead on the forehead rest of the tabletop autorefractometer and measurement was performed. The mean spherical and cylindrical values and spherical equivalents (SE) were recorded for all three methods. In addition, Jackson cross-cylinder values at axes of 0° (J0) and 45° (J45) were calculated to compare the variance in the astigmatic component between devices. SE was calculated as sphere + cylinder/2; J0 power as -(cylinder/2) x cos(2α); and J45 power as -(cylinder/2) x sin(2α), where α represents the axis value.[13]

Statistical Analysis

Data from right and left eyes were analyzed separately to prevent bias associated with interdependence of observations from the same subject. All statistical analyses were performed with the SPSS software package (version 22.0, IBM Corp., Armonk, NY, USA). The normality of distribution and the homogeneity of variances of the data were tested using the Shapiro-Wilk test. Based on the results, all parameters were analyzed by non-parametric tests. Wilcoxon signed-rank test was used to compare the spherical, cylindrical, SE, J0, and J45 values obtained with SVS, tabletop autorefractometer, and retinoscope. The degree of agreement between methods was evaluated using intraclass correlation coefficient (ICC). ICC values range from 0 to 1, and higher ICC indicates closer agreement between the compared methods. ICC values of 0.00-0.50, 0.50-0.75, 0.75-0.90, and 0.90-1.00 were interpreted as poor, moderate, good, and excellent correlation, respectively. Negative ICC values were considered unreliable for comparison. Bland-Altman plot and 95% limits of agreement, which was calculated as mean ±1.96 standard deviations (SD) of the inter-device difference, were used to visualize the level of correlation between two given methods.

Results

Eighty-eight eyes of 44 children were examined in the study; 16 (36%) of the subjects were female and 28 (64%) were male. The mean age was 7 years (range: 6 months-17 years). Ten (23%) of the cases were infants and toddlers (aged 0-3 years), 7 (16%) were preschool age (4-5 years), 22 (50%) were school age (6-11 years), and 5 (11%) were adolescents (aged 12-17 years). All subjects underwent SVS and retinoscopy measurements. Thirty-one (70.4%) cooperative subjects also underwent tabletop autorefractometer measurement, 4 (13%) of whom were preschoolers, 22 (71%) were school age, and 5 (16%) were adolescents. None of the infants and toddlers underwent autorefraction. The mean age of subjects who underwent autorefraction was 9 years (range: 4-17 years). The mean spherical values as measured by cycloplegic SVS, tabletop autorefractometer, and retinoscopy were 1.3±3.5 diopters (D), 1.1±4.6 D, and 1.0±3.9 D for the right eye and 1.7±3.3 D, 1.4±4.6 D, and 1.3±3.9 D for the left eye, respectively. There were no significant differences in spherical value between cycloplegic tabletop autorefractometer and cycloplegic retinoscopy for both right and left eyes ($p>0.05$). However, the mean spherical value obtained from SVS was more hyperopic than cycloplegic retinoscopy for the left eye ($p=0.02$). The mean SE value obtained with SVS was statistically significantly more hyperopic than retinoscopy for both eyes ($p=0.003$). There were no significant differences between SVS and retinoscopy in terms of cylindrical, J0, or J45 values (Wilcoxon signed rank test $p>0.05$). The mean spherical, cylindrical, SE, J0, and J45 values and results of statistical analysis are shown in Table 1.

For SE values, there was good to excellent agreement between retinoscopy and SVS (ICC: 0.924 and 0.888 for right and left eyes, respectively) and excellent agreement between retinoscopy and tabletop autorefractometer (ICC: 0.995 and 0.991 for right and left eyes, respectively).

For cylindrical values, the correlation between retinoscopy and SVS was noted to be moderate (ICC: 0.686 and 0.622 for right and left eyes, respectively), but good to excellent agreement was detected between retinoscopy and tabletop

autorefractometer (ICC: 0.838 and 0.966 for right and left eyes, respectively). J0 and J45 cross-cylinder power values determined by the SVS showed poor correlation with retinoscopy (J0: ICC=0.156 and 0.291, J45: ICC=0.472 and 0.278 for right and left eyes, respectively). There was also poor correlation between J45 cross-cylinder power values obtained by tabletop autorefractometer and retinoscopy (ICC=0.442 for the right eye). Negative ICC values were not taken into consideration (Table 2). However, Bland-Altman analysis showed that both the SVS and tabletop autorefractometer were compatible with retinoscopy for all parameters in the range of ±1.96 SD (Table 3, Figures 1, 2).

Discussion

Photoscreening and autorefraction devices are the preferred method for detecting refractive errors and amblyogenic risk factors in younger children.[14,15] Handheld autorefractors and photoscreeners are often able to provide a fast refractive measurement in uncooperative children and disabled patients. The reliability and validity of various autorefractometer and photoscreener models have been reported in the literature.[16,17,18,19,20,21]

The SVS is a photoscreener that has been evaluated in detail in multiple studies and is proven to be a good screening device for amblyopia risk factors in children.[8,9,10,22,23,24,25,26,27,28] Its sensitivity to detect refractive errors was reported to range between 60.9% and 96.0% and its specificity between 70.4% and 95.0% in various studies performed with children in different age groups.[8,9,10] However, a more recent study showed that although the device's overall sensitivity for refractive errors was 82.35%, its sensitivity for hyperopia was 27.27%, indicating a failure to overcome accommodation or an intrinsic technical weakness for the detection of hyperopia.[9]

This study stands out from previous ones in that it was designed to compare the refractive error measurements of retinoscopy, tabletop autorefractometer, and SVS under

Table 1. Refractive values obtained with the Spot Vision Screener, retinoscopy, and tabletop autorefractometer under cycloplegia

	Variables	Spot Vision Screener (n=44)	Retinoscopy (n=44)	Tabletop autorefractometer (n=31)	p 1	p 2
Right eye	**Sphere (D)** Mean ± SD Median (min/max)	1.3±3.5 0.75 (-7.5/7.0)	1.0±3.9 1.12 (-15.5/6.5)	1.1±4.6 2.25 (-16.0/6.5)	0.051	0.345
	Cylinder (D) Mean ± SD Median (min/max)	1.3±1.4 0.8 (-0.5/5.5)	1.3±1.3 1.0 (-0.5/4.5)	1.2±1.5 0.7 (-2.0/4.75)	0.209	0.680
	SE (D) Mean ± SD Median (min/max)	2.02±3.3 1.6 (-7.5/7.5)	1.7±3.7 1.7 (-13.75/6.9)	1.7±4.3 1.9 (-14.5/7.0)	0.003	0.176
	J0 (D) Mean ± SD Median (min/max)	0.1±0.6 0.05 (-1.7/2.1)	0.2±0.5 0.1 (-1.6/1.3)	0.1±0.7 0.08 (-1.7/2.1)	0.194	0.339
	J45 (D) Mean ± SD Median (min/max)	0.1±0.7 0.01 (-1.7/2.2)	0.3±0.6 0.2 (-1.5/1.8)	0.05±0.6 -0.05 (-1.5/2.2)	0.388	0.026
Left eye	**Sphere (D)** Mean ± SD Median (min/max)	1.7±3.2 1.4 (-7.5/7.25)	1.3±3.9 1.1 (-16.5/6.5)	1.4±4.6 2.0 (-16.75/7.0)	0.023	0.907
	Cylinder (D) Mean ± SD Median (min/max)	1.3±1.4 1.1 (-1.0/5.25)	1.3±1.4 0.8 (-0.75/5.5)	1.6±1.6 1.0 (-0.5/5.0)	0.185	0.089
	SE (D) Mean ± SD Median (min/max)	2.3±3.1 2.0 (-7.5/7.9)	1.9±3.6 1.6 (-14.75/6.6)	2.1±4.3 2.6 (-14.75/7.2)	0.003	0.457
	J0 (D) Mean ± SD Median (min/max)	0.1±0.6 0.1 (-2.2/1.4)	0.1±0.6 0.1 (-2.7/1.3)	0.06±0.8 0.04 (-1.4/1.8)	0.599	0.456
	J45 (D) Mean ± SD Median (min/max)	0.1±0.7 0.02 (-1.9/2.4)	0.09±0.7 0.1 (-2.2/1.8)	-0.1±0.8 -0.9 (-1.9/1.5)	0.953	0.198

p 1: Retinoscopy vs. Spot Vision Screener, Wilcoxon signed rank test, p 2: Retinoscopy vs. tabletop autorefractometer, Wilcoxon signed rank test, SD: Standard deviation, min/max: Minimum/maximum, D: Diopters, SE: Spherical equivalent, J0: Jackson cross-cylinder at the 0° axis, J45: Jackson cross-cylinder at the 45° axis

cycloplegia. The SVS and retinoscopy showed high agreement in terms of spherical and SE values according to ICC analysis. Mean spherical and SE values obtained with the SVS were both slightly more hyperopic than retinoscopy, although statistically insignificant. Our findings show that under cycloplegia, SVS is highly effective in the measurement of spherical refractive errors. Similarly, a study that compared the performance of the SVS for refractive error measurement before and after cycloplegia revealed that its sensitivity increased from 60.9% to 85.3%.[9] On the other hand, a recent study reported that the reliability of SVS measurements under cycloplegia decreased in eyes with high myopia.[29]

Agreement for cylindric values and J0 and J45 cross-cylinder power values was moderate to poor between the SVS and retinoscopy according to ICC. These findings agree with the literature, which reports lower sensitivity and specificity for astigmatism than spherical values.[8,22,23,24,25] Barugel et al.[9] reported 78.57% sensitivity and 89.71% specificity for astigmatism, which was lower than the overall sensitivity and specificity. Srinivasan et al.[28] stated that the device overestimated astigmatism in a patient group 6-36 months of age, with a greater difference in mean values at higher SE values. On the other hand, Bland-Altman plots showed that the SVS was compatible with retinoscopy for all parameters within the range of ±1.96 SD. This suggests that the statistical differences between the devices may be considered clinically insignificant, and SVS may be useful for obtaining a fast approximation of refractive error in disabled and uncooperative patients. In another study, de Jesus et al.[30]

Table 2. Agreement of cycloplegic Spot Vision Screener and Q Nidek QRK-530 tabletop autorefractometer with retinoscopy measurements according to intraclass correlation coefficients

	Variables	Spot Vision Screener vs. retinoscopy				Autorefractometer vs. retinoscopy			
		ICC	95% Confidence interval		p	ICC	95% Confidence interval		p
			Lower bound	Upper bound			Lower bound	Upper bound	
Right eye	Sphere	0.906	0.804	0.847	<0.001	0.995	0.990	0.998	<0.001
	Cylinder	0.686	0.491	0.816	<0.001	0.836	0.691	0.918	<0.001
	SE	0.924	0.865	0.958	<0.001	0.995	0.989	0.997	<0.001
	J0	0.156	-0.150	0.433	0.156	-0.403	-0.681	-0.45	0.986
	J45	0.472	0.210	0.672	0.001	0.442	0.122	0.682	0.003
Left eye	Sphere	0.866	0.767	0.924	<0.001	0.992	0.983	0.996	<0.001
	Cylinder	0.622	0.400	0.775	<0.001	0.966	0.928	0.984	<0.001
	SE	0.888	0.803	0.938	<0.001	0.991	0.981	0.996	<0.001
	J0	0.291	-0.009	0.541	0.028	-0.354	-0.656	0.026	0.967
	J45	0.278	-0.20	0.530	0.034	-0.583	-0.805	-0.253	1.000

ICC: Intraclass correlation coefficient, SE: Spherical equivalent, J0: Jackson cross-cylinder at the 0° axis, J45: Jackson cross-cylinder at the 45° axis

Table 3. Agreement of cycloplegic Spot Vision Screener and Q Nidek QRK-530 tabletop autorefractometer with retinoscopy measurements assessed with Bland-Altman analysis

		Spot Vision Screener vs. retinoscopy			Autorefractometer vs. retinoscopy		
	Variables	MD	SD	95% LOA (MD ± 1.96 SD)	MD	SD	95% LOA (MD ± 1.96 SD)
Right eye	Sphere	0.05	1.52	-2.9-3.0	-0.04	0.44	-0.9-0.8
	Cylinder	-0.06	1.03	-2.08-1.9	-0.05	0.3	-0.65-0.54
	SE	0.05	1.37	-2.6-2.7	0.03	0.44	-0.84-0.9
	J0	-0.006	0.5	-1.05-1.04	-0.08	0.27	-0.62-0.45
	J45	-0.003	0.52	-1.02-1.02	0.1	0.47	-0.8-1.03
Left eye	Sphere	-0.02	1.68	-3.3-3.2	-0.03	0.60	-1.2-1.1
	Cylinder	-0.1	1.03	-2.1-1.9	-0.17	0.34	-0.8-0.5
	SE	0.01	1.63	-3.1-3.2	-0.1	0.58	-1.2-1.03
	J0	-0.06	0.5	-1.1-1.02	-0.09	0.39	-0.8-0.6
	J45	-0.002	0.6	-1.2-1.2	-0.03	0.35	-0.7-0.6

MD: Mean difference, SD: Standard deviation, LOA: Limits of agreement, SE: Spherical equivalent, J0: Jackson cross-cylinder at the 0° axis, J45: Jackson cross-cylinder at the 45° axis

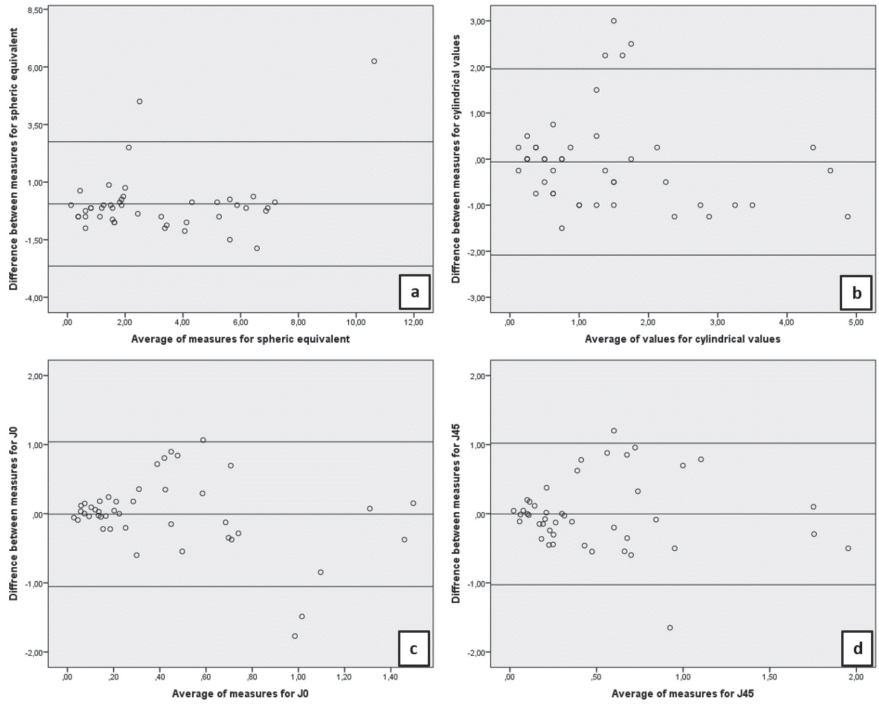

Figure 1. Analysis of agreement between cycloplegic Spot Vision Screener and retinoscopy measurements of spherical equivalent (a), cylindrical values (b), J0 values (c), and J45 values (d) with Bland-Altman plot. The middle line indicates the mean difference; the top and bottom lines show the 95% limits of agreement

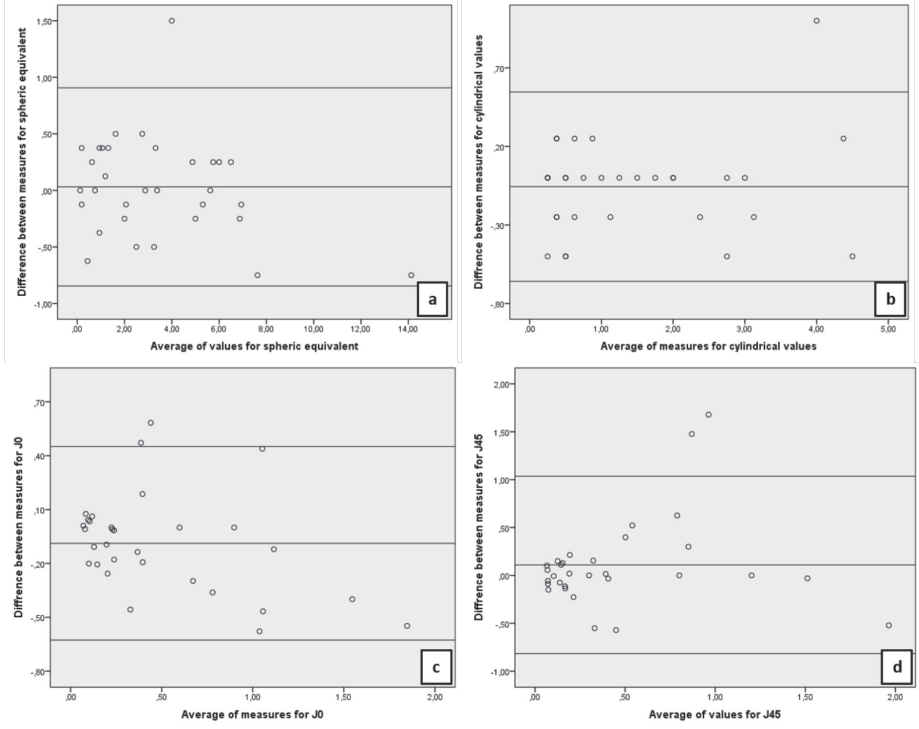

Figure 2. Analysis of agreement between cycloplegic tabletop autorefractometer and retinoscopy measurements of spherical equivalent (a), cylindrical values (b), J0 values (c), and J45 values (d) with Bland-Altman plot. The middle line indicates the mean difference; the top and bottom lines show the 95% limits of agreement

evaluated the efficacy of the SVS in measuring refractive errors under cycloplegia in a patient group ranging from 7 to 50 years of age. Although some statistically significant differences in SE, 90° axis, and 45° axis measurements were observed between SVS and retinoscopy, the authors of the study concluded that these differences were of little relevance in clinical settings and reported SVS as a reliable ancillary method for refractive error measurements.

We also compared the accuracy of cycloplegic tabletop autorefractometer with retinoscopy to evaluate the role of these devices in ophthalmic practice. Excellent agreement was found between tabletop autorefractometer and retinoscopy for spherical, cylindrical, and SE values obtained under cycloplegia. However, J0 and J45 cross-cylinder power values showed poor correlation with retinoscopy according to ICC analysis. Bland-Altman analysis showed that both SVS and tabletop autorefractometers were compatible with retinoscopy with all parameters in the range of ±1.96 SD. Previous studies have shown a good correlation between cycloplegic autorefractometer and retinoscopy measurements.[31,32] Choong et al.[32] compared three different autorefractometers and subjective refraction with cycloplegia and reported that all three autorefractors, including tabletop autorefractor, were accurate under cycloplegia as they found little difference for spherical, cylindrical, or axis values.

Study Limitations

Limitations of the present study are the small sample size and few subjects with high refractive errors. As a result, the performance of the SVS in patients with high D refractive errors may not have been sufficiently tested. Another limitation is the uneven age distribution between groups. The higher agreement of the tabletop autorefractometer with retinoscopy than that of the SVS may be because autorefraction was performed on more cooperative patients over the age of 4 years. On the other hand, only 23% of the children that underwent SVS measurements were in the 0-3 age group, which may have led to an underrepresentation of the refractive error measurements in more difficult and uncooperative cases.

Conclusion

According to the results of our small study, it seems that SVS may provide accurate refractive error measurements under cycloplegia. In contrast to its tendency to underdiagnose hyperopia in non-cycloplegic conditions, SVS measurements under cycloplegia showed excellent agreement with retinoscopy for spherical values under cycloplegia. While its agreement with retinoscopy was lower for cylindrical values and astigmatism, it seems to be acceptable in clinical conditions. Therefore, cycloplegic SVS measurements may be used as a tool to guide unexperienced clinicians assessing uncooperative or disabled patients. More studies are necessary to test its efficacy in cases of higher refractive errors.

Ethics

Ethics Committee Approval: Ankara University Clinical Research Ethics Committee (registration number: 2023/415, decision no: İ06-430-23, date: 27.07.2023).

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

Comparison of Two Presbyopia-Correcting Trifocal Intraocular Lenses: A Prospective Study

Hasan Ali Bayhan*, Yelda Yıldız Taşçı**, Seray Aslan Bayhan*, Tamer Takmaz**, İzzet Can*

*Yozgat Bozok University Faculty of Medicine, Department of Ophthalmology, Yozgat, Türkiye
**Ankara City Hospital, Clinic of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: To evaluate the clinical results of a new trifocal intraocular lens (IOL) with sinusoidal design by comparing with a traditional trifocal IOL.

Materials and Methods: A total of 79 patients undergoing uneventful microincisional cataract surgery with bilateral implantation of one of two types of trifocal IOLs, the Acriva Trinova IOL (VSY) or Acrysof IQ PanOptix IOL (Alcon), were enrolled in this prospective study. Visual and refractive outcomes, contrast sensitivity (CS), and defocus curve were assessed at 3 months after surgery. Patient satisfaction and incidence of photic phenomena were also evaluated.

Results: The number of patients/eyes were 48/96 in the Trinova group and 31/62 in the PanOptix group. There were no significant differences between the groups for monocular and binocular corrected/uncorrected distance or intermediate (at 60 cm) and near visual acuities (VA) postoperatively. The Trinova group had statistically significantly better intermediate VA at 80 cm than the PanOptix group ($p<0.05$). The CS results of both groups were within the normal limits. In the binocular defocus curve of both IOLs, we observed a peak of good VA at 0.0 diopters defocus and a useful wide range for intermediate distances. The incidence of photic phenomena in the Trinova group was lower at postoperative 1 month ($p<0.05$) but this difference disappeared at 3 months. A total of 47 patients (97.9%) in the Trinova group and 30 patients (96.7%) in the PanOptix group stated that they would recommend the same IOL.

Conclusion: Both trifocal IOLs provide good visual quality outcomes and patient satisfaction.

Keywords: Trifocal intraocular lens, sinusoidal, presbyopia

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Address for Correspondence: Hasan Ali Bayhan, Yozgat Bozok University Faculty of Medicine, Department of Ophthalmology, Yozgat, Türkiye
E-mail: alihasanbayhan@hotmail.com **ORCID-ID:** orcid.org/0000-0002-3364-6890
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Introduction

Today, cataract surgeons should aim not only for removal of the cataractous lens but also for satisfactory refractive and clinical outcomes of surgery. Thus, the goals of an ideal cataract surgery are to achieve a vision-related quality-of-life that is equal to pre-presbyopic levels and to maintain this state throughout the remaining life of the patient without any further intervention.

Studies of multifocal intraocular lenses (IOLs) providing both distance and near visual acuity have been available since the late 1980s.[1] Reasonable spectacle independence was reported with the initial multifocal IOL optics.[2] However, potential for halos and glare, loss of contrast sensitivity (CS), and poorer results for intermediate-distance tasks performed at arm's length, such as cooking or viewing computer monitors, led to the development of newer IOL designs.[3,4,5] Hence, trifocal diffractive IOLs of different models were designed to address this limitation.[6]

Trifocal IOLs separate light into three different foci in order to provide unaided near, intermediate, and far vision. Part of the light is also dispersed during this process.[4] Though multifocal/trifocal IOLs increased spectacle independence, some patients may be dissatisfied and report symptoms of photic phenomena and blurred vision.[6,7] Traditional trifocal IOLs have a diffractive overlapping pattern with differences in the amount of energy allocated to each focus and in the proportion of the energy loss.[8] It is known that photic phenomena are reported more with diffractive IOLs than monofocal IOLs and have even necessitate IOL exchange in some cases.[9,10]

A next-generation trifocal IOL has recently been introduced, the Acriva Trinova IOL (VSY Biotechnology, Netherlands). The shape of the Trinova IOL is derived from sinusoidal functions. This sinusoidal pattern was designed to provide an IOL optical surface with no sharp edges. Clinical studies evaluating this new trifocal IOL model and pattern are crucial because the results might suggest a course of action in trifocal technology and IOL designs in the future.

The aim of the current study was to assess the clinical performance of the new sinusoidal trifocal IOL (Acriva Trinova, VSY Biotechnology) and compare its performance with a well-known, previously studied diffractive trifocal IOL (Acrysof IQ PanOptix, Alcon Laboratories). To the best of our knowledge, this is the first study evaluating the clinical outcomes of the Acriva Trinova trifocal IOL with its unique sinusoidal profile.

Materials and Methods

Study Design

This prospective, comparative study included a total of 79 patients (158 eyes) undergoing uneventful microincisional cataract surgery with bilateral implantation of either the Acriva Trinova (VSY Biotechnology) or Acrysof IQ PanOptix (Alcon Laboratories) trifocal IOL. All surgeries were performed by three experienced surgeons (H.A.B., T.T., İ.C.) in three different centers. The same study protocol and devices were used in all centers during the study.

All subjects enrolled in the study agreed to participate, met the inclusion criteria, and signed an informed consent agreement before any procedures were performed. The study was approved by a Yozgat Bozok University Clinical Research Ethics Committee (protocol number: 2017-KAEK-189_2020.02.26_26, date: 26.02.2020) and was performed in accordance with the ethical principles described in the Declaration of Helsinki.

Inclusion criteria were an interest in spectacle/contact lens independence and a diagnosis of bilateral grade 2-3 age-related cataract according to Lens Opacities Classification System III staging system.[11] Patients who had any ocular disease that could affect postoperative visual acuity (e.g., amblyopia, pathologic miosis, glaucoma, uveitis, corneal or retinal abnormalities), a history of previous ocular surgery, preoperative corneal astigmatism >0.75 diopters (D), axial length over 25 mm or shorter than 22 mm, or intraoperative complications were excluded.

Each patient was implanted with the same IOL model in both eyes and the patients were divided into two groups according to the type of IOL implanted (the Trinova and PanOptix groups). In all patients, there was an average interval of one week between the surgeries on the first eye and fellow eye.

Preoperative Evaluation

Before surgery, all patients underwent a detailed ophthalmologic examination that included corrected distance visual acuity measurement, anterior segment biomicroscopy, dilated fundus examination, optical biometry (Lenstar LS 900, Haag-Streit AG, Switzerland), and corneal topography (Sirius, CSO, Italy). IOL power was based on optical biometry targeting emmetropia and calculated using the Barrett Universal II formula.

Intraocular Lenses

Ninety-six eyes received the Trinova trifocal IOL (VSY Biotechnology, Netherlands) with plate haptic design. This aspheric trifocal IOL is made of hydrophilic acrylic with a hydrophobic surface. The total length is 11.0 mm and the optic diameter is 6.0 mm. The optic has unique sinusoidal pattern with twelve ridges that, according to the manufacturer, was designed to provide ideal continuous vision and reduce halo and glare by eliminating sharp edges. It also has a 360-degree continuous square optic and haptic edge to reduce posterior capsule opacification formation.

The other 62 eyes in the study received the Acrysof IQ PanOptix trifocal IOL (Alcon Laboratories, USA). This IOL has a central nonapodized diffractive zone of 4.5 mm with 15 diffractive rings and a peripheral refractive zone from 4.5 to 6.0 mm. The lens has a negative asphericity of -0.10 µm and its overall diameter is 13.0 mm.

At 3 months after the second eye surgery, binocular performance on the curve of defocus and CS chart was evaluated. Defocus curve testing was performed under photopic conditions starting from -3.0 D to 0.0 D with 0.5-D increments. CS was assessed with a standardized CS chart (CSV 1000, Vector Vision Co., Ohio, USA).

For evaluation of symptoms, participants completed the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) at postoperative 3 months. The NEI VFQ-25 includes primary patient-reported outcome measures, which are subdivided into 12 subscales: general vision, near vision, distance vision and driving, peripheral vision, color vision, ocular pain, general health, vision-related role limitations, dependency, social function, and mental health. The highest score is 100 and represents the best functional state. In the current study, the patients were also asked additional questions about the presence of halo (rings around a light), glare (trouble seeing street signs due to bright light or oncoming headlights), double vision, and ghosting at 1 month and 3 months after the second eye surgery. Particular emphasis was placed on driving at night, and the examiner showed standard photographs demonstrating examples of these photic phenomena. If the answer was yes, the type of symptom was noted and the patients were asked to rate the impact of these symptoms on their daily lives. The patients were also questioned about spectacle independence for near, intermediate, and far vision, and whether they would recommend the same IOL and procedure to their family and friends. The answers to these additional questions were assessed independently of the NEI VFQ-25.

Statistical Analysis

All data were analyzed using SPSS software (version 22.0, IBM Corp., Armonk, NY, USA). The chi-square (χ^2) test was used to make comparisons of categorical data and the independent samples t-test was used for comparisons of continuous data. Evaluations were made at a 95% confidence level, and a p value <0.05 was considered statistically significant.

Results

The final number of patients/eyes was 48/96 in the Trinova group and 31/62 in the PanOptix group. All patients (n=79) included in the statistical analysis completed the 3-month

follow-up. Table 1 shows the patient demographics and preoperative characteristics. There was no statistically significant difference between groups in any preoperative or intraoperative parameter.

At postoperative 3 months, the mean spherical equivalent was -0.10±0.28 D in the Trinova group and -0.16±0.31 D in the PanOptix group (p=0.218).

There were no significant differences between the groups in corrected/uncorrected distance and near and intermediate (at 60 cm) visual acuities 3 months after surgery. The Trinova group had a statistically significantly better visual acuity performance at 80 cm than the PanOptix group (Table 2). Binocular uncorrected intermediate visual acuity (UIVA) at 60 cm was 0.0 logarithm of the minimum angle of resolution (logMAR) or better in 32 patients (66.6%) in the Trinova group and 22 patients (70.9%) in the PanOptix group. Binocular UIVA at 80 cm was 0.0 logMAR or better in 36 patients (75%) in the Trinova group and 11 patients (35.4%) in the PanOptix group and was 0.15 logMAR or better in 47 patients (97.9%) in the Trinova group and 27 patients (87%) in the PanOptix group.

With respect to photic symptoms, 33 of 48 patients (68%) in the Trinova group and 27 of 31 patients (87%) perceived optical phenomena at 1 month after surgery (p=0.028). On the other hand, the difference in the incidence of photic phenomena between groups was not statistically significant at postoperative 3 months (Trinova: 64.5% vs. PanOptix: 67.7%, p>0.05). Halo was the most frequent dysphotopic phenomena in both groups. None of the patients reported double vision in any visit, whereas two patients in the PanOptix group reported mildly bothersome ghosting at 1 month that disappeared at 3 months after surgery. Table 3 summarizes the patients' subjective evaluation of halo and glare during follow-up.

According to the binocular defocus curve results, the best visual acuity in the Trinova group and PanOptix group was at 0.0 D defocus (-0.07 logMAR and -0.08 logMAR, respectively), which simulates far distance. The binocular defocus curve of both IOLs showed a useful wide range for intermediate distances. From -2.50 D defocus to -3.0 D defocus, there was a decrease of the curve in both IOL groups (Figure 1).

CS measurements of the groups are shown in Table 4. CS measurements (with and without glare) at any spatial frequencies were within the normal range for normal subjects of similar age in both IOL groups.

As regards spectacle use, 47 patients (97.9%) in the Trinova group, and 29 patients (93.5 %) in the PanOptix group reported that they never needed glasses/contact lenses (in the last month)

Table 1. Patient demographics and preoperative data

Parameter	Trinova group	PanOptix group	p value
Mean age (years)	63.58±7.86	63.16±8.22	0.828
Sex (n female/male)	23/25	15/16	0.575
Mean CDVA (logMAR)	0.58±0.26	0.54±0.21	0.632
Mean corneal toricity (D)	0.36±0.29	0.33±0.23	0.784
Angle kappa (mm)	0.25±0.13	0.26±0.16	0.328
Axial length (mm)	23.32±1.06	23.26±1.12	0.416

CDVA: Corrected distance visual acuity, logMAR: Logarithm of the minimum angle of resolution, D: Diopters

Table 2. Comparison of visual outcomes (in logMAR) between the groups at postoperative 3 months

Parameter (mean)	Trinova group	PanOptix group	p value
Monocular UDVA	0.04±0.12	0.05±0.13	0.702
Binocular UDVA	-0.02±0.09	0.00±0.10	0.643
Monocular CDVA	-0.07±0.06	-0.07±0.07	0.831
Monocular UIVA (60 cm)	0. 07±0.15	0.06±0.12	0.722
Binocular UIVA (60 cm)	0.05±0.12	0.04±0.10	0.686
Monocular DCIVA (60 cm)	0.04±0.11	0.04±0.08	0.852
Monocular UIVA (80 cm)	0.06±0.12	0.14±0.13	0.02
Binocular UIVA (80 cm)	0.00±0.11	0.08±0.11	0.02
Monocular DCIVA (80 cm)	0.00±0.10	0.07±0.13	0.01
Monocular UNVA	0.06±0.13	0.05±0.11	0.513
Binocular UNVA	0.01±0.09	0.00±0.10	0.786
Monocular DCNVA	0.05±0.07	0.05±0.10	0.658

logMAR: Logarithm of the minimum angle of resolution, CDVA: Corrected distance visual acuity, DCIVA: Distance-corrected intermediate visual acuity, DCNVA: Distance-corrected near visual acuity, UDVA: Uncorrected distance visual acuity, UIVA: Uncorrected intermediate visual acuity, UNVA: Uncorrected near visual acuity

to correct their vision. For near vision, one patient in the Trinova group and one patient in the PanOptix group sometimes used spectacles. One patient in the PanOptix group reported using spectacles sometimes for intermediate vision. None of the patients in either group needed spectacles for far vision. The difference in the spectacle independency between groups was not statistically significant (p>0.05).

The assessment of VFQ-25 showed very high scores in both groups (sum score: PanOptix group=88.3±8.6, Trinova group=87.9±11.8). The difference between groups was not statistically significant (p>0.05). A total of 47 patients (97.9%) in the Trinova group and 30 patients (96.7%) in the PanOptix group stated that they would recommend the same IOL and procedure to their family and friends.

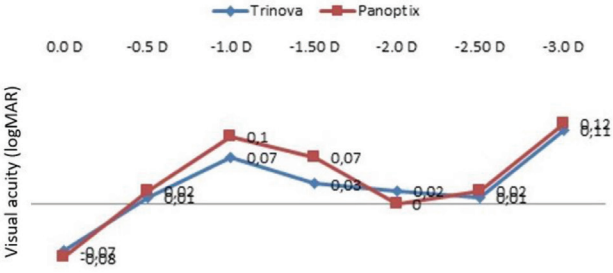

Figure 1. Binocular distance-corrected defocus curves at postoperative 3 months
D: Diopters, logMAR: Logarithm of the minimum angle of resolution

At the 3-month follow-up, none of the eyes in either group had developed posterior capsule opacification. All IOLs in both groups were well positioned, with no change in IOL position up to 3 months postoperatively, and no complications were reported during the follow-up.

Discussion

Presbyopia is an age-related reduction in the accommodative ability of the eye that affects more than a billion people.[12] This study evaluated the presbyopia correction and patient satisfaction results of two different types of trifocal IOLs.

The analysis of the visual outcomes demonstrated that both IOLs provided very good mean visual acuities at near, intermediate, and far distances. Distance vision, intermediate vision at 60 cm, and near vision showed comparable visual acuity between the two study groups. However, the Trinova group had a significantly better UIVA at 80 cm than the PanOptix group. Mencucci et al.[13] reported that the PanOptix IOL had worse intermediate visual outcomes at 80 cm than the Zeiss AT LISA tri 839MP IOL and TECNIS Symfony IOL, whereas the performance of the PanOptix IOL at 60 cm was similar to that of the AT LISA tri at 80 cm in photopic conditions. Kohnen et al.[14] also reported that the PanOptix IOL has an intermediate focal point shift from 80 cm to 60 cm and the intermediate performance of the IOL is slightly better at 60 cm compared to 80 cm. In our study, though there was a difference

Table 3. Subjective evaluation of photic phenomena during follow-up

Parameter		1 month		3 months	
		Trinova	PanOptix	Trinova	PanOptix
Halo	None, n (%)	17 (35.4)	6 (19)	24 (50.0)	13 (41.9)
	Mildly bothersome, n (%)	22 (45.8)	16 (51.6)	23 (47.9)	18 (58.1)
	Moderately bothersome, n (%)	9 (18.7)	9 (29.0)	1 (2.1)	0 (0.0)
	Very bothersome, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glare	None, n (%)	31 (64.5)	15 (48.3)	36 (75)	24 (77.4)
	Mildly bothersome, n (%)	12 (25.0)	10 (32.2)	11 (22.9)	6 (19.4)
	Moderately bothersome, n (%)	5 (10.4)	6 (19.4)	1 (2.1)	1 (3.2)
	Very bothersome, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 4. Contrast sensitivity measurements (in logCS) of the groups 3 months postoperatively

Spatial frequencies		Trinova group	PanOptix group
Without glare	3 cpd	1.62±0.16	1.59±0.19
	6 cpd	1.73±0.22	1.70±0.26
	12 cpd	1.44±0.17	1.40±0.19
	18 cpd	1.10±0.25	1.08±0.23
With glare	3 cpd	1.59±0.19	1.57±0.18
	6 cpd	1.62±0.24	1.60±0.21
	12 cpd	1.38±0.22	1.35±0.19
	18 cpd	1.07±0.27	1.05±0.26

cpd: Cycles per degree

in intermediate visual performance of the IOLs at 80 cm, both IOLs performed well binocularly and most patients achieved a binocular UIVA of 0.15 logMAR or better at 80 cm and better than 0.10 logMAR at 60 cm. Because most tasks are performed at arm's length (60 to 70 cm), both IOLs had high acceptance and patient satisfaction by making near and intermediate vision very comfortable, and almost all patients achieved good functional state levels in the VFQ-25 questionnaire with both IOLs. We also found no statistically significant differences in uncorrected distance, corrected distance, and uncorrected near visual acuity values with the Trinova IOL and PanOptix IOL. When compared with previous studies, the high visual performance of the Trinova IOL and PanOptix IOL are consistent with results obtained with the PanOptix IOL in a previous study and better than the near visual performance of the various types of multifocal IOLs.[14,15,16] The Trinova IOL has +3.0 D near addition and +1.50 D intermediate addition that theoretically provides up to 80 cm reading distance. The preferred reading distance for the Trinova IOL is 38 cm, which is similar to the preferred reading distance of the PanOptix IOL. Very good visual acuities for near and preferred reading distance were achieved with both the Trinova and PanOptix IOLs in the current study. Another previous study comparing the PanOptix and Trinova IOLs suggested that the PanOptix IOL provides better intermediate and near vision results and may be a good choice for patients who want to be independent of glasses.[17] Contrary to that study, we observed no significant difference in spectacle independence between the two IOLs in our study. At postoperative 3 months, this rate was 97.9% and 93.5% in the Trinova and PanOptix groups, respectively. Compared to bifocal IOLs and a low-near-add asymmetric IOL (+1.50 D) and a diffractive IOL (+1.75 D), both trifocal IOLs implanted in this study provided equivalent or better visual acuity and spectacle independence at near, intermediate, and distance.[18,19,20] This alleviates concerns that the addition of an intermediate focus will result in a reduction in performance at near and distance foci.

Multifocal IOLs are based on a non-physiological optical method to achieve near and intermediate vision, because light dispersion to different foci and subsequently at the level of the retina is not present in the natural human visual system. Also, traditional overlapping of the different foci in diffractive trifocal IOLs is neither normal nor physiological.[4] The optical surface of the Trinova IOL does not have any sharp edges. Vega et al.[21] experimentally assessed the through focus energy efficiency of the Acriva Trinova lens and demonstrated a smooth distribution with slightly more energy allocated to the distance focus. The smoothly transitioning surface profile of the lens is a unique patent-pending technology called sinusoidal vision technology. This optical surface pattern provides up to 92% light transmission to the retina, the highest value among all available trifocal IOLs. Thus, reduced light scattering by the stepless diffractive zones of the Trinova IOL might have a mitigating effect on dysphotopsia symptoms.

Angle kappa, the difference between the visual axis and pupillary axis, should also be kept in mind when evaluating pseudophakic photic phenomena. Prakash et al.[22] reported that large angle kappa values correlated with patients' photic complaints after multifocal IOL implantation. Additionally, a large angle kappa is thought to cause functional decentration of multifocal IOLs. It is noticed that if a patient has an angle kappa greater than half of the diameter of the central optical zone of the implanted multifocal IOL, then light may pass through one of the multifocal rings instead of the central optical zone of the lens. This leads to photic phenomena and an unacceptable multifocal IOL.[23] The PanOptix IOL has 15 overlapping diffractive rings surrounding a ~1.16-mm refractive zone, whereas the Trinova IOL has 12 sinusoidal diffractive zones surrounding a 1.4-mm central ring. Since the central ring diameter of the Trinova IOL is slightly larger than that of the PanOptix, greater tolerance to kappa angle and minimal decentration are expected. This might also have an influence on the difference in photic symptoms between the two study IOLs in the early period (1 month).

Despite the difference in the first month, there was no significant difference in photic symptoms between the two IOLs at postoperative 3 months. A functional magnetic resonance imaging study showed that multifocal IOL implantation is followed by a change in visual input, modification of the cortical circuitry, and increased activity in the caudate nucleus (cortical area of planning of adaptive behaviors). These processes, likely representing the beginning of neuroadaptation, are more pronounced in patients with more photic complaints.[24] Alió et al.[3] reported that at postoperative 1 month, significantly more patients in the AT LISA and RESTOR groups expressed that they would choose the same IOL again compared to the AT LISA tri group, whereas this difference in patient satisfaction disappeared at postoperative 6 months. The authors speculated that a longer period of neuroadaptation is needed for the trifocal lens.[3] In the present study, neural processing and neuroadaptation to pseudophakic optical patterns might play a role in the equalization of photic symptom rates in the two groups at 3 months after surgery.

The defocus curve illustrates vision quality at each dioptric level of spectacle defocus and would be linear at 0.0 logMAR from plano all the way through 3.0 D defocus in an ideal eye.[25] In the current study, regarding the continuous range of visual acuity, both IOLs provided a visual acuity of 0.10 logMAR or better for binocular defocus levels from 0.0 D to -2.50 D defocus. This result shows that both IOLs provide good functionality and sufficient visual acuity levels from near to distance. Similar to our results, Galvis et al.[26] also reported an absence of distinct peaks throughout the defocus curve with the PanOptix IOL.

Study Limitations

The lack of 6-month results is one of the limitations of our study. However, our study is the first comprehensive study in the literature to evaluate the Trinova and PanOptix IOLs together with many important parameters related to multifocal IOLs, including visual acuity, CS, defocus curve results, the VFQ-25 questionnaire, and spectacle independence.

Conclusion

The new sinusoidal trifocal IOL Trinova provided good visual outcomes, with uncorrected monocular and binocular visual acuities for all distances consistent with those of the PanOptix IOL. The defocus curve and CS results of the Trinova IOL suggest that an aspheric optic and smooth sinusoidal surface profile provide satisfactory, high-quality vision. The Trinova IOL had significantly better subjective dysphotopsia ratings than the PanOptix IOL at postoperative 1 month, whereas photic phenomena were reported to be mild and not disabling for both IOLs at 3 months.

Ethics

Ethics Committee Approval: Yozgat Bozok University Clinical Research Ethics Committee (protocol number: 2017-KAEK-189_2020.02.26_26, date: 26.02.2020).

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

The Role of *FOXP3* Polymorphisms in Graves' Disease with or without Ophthalmopathy in a Turkish Population

Fulya Yaylacıoğlu Tuncay*, Kübra Serbest Ceylanoğlu**, Sezen Güntekin Ergün***, Berçin Tarlan****, Onur Konuk****

*University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Department of Medical Biology, Ankara, Türkiye
**University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
***Hacettepe University Faculty of Medicine, Department of Medical Biology, Ankara, Türkiye
****Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: Forkhead box P3 (*FOXP3*) gene polymorphisms have been evaluated in many autoimmune diseases, including Graves' disease (GD), in different populations. However, those polymorphisms have not been analyzed in GD or Graves' ophthalmopathy (GO) in the Turkish population. In this study, we aimed to evaluate the frequency of *FOXP3* polymorphisms in GD with or without ophthalmopathy in a Turkish population.

Materials and Methods: The study included 100 patients with GO, 74 patients with GD without ophthalmopathy, and 100 age- and sex-matched healthy controls. In all study participants, rs3761547 (-3499 A/G), rs3761548 (-3279 C/A), and rs3761549 (-2383 C/T) single nucleotide polymorphisms (SNPs) were detected using the polymerase chain reaction-restriction fragment length polymorphism method. The chi-square test was used to evaluate genotype and allele frequencies. Odds ratios and 95% confidence intervals were calculated for genotype and allele risks.

Results: In the patient group (including GD with or without ophthalmopathy), the rs3761548 AC and AA genotype and rs3761549 CT genotype were significantly more frequent than in the control group (all $p<0.05$). No genotypic and allelic differences were observed for rs3761547 between the patient and control groups (all $p>0.05$). There was no statistically significant difference between the GO and GD without ophthalmopathy groups concerning the allele and genotype frequencies of all three *FOXP3* SNPs (all $p>0.05$).

Conclusion: The AC and AA genotypes of rs3761548 (-3279) and CT genotype of rs3761549 (-2383 C/T) were shown to be possible risk factors for GD development in the Turkish population. However, none of the three SNPs was shown to be associated with the development of GO in patients with GD.

Keywords: Forkhead box P3, Graves' disease, Graves' ophthalmopathy, single nucleotide polymorphisms

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Address for Correspondence: Fulya Yaylacıoğlu Tuncay, University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Department of Medical Biology, Ankara, Türkiye
E-mail: drfulyatuncay@gmail.com **ORCID-ID:** orcid.org/0000-0002-2088-3416
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Introduction

Graves' disease (GD) is an autoimmune disorder that causes diffuse enlargement of the thyroid gland and hyperthyroidism with elevated thyroid-specific autoantibody levels. GD is more common in women, and it usually occurs between the ages of 20 and 40 years.[1,2] Up to 50% of GD patients also develop Graves' ophthalmopathy (GO), which is another autoimmune disease that affects the orbital structures.[3] GO varies in clinical severity and is assessed according to the European Group on Graves' Ophthalmopathy (EUGOGO) classification.[3]

Thyroid-stimulating hormone receptor (TSHR) was shown to be the main autoantigen in GO, as in GD.[4] Both diseases have a complex pathogenesis involving interactions between genetic and environmental factors.[5] Among the genetic factors, *CTLA-4, TSHR, Tg, CD40,* and *PTPN22* polymorphisms and HLA class II gene variants were shown to be shared risk factors between GO and GD.[6] However, one polymorphism in *IL1A* was found to favor GO development in GD compared to GD patients without GO.[7] Additionally, another study in the Polish population showed that a *VDR* polymorphism may contribute to the development of GO.[8] From a clinical point of view, it is essential to identify patients with higher risk of developing GO in the course of GD, and we still need reliable genetic risk factors to act upon.

The immune system is primarily under the control of regulatory T-cells (Tregs).[9] Tregs were shown to be pivotal factors in the pathogenesis of human autoimmune diseases, including GD and GO.[10,11,12] The Forkhead box P3 (*FOXP3*) gene is located on the X chromosome, and its protein product FoxP3 is predominantly expressed in Tregs as a transcription factor. A deficiency of FoxP3 may impair the immunosuppressive effect of Tregs and lead to autoimmune diseases.[13,14] An association between *FOXP3* polymorphisms and the development of GD has been reported in different populations.[10,13,15,16,17,18,19,20,21,22] According to a recent meta-analysis of seven case-control studies, the *FOXP3* polymorphism rs3761548 was associated with GD susceptibility in Asians, and rs3761549 was associated in both Asians and Caucasians.[15] Despite several studies about the relationship between *FOXP3* single-nucleotide polymorphisms (SNPs) and GD susceptibility, none have been conducted in the Turkish population. Additionally, only two studies with small numbers of GO patients investigated the relationship between *FOXP3* SNPs and the risk of GO in GD patients.[13,17] Therefore, our study is the first to investigate three SNPs in the *FOXP3* gene (-2383 C/T, -3279 C/A, and -3499 A/G) in Turkish GD patients. In addition, we evaluated whether any of those SNPs favor GO development in a larger GD patient population.

Materials and Methods

Participants

This prospective case-control study was conducted between January 2019 and January 2022 and included 174 patients with GD (74 without GO [non-GO] and 100 with GO) and 100 healthy controls. The diagnosis of GD was made in the Department of Endocrinology and Metabolic Diseases based on the guidelines of the American Association of Clinical Endocrinologists.[23] The diagnostic criteria included hyperthyroidism, elevated thyrotropin receptor antibody level, and typical thyroid ultrasound patterns. The presence of ophthalmopathy was evaluated by three ophthalmologists (K.S.C., B.T., and O.K.), and its severity was assessed according to the EUGOGO classification.[3] Patients who had GD for at least five years and did not have ophthalmopathy were included in the non-GO group. The healthy control group included age- and sex-matched individuals who had no history of GD, allergic diseases, or other autoimmune disease. Age at onset, disease duration, cigarette smoking status, and family history of GD were collected from hospital records.

We obtained written informed consent from all participants before collecting samples. The study protocol was approved by the Clinical Research Ethics Committee of Gazi University (decision no: 2018-824/1, date: 12.11.2018). This study also met the standards of the Declaration of Helsinki.

Sample Collection and Genotyping

Four milliliters of peripheral blood was collected from the patients and healthy controls in tubes with ethylenediamine tetraacetic acid for genotyping. Genomic DNA was isolated using the QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA, USA). The genotypes of rs3761548, rs3761549, and rs3761547 in the *FOXP3* gene (gene ID: 50943, Xp11.23) were determined by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) assay.

For PCR, a total volume of 25 µL mixture was prepared using 50 ng genomic DNA template, 1×PCR buffer (Thermo Scientific™-Thermo Fisher Scientific Inc., USA) with 2 mM $MgCl_2$, 0.4 µmol of primers (IDT-Integrated DNA Technologies, Inc., USA), 0.20 mM dNTPs (Invitrogen-Thermo Fisher Scientific Inc., USA), and 1 U DNA polymerase (Thermo Scientific™-Thermo Fisher Scientific Inc., USA). In the standard PCR procedure, the first step is to denature the DNA at 95 °C for 5 minutes, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 59 °C (rs3761547 and rs3761548) or 60 °C (rs3761549) for 30 seconds, and extension at 72 °C for 30 seconds. Ten µL of the PCR products were used for RFLP. The restriction enzyme Pst1 (New England Biolabs GmbH, Germany) was used for detection of rs3761547 (1 U at 37 °C for 16 h), BseN1 (BsrI) (New England Biolabs GmbH, Germany) was used for rs3761548 (1 U at 65 °C for 16 h), and PvuII (New England Biolabs GmbH, Germany) was used for rs3761549 (1 U at 37 °C for 16 h). Undigested and digested PCR products were analyzed by 3% agarose gel electrophoresis. The primers and restriction enzymes used for this assay and the product sizes before and after digestion were shown in Table 1.

Statistical Analysis

Statistical data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). We used Student's t-test for normally distributed variables and the chi-square test for categorical variables (sex, family history). The Hardy-Weinberg equilibrium (HWE) for SNP polymorphisms was calculated using the chi-square test. The chi-square test was also used to compare the genotype and allele frequency distributions of the polymorphisms in the patient and control groups. We used logistic regression analyses to determine odds ratios (ORs) with 95% confidence intervals (CIs) for specific genotypes and alleles. A p value <0.05 was considered statistically significant.

Results

Characteristics of the Participants

One hundred GD patients with GO, 74 GD patients without GO, and 100 control participants were enrolled in this study. There was no significant difference in age and sex distribution among the groups. The mean age was 36.1±12 years for controls and 37±12.6 years for the study group (p=0.33). The respective distributions of males and females were 24.3% and 75.7% in the non-GO group, 26.0% and 74.0% in the GO group, and 32.0% and 68.0% in the control group (p=0.48) (Table 2).

FOXP3 SNP Allele and Genotype Frequencies

The distribution of allelic and genotypic frequencies of the three analyzed *FOXP3* polymorphisms in the patient group (non-GO and GO) and the control group, along with their associations with the risk of GD, are summarized in Table 3.

Table 1. Primers for *FOXP3*

Position	Enzyme	Forward primer (5'→3') Reverse primer (3'→5')	Amplicon size	RFLP pattern
-2383 C/T, rs3761549	Bsrl1	gcctggcactctcagagcttcaa cgacaccacggaggaagagaaga	487 bp	CC-329bp, 15 bp AC-487bp, 329bp, 158bp AA-48bp
-3279 C/A, rs3761548	Pst1	cctctccgtgctcagtgtag gcctcagccttcgccaata	261 bp	CC-184bp, 127bp, 77bp CT-261bp, 184bp, 127bp, 77bp TT-261bp, 127bp
-3499 A/G, rs3761547	Pvu11	gcaatcctcctctcgcacac tgcagggcttcaagttgacag	158 bp	AA-158bp AG-158bp, 123bp, 35bp GG-123 bp, 35 bp

FOXP3: Forkhead box P3, RFLP: Restriction fragment length polymorphism

In controls, all SNPs were in HWE (rs3761547, p=0.871; rs3761548, p=0.126; and rs3761549, p=0.068). For the patient group, rs3761547 (p=0.992) and rs3761548 (p=0.143) were in HWE, whereas rs3761549 was not in HWE (p=0.036).

For rs3761547, the frequencies of the AA, AG, and GG genotypes respectively were 147 (84.5%), 26 (15%), and 1 (0.5%) in GD patients and 90 (90%), 10 (10%), and 0 (0%) in the control group. The statistical analysis showed that the distribution of alleles and genotypes of the *FOXP3* rs3761547 polymorphism were not significantly different in GD patients and controls (p=0.23 and p=0.17, respectively) (Table 3).

For rs3761548, the frequencies of the CC, CA, and AA genotypes were 50 (28.7%), 74 (42.5%), and 50 (28.7%) in the patient group (non-GO and GO), compared to 66 (66%), 26 (26%), and 8 (8%) in the control group, respectively. The distribution of genotypes differed significantly between study patients and healthy controls (p<0.0001). When the most common genotype in the control group, CC, was used as a reference, it was found that the CA genotype was associated with a higher risk of GD (OR: 3.8; 95% CI: 2.1-6.7). Moreover, the frequency of the A allele was significantly higher in patients than controls (50% vs. 21%, p<0.0001), showing that carriers of the A allele have a significant risk for developing GD (OR: 3.8; 95% CI: 2.5-5.6) (Table 3).

For rs3761549, the respective frequencies of the CC, CT, and TT genotypes were 131 (75.3%), 35 (20.1%), and 8 (4.6%) in the patient group (non-GO and GO) versus 88 (88%), 10 (10%), and 2 (2%) in the control group. The genotypic distribution differed significantly between GD patients and healthy controls (p=0.02). Using the most common genotype in the control group (CC) as a reference, the CT genotype was found to be associated with a higher risk of GD (OR: 2.3; 95% CI: 1.1-4.9). Additionally, the frequency of the T allele was significantly higher in patients than controls (14.7% vs. 7%, p=0.007), showing that carriers of the T allele have a significant risk for developing GD (OR: 2.3; 95% CI: 1.2-4.2) (Table 3).

Comparison of genotypic and allelic distributions of each of the three *FOXP3* SNPs between the GO and non-GO groups showed no statistically significant difference (Table 4). Furthermore, the association between the *FOXP3* genotypes (-2383 C/T and -3279 C/A) and demographic variables was also carefully analyzed. We found no association between the investigated *FOXP3* polymorphisms and patients' age, family history, sex, or smoking status (Table 5).

Discussion

FoxP3 is predominantly expressed in CD34+ CD25 Tregs and plays a critical role in maintaining the suppressive function of Tregs.[13,14] Genetic variations in the *FOXP3* gene play a role in the pathogenesis of GD by weakening the suppressive functions of Tregs and enhancing autoimmune responses.[15,16,20] Although the relationship between *FOXP3* SNPs and GD has been demonstrated in several studies in different populations, few studies to date have compared the frequency of *FOXP3* SNPs between GD patients with and without orbitopathy.[13,17] This is the first study that investigated the relationship between three

Table 2. Demographic characteristics of groups

Variables	Non-GO n=74	GO n=100	Control n=100	p value
Age at onset of disease (mean ± SD)	35.5±12.1	37.8±12.4	-	0.66
Sex, n female/male	56/18	74/26	68/32	0.48
Duration of disease (years), mean ± SD	9.1±3.0	6.7±5.2	-	0.15
Family history (positive/negative)	38/36	58/42	-	0.42

GO: Graves' ophthalmopathy, SD: Standard deviation

Table 3. Genotypic and allelic distribution of the study and control groups				
Genotype	**Control group n=100**	**Study group (non-GO + GO) n=174**	**p value**	**OR (95% CI)**
rs3761548 (-3279 C/A)				
CC	66 (66%)	50 (28.7%)	-	1.0[a]
AC	26 (26%)	74 (42.5%)	**<0.0001**	3.8 (2.1-6.7)
AA	8 (8%)	50 (28.7%)	**<0.0001**	8.25(3.6-18.9)
Allele				
C	158 (79%)	174 (50%)	-	1.0[a]
A	42 (21%)	174 (50%)	**<0.0001**	3.8 (2.5-5.6)
rs3761549 (-2383 C/T)				
CC	88 (88%)	131 (75.3%)	-	1.0[a]
CT	10 (10%)	35 (20.1%)	**0.02**	2.3 (1.1-4.9)
TT	2 (2%)	8 (4.6%)	0.3	8.25 (0.5-12.9)
Allele				
C	186 (93%)	297 (85.3%)	-	1.0[a]
T	14 (7%)	51 (14.7%)	**0.007**	2.3 (1.2-4.2)
rs3761547 (-3499 A/G)				
AA	90 (90%)	147 (84.5%)	-	1.0[a]
AG	10 (10%)	26 (15%)	0.23	1.58 (0.73-3.43)
GG	0	1 (0.5%)	-	-
Allele				
A	190 (95%)	320 (92%)	-	1.0[a]
G	10 (5%)	28 (8%)	0.17	1.67 (0.73-3.43)

[a]The first listed allele/genotype is considered the reference value, bold values indicate statistical significance. Frequencies of genotypes and alleles were compared using chi-square test
GO: Graves' ophthalmopathy, OR: Odds ratio, n: Number, CI: Confidence interval

common polymorphisms in the *FOXP3* gene (rs3761549 [-2383 C/T], rs3761548 [-3279 G/T], and rs3761547 [-3499 T/C]) and GD in a Turkish population. The results showed that the AC and AA genotypes of -3279 and the CT genotype of -2383 are possible risk factors for GD. However, the development of GO in GD patients could not be associated with the investigated *FOXP3* polymorphisms in our study population.

For polymorphism -3279, an association between genotypes AA and AC and autoimmune diseases such as systemic lupus erythematosus and vitiligo has been shown in the literature.[10,12] The association with GD varies in the literature according to ethnicity. Although there are genotypic differences, the -3279 polymorphism has been reported to be a risk factor for GD in the Asian population.[10,13,17,19,21,22] It has been noted that the AC genotype of -3279 in the Kashmiri population, the AA and AC genotypes of -3279 in the Chinese Han population, and the AA genotype of -3279 in the female Southwest Chinese Han population pose a risk for GD.[13,19,22] In addition, a high frequency of the A allele was reported in patients with high thyroid-stimulating hormone (TSH) levels or low TSHR levels.[21] Like many studies, the A allele was observed more frequently in the GD group in the current study.[13,17,21] There are no studies in the Caucasian population reporting risk factors for -3279 polymorphisms.[18,20] Similar to the Kashmiri and Polish populations, the genotype distribution did not significantly differ between males and females in our study population (Table 5).[17,20] However, in the Asian population, the genotype distribution was reported to be significantly different between males and females.[13,22]

Polymorphism -2383 has been reported to increase GD susceptibility similarly to polymorphism -3279.[13,17,18,20] Bossowski et al.[20] reported that among Caucasians, the CT genotype of the -2383 polymorphism was more common in healthy females. Shehjar et al.[17] reported that the TT genotype of the -2383 polymorphism was a risk factor for developing GD in the Kashmiri population, but there were no sex differences in allelic or genotypic frequency distribution. In another study conducted in the Chinese Han population, carriers of the TT genotype of -2383 had a higher free triiodothyronine level than those with the CC/CT genotypes, but there was no significant difference between GD and control groups regarding genotype frequencies.[13] In our study, we found an association between the development of GD and the CT genotype of -2383, and the T allele was significantly more frequent in the study group. However, the genotype distribution did not differ significantly between males and females in our study population (Table 5). The differences in allelic and genotypic associations with GD in studies may be explained by ethnic differences.

Table 4. Genotypic and allelic distribution of non-GO and GO patients				
Genotype	**Non-GO**	**GO**	**p value**	**OR (95% CI)**
	n=74	**n=100**		
-3279 C/A				
CC	18 (24.3%)	32 (32%)	0.26	1.38 (0.7, 2.72)
AC	34 (45.9%)	40 (40%)	0.43	0.8 (0.44, 1.47)
AA	22 (29.7%)	28 (28%)	0.80	0.92 (0.47, 1.78)
Allele			0.38	1.21 (0.79, 1.85)
A	78 (47.3%)	96 (48%)		
C	70 (52.7%)	104 (52%)		
-2383 C/T				
CC	58 (78.4%)	73 (73%)	0.41	0.75 (0.37, 1.51)
CT	10 (13.5%)	25 (25%)	0.61	2.13 (0.95, 4.77)
TT	6 (8.1%)	2 (2%)	0.06	0.23 (0.05, 1.18)
Allele			0.71	0.89 (0.49, 1.63)
C	116 (84%)	171 (85.5%)		
T	22 (16%)	29 (14.5%)		
-3499 A/G				
AA	62 (83.8%)	85 (85%)	0.82	1.1 (0.48, 2.51)
AG	12 (16.2%)	14 (14%)	0.70	0.16 (0.06, 0.43)
GG	0	1 (1%)	-	-
Allele			0.75	1.13 (0.52, 2.46)
A	156 (82.9%)	184 (92%)		
G	12 (7.1%)	16 (8%)		

Frequencies of genotypes and alleles were compared using chi-square test
GO: Graves' ophthalmopathy, OR: Odds ratio, n: Number, CI: Confidence interval

Table 5. Analysis of the association between *FOXP3* genotypes and demographic variables in the patient group (GO and non-GO)						
Characteristics	***FOXP3* -2383 C/T**			***FOXP3* -3279 C/A**		
	CC (n=131)	**CT+TT (n=43)**	**p**	**CC (n=50)**	**AC+AA (n=124)**	**p**
Age at onset			0.11			0.49
≤40 years	76 (58%)	31 (72.1%)		33 (66%)	17 (34%)	
>40 years	55 (42%)	12 (27.9%)		74 (59.7%)	50 (40.3%)	
Sex			0.42			0.57
Female	100 (76.3%)	30 (69.8%)		39 (30%)	91 (70%)	
Male	31 (23.7%)	13 (30.2%)		11(25%)	33 (75%)	
Family history			0.48			0.87
Positive	70 (53.4%)	26 (60.5%)		27 (28.1%)	69 (71.9%)	
Negative	61 (46.6%)	17 (39.5%)		23 (29.5)	70.5 (55%)	
Smoking			0.48			>0.99
Yes	73 (77.7%)	21 (22.3%)		26 (52%)	63 (48%)	
No	58 (72.5%)	22 (27.5%)		24 (50.8%)	61 (49.2%)	

Genotype frequencies were compared using chi-square test
GO: Graves' ophthalmopathy, *FOXP3*: Forkhead box P3

For polymorphism -3449, we found no statistically significant difference between groups, consistent with the literature.[10,13,17,20,21,22] Only one study in the literature reported that free triiodothyronine and thyroxine levels and the -3499 A/G polymorphism were associated with GD.[20] It can be surmised that -3499 is not associated with altered *FOXP3* expression and does not affect Tregs functions.

In our study, none of the *FOXP3* genotypes or alleles was found to be associated with GO despite the higher number of GO patients in our study population. Similarly, Zheng et al.[13] and Shehjar et al.[17] could not show any associations between *FOXP3* SNPs and ophthalmopathy in GD in Asian populations. In the literature, Aydın et al.[24] found an association between the endothelin receptor type A (*EDNRA*) C+70G gene and the development of ophthalmopathy in GD patients. Another study reported that new SNPs in *CD74* (AG genotype of rs2569103) increased the risk of developing GO by affecting adipocyte proliferation and differentiation.[25] There are still many unanswered questions about the risk of ophthalmopathy in GD. For a better understanding of ophthalmopathy development, both genetic and non-genetic factors should be evaluated.

Study Limitations

Our study has several limitations. First, the number of participants in each group was limited, which might have reduced the power of the research and prevented us from showing significant differences between subgroups, such as gender and the presence of orbitopathy. Second, the study included only a small proportion of the GD patients in Türkiye. Therefore, whether our results could be generalized to the Turkish population is unclear. Third, we could not do a haplotype analysis due to the limited size of the study population. Fourth, our study was not longitudinal, and we could not control the other GO-related factors in study groups that might confound the risk of GO development in GD patients.

Conclusion

This study is the first to explore the association between *FOXP3* polymorphisms and GD with and without GO in a Turkish sample. We showed that the AC and AA genotypes of -3279 and the CT genotype of -2383 may be risk factors for GD development in our study population. However, we could not find any association between *FOXP3* SNPs and GO development in GD. More extensive population studies or meta-analyses of available data may reveal the impact of *FOXP3* polymorphisms on the risk of GO development in patients with GD.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gazi University (decision no: 2018-824/1, date: 12.11.2018).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: K.S.C., B.T., O.K., Concept: F.Y.T., K.S.C., S.G.E., O.K., Design: F.Y.T., K.S.C., S.G.E., O.K., Data Collection or Processing: F.Y.T., K.S.C., S.G.E., Analysis or Interpretation: F.Y.T., K.S.C., S.G.E., Literature Search: F.Y.T., K.S.C., Writing: F.Y.T., K.S.C., S.G.E.

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Original Article

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Assessment of Serum Atherogenic Indices and Insulin Resistance in Retinal Vein Occlusion

Şaban Gönül*, Serhat Eker**

*Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye
**Yalvaç State Hospital, Clinic of Ophthalmology, Isparta, Türkiye

Abstract

Objectives: This study aimed to investigate serum atherogenic indices as novel cardiovascular risk factors associated with retinal vein occlusion (RVO).

Materials and Methods: This retrospective case-control study included 57 patients with newly diagnosed RVO whose plasma lipid profile (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglycerides [TG]) and insulin resistance were examined. Serum atherogenic indices (LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, and non-HDL-C/HDL-C ratios) and presence of insulin resistance were compared between the patients and 63 healthy subjects. Cut-off values were determined by receiver operating characteristic curve analysis.

Results: The mean age of the RVO patients was 63.7±9.4 years. Plasma levels of LDL-C, HDL-C, TC, and TG showed no significant difference between the patient and control groups (p>0.05). However, LDL-C/HDL-C, non-HDL-C/HDL-C, and TC/HDL-C ratios were higher in the RVO group compared to healthy subjects (p=0.015, p=0.036, and p=0.015, respectively). Fasting insulin concentrations, plasma insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) index were higher in the RVO patients compared to controls (p=0.003, p=0.001, and p=0.001, respectively).

Conclusion: LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C ratios were found to be increased in RVO. Compared to the traditional plasma lipid profile, serum atherogenic indices were found to be superior predictors of RVO development. Measurement of HOMA-IR index should be taken into consideration in the evaluation of insulin resistance. High serum atherogenic indexes in RVO patients reveal the need to take precautions against the risk of cardiovascular disease and stroke.

Keywords: Retinal vein occlusion, serum atherogenic index, serum lipid profile, insulin resistance, HOMA-IR

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disease that can lead to visual impairment.[1] The prevalence of RVO has been reported as between 0.3% and 1.6%.[1,2] Its relatively high prevalence warrants attention to the prevention and management of the disease. Although there is still uncertainty regarding the pathogenesis of RVO, comprehensive studies have found an increased risk in patients with cardiovascular diseases such as arterial hypertension, hypercholesterolemia, atherosclerosis, and diabetes mellitus (DM).[3] Other identified risk factors for RVO development include aging, smoking, obesity, insulin resistance, trauma, open-angle glaucoma, thrombophilia, and hyperviscosity.[4,5,6]

The clinical signs of RVO include disseminated superficial and deep retinal hemorrhages, retinal edema, venous dilation, venous sheathing, anastomotic vessels, intraretinal microvascular disturbances, optic disc hyperemia, and optic disc edema. According to the location and findings of the affected vein, RVO is divided into the subtypes of branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).[7,8] Visual symptoms and prognosis rely on the subtype of RVO and the degree of macular involvement.

The significant relationship with cardiovascular risk factors necessitates a systemic evaluation including assessment of blood pressure, complete blood count, lipid profile, glucose metabolism, and insulin resistance for all patients with RVO

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Address for Correspondence: Serhat Eker, Yalvaç State Hospital, Clinic of Ophthalmology, Isparta, Türkiye
E-mail: drserhateker@gmail.com **ORCID-ID:** orcid.org/0000-0003-4107-7402
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during the diagnosis and treatment process. Regarding the traditional fasting plasma lipid profile (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), the relationship between these parameters and RVO is well-established in the literature.[2,5,7,9,10,11,12] The use of lipid ratios allows assessment of both antiatherogenic and atherogenic lipid parameters.[13] There are previous studies evaluating these ratios as novel biomarkers in cardiovascular diseases. However, according to our knowledge based on a review of the literature, no comprehensive study has evaluated TG/HDL-C, LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C ratios in patients with RVO. The purpose of this study was to investigate serum atherogenic indices as novel cardiovascular risk factors associated with RVO and contribute to the overall health status of patients with RVO.

Materials and Methods

Subjects and Clinical Data

This retrospective case-control research included 57 patients with newly diagnosed RVO who underwent detailed examination in the ophthalmology department of Selçuk University Faculty of Medicine from January to December 2019 and had their plasma lipid concentrations and insulin resistance assessed. The study conformed to the guidelines of the Declaration of Helsinki and was authorized by the Selçuk University Institutional Review Board and Ethics Committee (decision no: 2021/104, date: 24.02.2021). Informed consent was obtained from each participant.

The diagnosis of RVO was determined by an experienced retina specialist (Ş.G.) based on ophthalmoscopic examination of the fundus demonstrating typical clinical findings (e.g., retinal hemorrhages, retinal edema, venous dilation, venous sheathing, optic disc hyperemia, and optic disc edema) and was objectively confirmed by fundus fluorescein angiography. Based on the findings, the patients were classified into subgroups as CRVO (diffuse vascular findings in all retinal quadrants) or BRVO (vascular findings only in a wedge-shaped area). In addition, autorefractometer results (Tonoref III, Nidec Co. Ltd, Aichi, Japan), intraocular pressure measured by Goldmann applanation tonometry, best corrected visual acuity as determined on the standard Snellen eye chart, demographic data, and medical and ocular history were collected from the records of Selçuk University Faculty of Medicine. We only included patients with onset of symptoms within the last 72 hours, because the onset of the RVO could not be ascertained exactly.

Exclusion criteria were having additional notable systemic disease such as renal abnormalities, liver dysfunction, chronic infections, blood dyscrasias, collagen disease, or neoplastic disease; history of a surgical intervention within the last 3 months; current treatment with anticoagulant drugs, insulin for DM, postmenopausal hormone replacement, or antihyperlipidemic drugs; and any comorbid ocular disease (e.g., ocular trauma, uveitis, or retinal condition other than RVO).

After the evaluation of inclusion and exclusion criteria, 57 patients diagnosed with RVO were enrolled in this study. The healthy control group comprised 63 age- and sex-matched subjects who presented with symptoms of presbyopia and had normal findings on ophthalmological examination. Serum atherogenic indices and presence of insulin resistance were compared between patients and controls.

Laboratory Analysis

Blood samples were drawn into plain tubes without anticoagulant for analyses of serum lipids, hemoglobin A_{1c} (HbA1c), plasma glucose, and insulin. All samples were obtained after a 12-hour overnight fast by cubital venipuncture between 8:30 and 10:30 a.m. TC, HDL-C, and TG serum concentrations were examined on an ARCHITECT C16000 chemistry analyzer (Abbott Diagnostics, IL, USA) by enzymatic colorimetric methods according to the manufacturer's instructions. The Friedewald formula was used to determine LDL-C levels.[14] Non-HDL-C was computed as TC minus HDL-C.

HbA1c was calculated by standard laboratory techniques. Fasting plasma glucose (FPG) was detected using the glucose oxidase method. Concentrations of fasting insulin were measured by radioimmunoassay.

The lipid ratios TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C were calculated using lipid profile data. In addition, Framingham risk score for coronary heart disease was used to estimate the 10-year risk of myocardial infarction or death for all subjects. Comparisons were made using the standardized Framingham risk formula including age, sex, systolic blood pressure, TC, HDL-C, and smoking status.[15,16] Scores were calculated according to the values and categories, and the 10-year risk percentage was determined. The risk of coronary events in the next 10 years was classified as low (<10%), intermediate (10-20%), or high (>20%).[16]

Definitions of Diabetes Mellitus, Hypertension, and Insulin Resistance

DM was defined as a self-declared history of a previous diagnosis of diabetes and the use of antidiabetic medications. HT was defined as being treated with any antihypertensive drug. Insulin resistance was determined through the homeostasis model assessment of insulin resistance (HOMA-IR) according to the method of Matthews et al.[17]: HOMA-IR = plasma insulin (mIU/mL) × FPG (mg/dL)/22.5. Using a cut-off of 2.5, the participants were classified as those with insulin resistance (HOMA-IR ≥2.5) and those without insulin resistance (HOMA-IR <2.5).[18]

Statistical Analysis

Data were analyzed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Measurements are expressed as the mean ± standard deviation. The normality of each variable in the groups was measured using the Kolmogorov-Smirnov test. Comparisons of categorical data between groups were made using Pearson's chi-square test. For comparisons of continuous data, independent samples t-test was applied for variables with normal distribution

and the Mann-Whitney U test was performed for variables with abnormal distribution. We used the Spearman correlation coefficient to detect correlations between parameters. Receiver operating characteristic (ROC) curve analysis was utilized to show the sensitivity and specificity of serum lipid ratios and their cut-off values for predicting RVO, BRVO, and CRVO. The predictive validities were measured as area under the ROC curve. $p<0.05$ was regarded as statistically significant.

Results

There were 57 RVO patients with a mean age of 63.7±9.4 years. The healthy control group included 63 individuals with a mean age of 62.2±5.7 years. The age and sex distribution of the individuals in the groups did not differ significantly ($p>0.05$). While the frequency of HT differed significantly between the patient group and the control group ($p=0.011$), there was no difference in the frequency of DM ($p>0.05$). The demographic data of the subjects are summarized in Table 1.

Serum TG, TC, LDL-C, and HDL-C showed no statistical differences between the groups ($p>0.05$). Non-HDL-C was higher in the RVO group ($p=0.042$). In addition, LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C ratios were also higher in RVO patients compared to healthy subjects ($p=0.036$, $p=0.015$, and $p=0.015$, respectively). On the other hand, TG/HDL-C ratio showed no significant difference ($p>0.05$). Correlation analysis revealed that TG/HDL-C was correlated with FPG ($r=0.211$, $p=0.021$), insulin ($r=0.308$, $p=0.001$), HbA1c ($r=0.299$, $p=0.001$), and HOMA-IR ($r=0.317$, $p=0.0001$). Details are given in Table 2.

Regarding glucose metabolism, the RVO group had higher fasting insulin concentrations, plasma insulin, and HOMA-IR index ($p=0.003$, $p=0.001$, and $p=0.001$, respectively). The proportion of subjects with insulin resistance (HOMA-IR ≥2.5) was significantly higher in RVO compared to controls ($p=0.0001$). However, mean HbA1c values did not differ significantly between the groups ($p>0.05$) (Table 2).

Table 1. Demographic data of study subjects

	RVO group (n=57)	Control group (n=63)	p value
Mean age ± SD (years)	63.7±9.4	62.2±5.7	0.275*
Male/female ratio (n)	25/32	26/37	0.774**
Hypertension (n)	24	13	**0.011****
Diabetes mellitus (n)	22	17	0.175**

Statistically significant values ($p<0.05$) shown in bold. *Independent samples t-test, **Chi-square test
SD: Standard deviation, RVO: Retinal vein occlusion

Table 2. Parameters of all RVO patients and healthy participants

	RVO group (n=57)		Control group (n=63)		p value
	Mean ± SD	Median	Mean ± SD	Median	
TC (mg/dL)	211.2±46.3	210	198.1±40.1	129	0.101*
LDL-C (mg/dL)	133.2±32.3	139	122±35.2	129	0.1**
HDL-C (mg/dL)	47.5±12.3	46	49.5±10	48	0.129**
TG (mg/dL)	162.5±91.1	125	132±38.1	129	0.378**
Non-HDL-C (mg/dL)	163.6±41.3	163	148.6±38.3	148	**0.042***
TC/HDL-C	4.5±1	4.6	4.11±1	4.1	**0.015***
TG/HDL-C	3.6±2.2	2.9	2.81±1	2.6	0.092**
LDL-C/HDL-C	2.9±0.7	3	2.55±0.8	2.6	**0.036****
Non-HDL-C/HDL-C	3.5±1	3.6	3.11±1	3.1	**0.015***
FPG (mg/dL)	116.5±41.4	107	96.9±13.8	95	**0.003****
HbA1c (%)	6.4±1.3	6	6.1±0.6	5.9	0.410**
Insulin (mIU/mL)	10±5.2	9.7	6.2±2	6	**0.001****
HOMA-IR	3.13±2.48	2.3	1.5±0.6	1.6	**0.001****
HOMA-IR ≥2.5, n (%)	27 (52.6)		5 (7.9)		**0.0001*****

Statistically significant values ($p<0.05$) shown in bold. *Independent samples t-test, **Mann-Whitney U test, ***Chi-square test, RVO: Retinal vein occlusion, SD: Standard deviation, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance

In subgroup analysis, 68.4% (n=39) of patients with RVO showed characteristics of BRVO, while 31.6% (n=18) of them had the presentation of CRVO. Of all the lipid and glucose metabolism parameters, only LDL-C differed significantly between subgroups. The frequency of HT was higher in CRVO (p=0.011). The characteristics of the CRVO and BRVO subgroups are shown in Table 3.

The Framingham 10-year risk in subjects with RVO was 10.8%, which was significantly greater than in the control group (p<0.05). Men in particular had significantly higher Framingham risk scores than women in the RVO group (p=0.0001). The mean score was 10.48% in BRVO patients and 11.75% in the CRVO group. Although patients with CRVO had higher Framingham 10-year risk, there was no significant difference between BRVO and CRVO subjects in analysis (p>0.05).

ROC curve analysis was performed to determine the specificity and sensitivity of atherogenic indices in differentiating RVO patients from controls, as well as cut-off values for predicting RVO, BRVO, and CRVO. According to our results, values higher than the following cut-off values were significant in terms of RVO risk: 4.44 for TC/HDL-C values (64% sensitivity, 65% specificity), 3.41 for non-HDL-C/HDL-C (64% sensitivity, 63% specificity), 2.64 for TG/HDL-C (68% sensitivity, 50% specificity), and 2.89 for LDL-C/HDL-C (63% sensitivity, 65% specificity). In addition, TC/HDL-C values >4.52 (72% sensitivity, 68% specificity) and LDL-C/HDL-C values greater than >2.9 (66% sensitivity, 68% specificity) were found to be significant in predicting CRVO. ROC curve analysis and the cut-off values for RVO, BRVO, and CRVO are shown in Table 4.

Discussion

RVO is the most common retinal vasculopathy following diabetic retinopathy and occurs due to disturbances of the retinal venous circulation.[8] The most common known risk factors for cardiovascular comorbidities are also strongly associated with RVO. Previously, studies have investigated parameters associated with cardiovascular health in RVO.[2,5,7,10,11,12,19] Khan et al.[20] stated that patients with RVO have an elevated 10-year Framingham risk score for cardiovascular disease. Furthermore, it has been emphasized that therapy aimed at controlling risk factors should be planned in these patients. Therefore, patients diagnosed with RVO should be examined in terms of cardiovascular health.

Dyslipidemia, presenting as elevated levels of TG, LDL-C, and TC and a low level of HDL-C, is a well-defined traditional risk factor for RVO.[5,11,12,20] However, it has been reported that lipoproteins and some of their ratios (TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C) show a stronger statistical relationship with the severity and prevalence of coronary artery disease in determining the risk of atherosclerosis compared to measurements of lipid levels alone.[21] The current

Table 3. Details of the BRVO and CRVO patient subgroups

	BRVO Group (n=39)		**CRVO Group (n=18)**		**p value**
Sex (male/female), n (%)	15 (38.5)/24 (61.5)		10 (55.6)/8 (44.4)		0.227*
	Mean ± SD	**Median**	**Mean ± SD**	**Median**	
Age	64.6±6.9	64	61.7±13.3	64.5	0.692**
TC (mg/dL)	205±46.8	210	224.6±43.3	225.5	0.140***
LDL-C (mg/dL)	128.4±33.3	132	143.6±28	145.5	**0.032****
HDL-C (mg/dL)	46.8±11.6	45	49.2±14	46.5	0.513**
TG (mg/dL)	157.5±87.2	125.0	173.3±100.8	143.5	0.778**
Non-HDL-C (mg/dL)	158.2±43.2	156	175.3±35.1	177	0.147***
TC/HDL-C	4.5±1.1	4.4	4.74±0.9	4.9	0.497***
TG/HDL-C	3.5±2.2	2.7	3.81±2.32	3.2	0.830**
LDL-C/HDL-C	2.8±0.8	2.9	3±0.5	3	0.152**
Non-HDL-C/HDL-C	3.5±1.1	3.4	3.7±0.9	3.9	0.497***
FPG (mg/dL)	118.2±44.9	108	112.8±33.4	97	0.486**
HbA1c (%)	6.3±1.2	6	6.4±1.48	5.9	0.730**
Insulin (mIU/mL)	10.1±5.04	9.7	9.9±5.8	9.3	0.624**
HOMA-IR	3.1±2.4	2.7	3±2.5	2	0.643**
HOMA-IR ≥2.5, n (%)	20 (51.3)		7 (38.9)		0.384*
Diabetes mellitus, n (%)	16 (41.0)		6 (33.3)		0.579*
Hypertension, n (%)	12 (30.8)		12 (66.7)		**0.011***

Statistically significant values (p<0.05) shown in bold. *Chi-square test, **Mann-Whitney U test, ***Independent samples t-test, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, SD: Standard deviation, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance

Table 4. Receiver operating characteristic curve analysis for atherogenic indices in predicting retinal vascular occlusion						
	Index	**AUC (95% CI)**	**Cut-off value**	**p value**	**Sensitivity (%)**	**Specificity (%)**
RVO	TC/HDL-C	0.626 (0.526-0.727)	4.44	**0.017**	64	65
	LDL-C/HDL-C	0.611 (0.509-0.713)	2.89	**0.036**	63	65
	TG/HDL-C	0.589 (0.485-0.694)	2.64	0.092	68	50
	Non-HDL-C/HDL-C	0.626 (0.526-0.727)	3.41	**0.017**	64	63
BRVO	TC/HDL-C	0.603 (0.492-0.714)	4.37	0.081	61	63
	LDL-C/HDL-C	0.582 (0.471-0.693)	2.67	0.165	59	54
	TG/HDL-C	0.58 (0.461-0.699)	2.78	0.176	51	52
	Non-HDL-C/HDL-C	0.603 (0.492-0.714)	0.61	0.081	61	63
CRVO	TC/HDL-C	0.676 (0.544-0.809)	4.52	**0.023**	72	68
	LDL-C/HDL-C	0.675 (0.548-0.801)	2.9	**0.024**	66	68
	TG/HDL-C	0.609 (0.431-0.788)	2.86	0.159	55	57
	Non-HDL-C/HDL-C	0.676 (0.544-0.809)	3.52	0.544	72	68

Statistically significant values ($p<0.05$) shown in bold. AUC: Area under the curve, CI: Confidence interval, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglycerides

study aimed to evaluate the serum lipid ratios and insulin resistance status of newly diagnosed RVO patients.

It is known that a high TG/HDL-C ratio is associated with abdominal obesity and insulin resistance, even with no change in LDL-C levels, as well as high BMI and hyperinsulinemia.[22,23,24] Furthermore, the TG/HDL-C ratio was reported to be a strong predictor of mortality and cardiovascular health in women with presumed myocardial ischemia.[25] In another large population survey of participants aged 20-90 years, an association was demonstrated between the TG/HDL-C ratio and cardiovascular disease.[26] Çelik and Gökçe[27] reported that RVO patients had a significantly higher atherogenic index of plasma (log [TG/HDL-C]) than the control group. This parameter was also reported to be related with metabolic-associated fatty liver disease and unfavorable prognosis of percutaneous coronary intervention.[28,29] In our study, the TG/HDL-C ratio was higher in the RVO group. However, no statistically significant difference was determined. Moreover, we observed that the TG/HDL-C ratio was correlated positively with HOMA-IR, insulin, HbA1c, and FPG. Therefore, this ratio should be evaluated together with glucose metabolism and insulin resistance markers. FPG, insulin, and HOMA-IR index were found to be increased in RVO patients compared to the control group. The average HbA1c value of the patients and healthy group was above 6%, and no statistical difference was found between the groups. In our study of RVO patients, TG/HDL-C ratio and HbA1c were not good indicators for the evaluation of insulin resistance. However, HOMA-IR index calculated with insulin level and FPG was found to be markedly higher in the RVO group. Therefore, we believe this is a crucial parameter that should be used in the evaluation of insulin resistance in subjects with RVO. In the literature, FPG with insulin level and HbA1c ratio have been previously evaluated in RVO patients.[9,30,31] As far as we know, the current study is the first in which the HOMA-IR index was applied in the assessment of insulin resistance in RVO patients.

Ratios of cholesterol ester-rich lipoprotein levels (LDL-C/HDL-C and TC/HDL-C) are among the well-known markers of ischemic heart disease, and elevated ratios indicate a disorder in cholesterol metabolism.[32,33] TC/HDL-C ratio is a parameter of coronary heart disease and includes both an atherogenic and an antiatherogenic lipid parameter.[34] Since the LDL-C level is determined based on TG, TC, and HDL-C concentrations, it cannot be calculated with traditional formulas in patients with a TG level of more than 399.[14] In this case, direct evaluation of the TC/HDL-C ratio can provide information in terms of atherogenic lipid components. Earlier studies regarding serum lipid profiles in coronary heart disease patients indicated that TC/HDL-C ratios were high when compared to controls.[23,35,36] Stampfer et al.[33] demonstrated that a higher LDL/HDL ratio was associated with an elevated risk of myocardial infarction. In a 20-year prospective study of 3914 patients with stroke, low HDL-C and high TC/HDL-C ratio were emphasized to be related to the risk of total and ischemic stroke in male and female patients.[37] In our study, the TC/HDL-C ratio was higher in RVO patients than the healthy subjects. In their biochemical analysis of 60 patients with ischemic heart disease, Ghosh et al.[36] reported a TC/HDL-C ratio of 4.9±1.2, which was notably higher than the control group. We think that the high TC/HDL-C and LDL-C/HDL-C ratios in RVO patients suggest that these parameters may be associated with worse cardiovascular health status and clinical outcomes.

As is known, atherosclerosis is a crucial risk factor for RVO, and abnormalities in cholesterol metabolism also pose a threat.[3] Previously, non-HDL-C has been reported to be a superior predictive marker of arterial vessel wall stiffness compared to LDL-C.[38] Therefore, the ratio of non-HDL-C/HDL-C is easy,

convenient, and better for the assessment of coronary artery disease and arterial stiffness risk than lipid parameters alone.[39,40] In the current study, non-HDL-C levels and non-HDL-C/HDL-C ratios were observed to be increased in the RVO patients compared to the healthy subjects. This result undoubtedly reveals the necessity of further cardiovascular examination of patients diagnosed with RVO. Moreover, it demonstrates the importance of vascular health both in protecting the health of the fellow eye and in the recovery of the eye affected by RVO.

In subgroup analysis, the frequency of hypertension was higher in the group with CRVO, consistent with the literature.[5] In terms of serum lipids, however, only LDL-C levels were found to be increased in the CRVO group. ROC analysis revealed that TC/HDL-C and LDL-C/HDL-C ratios were significant for predicting CRVO, while none of the ratios were significant for BRVO. The fact that TC/HDL-C and LDL-C/HDL-C ratios are indicative of CRVO may demonstrate a higher risk of cardiovascular disease. More comprehensive studies should be done on serum lipids and atherogenic indices to reveal the differences between CRVO and BRVO.

The Framingham risk score has been used for many years to estimate the 10-year risk of myocardial infarction or death in various populations.[20] In our study, the Framingham risk score was higher in RVO patients (10.8%), and especially in men. Similarly, a meta-analysis showed the 10-year Framingham risk score in subjects with RVO to be 10.1%.[20] In the current study, no significant difference was seen in the Framingham risk score between CRVO and BRVO patients. We attributed the slightly higher Framingham risk score in CRVO cases to the higher frequency of hypertension. In another study, higher 10-year risk of coronary heart disease was reported in BRVO patients due to the frequency of hypertension and other cardiovascular risk factors.[41] In our study, there was intermediate risk of coronary events in both BRVO and CRVO. Although the Framingham risk score was not found to differ in CRVO cases, TC/HDL-C and LDL-C/HDL-C ratios were predictive of CRVO. As can be seen from these results, it is necessary to evaluate cardiovascular health status in RVO patients.

Study Limitations

To the best of our knowledge, the current study is the first to evaluate serum lipid ratios as serum atherogenic indices and the HOMA-IR index in patients with RVO. However, the study had some limitations. The small sample size and single-center design are the most important of them. Additionally, the study may have biased because the sample consisted of subjects presenting for care. Finally, causality between dyslipidemia and RVO cannot be established because of the cross-sectional study design. Future research should focus on the effect of changes in serum lipid ratios on the recovery process by examining the outcomes of RVO treatment in prospective cohort studies.

Conclusion

The current study showed that RVO was associated with increased ratios of TC/HDL-C, LDL-C/HDL-C and non-HDL-C/HDL-C compared to healthy subjects. The results suggest that measurement of HOMA-IR index should be considered in the evaluation of insulin resistance in RVO cases. These abnormalities may contribute to the pathogenesis of RVO and the associated risk of cardiovascular disease and stroke in these patients.

Ethics

Ethics Committee Approval: Selçuk University Institutional Review Board and Ethics Committee (decision no: 2021/104, date: 24.02.2021).

Informed Consent: Obtained.

Authorship Contributions

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

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Review

Is Glaucoma a Two-Pressure-Related Optic Neuropathy? A Systematic Review and Meta-Analysis

Tung Thanh Hoang*, **, ***, Bui Van Anh****, Prem Subramanian*****

*Hanoi Medical University, Department of Ophthalmology, Hanoi, Vietnam
**Hanoi Medical University Hospital, Division of Ophthalmology, Hanoi, Vietnam
***The University of Sydney School of Medicine, Save Sight Institute, Sydney, Australia
****Vietnam National Eye Hospital, Department of Glaucoma, Hanoi, Vietnam
*****University of Colorado School of Medicine, Department of Ophthalmology, Aurora, USA

Abstract

Objectives: To review the current literature related to the correlation between translaminar pressure difference (TLPD) and glaucoma.

Materials and Methods: In this article, we conducted a literature review using MEDLINE via PubMed, Cochrane Eyes and Vision, and Google Scholar from 01/01/2010 to 31/12/2022. Search terms included "glaucoma", "intraocular pressure", "translaminar cribrosa pressure gradient/difference", "intracranial pressure", and "cerebrospinal fluid pressure". Of 471 results, 8 articles were selected for the meta-analysis.

Results: Our meta-analysis demonstrated significantly higher intraocular pressure, lower cerebrospinal fluid pressure (CSFp), and greater TLPD in high-tension and normal-tension glaucoma groups compared to healthy groups.

Conclusion: The differences in CSFp and TLPD between glaucoma and healthy people detected in current studies suggests a potential relationship between TLPD and glaucoma.

Keywords: Glaucoma, intraocular pressure, translaminar cribrosa pressure gradient/difference, cerebrospinal fluid pressure, intracranial pressure

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Address for Correspondence: Tung Thanh Hoang, Hanoi Medical University, Department of Ophthalmology; Hanoi Medical University Hospital, Division of Ophthalmology, Hanoi, Vietnam; The University of Sydney School of Medicine, Save Sight Institute, Sydney, Australia
E-mail: tung.hoang@sydney.edu.au **ORCID-ID:** orcid.org/0000-0002-8098-5879
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Introduction

Glaucoma is a chronic, irreversible optic neuropathy characterized by damage to retinal ganglion cells with or without elevated intraocular pressure (IOP). The current global prevalence of glaucoma is 3.5% in the 40- to 80-year-old population. In 2013, the number of people in this age group suffering from glaucoma was 64.3 million and was predicted to rise to 76 million in 2020 and 112 million in 2040.[1]

Elevated IOP has long been considered the main and only modifiable risk factor in the pathogenesis of glaucoma. Nonetheless, patients may be diagnosed with normal-tension glaucoma (NTG) or exhibit disease progression even with well-controlled IOP and in the absence of cardiovascular risk factors.[2,3] Because IOP exerts its force at the anterior lamina cribrosa and is theoretically countered by the cerebrospinal fluid pressure (CSFp) within the optic nerve sheath which exerts force at the back of the globe, researchers have explored the potential relationship between glaucoma and CSFp.[4,5,6,7] CSFp can be calculated by invasive (lumbar puncture) and non-invasive (formula,[8,9,10,11] transcranial Doppler[12]) methods. The resulting translaminar pressure difference (TLPD = IOP - CSFp)[13] may be normal/balanced or abnormal/imbalanced in either direction. If the intraocular force (IOP) is in excess, glaucoma may result. On the other hand, a TLPD with excessive CSFp and normal IOP has been implicated in the optic disc swelling and posterior globe flattening that may be seen in disorders of elevated intracranial pressure (idiopathic intracranial hypertension) and in astronauts after long-duration spaceflight.[14,15] The reverse effect of the TLPD theory can also be seen in ocular hypotony, in which low IOP and normal CSFp can cause optic disc edema.[16] Some animal and experimental studies have suggested the possible role of TLPD in glaucoma.[17,18,19] We conducted this review because a

potential intervention to increase CSFp, reduce IOP, or alter the gradient might have implications in the broader management of glaucoma.

In 2015, Siaudvytyte et al.[20] published the first systematic review and meta-analysis about the correlation between CSFp and glaucoma. Their study showed a higher TLPD in subjects with glaucoma compared to healthy controls, as well as a correlation between TLPD and glaucomatous optic neuropathy.[20] Most current reviews are qualitative literature searches without any quantitative analysis. Therefore, we conducted this study to systematically evaluate the current evidence that links glaucoma development and progression to alterations in the TLPD.

Materials and Methods

Literature Search

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. We searched MEDLINE through PubMed, Cochrane Eyes and Vision, and Google Scholar from 01/01/2010 to 31/12/2022. Keywords included "glaucoma", "intraocular pressure", "translaminar cribrosa pressure gradient/difference", "intracranial pressure", and "cerebrospinal fluid pressure". Two independent reviewers (T.T.H. and V-A.B.) independently reviewed all PubMed, Cochrane Eyes and Vision, and Google Scholar abstracts to assess eligibility.

Eligibility Criteria

Peer-reviewed English papers with cross-sectional, case-control, or cohort designs including high-tension glaucoma (HTG) (primary open-angle glaucoma [POAG] or angle-closure glaucoma [PACG]) and NTG participants in the case group and healthy individuals in the control group were selected. Variables such as glaucoma type, IOP, CSFp, and TLPD must have been clearly described. We excluded literature or narrative reviews, animal and computer model studies, and studies not analyzing IOP, CSFp, and TLPD in glaucoma patients. Eligible full-length articles were finally selected by two reviewers (T.T.H. and V-A.B.). The Newcastle-Ottawa Scale, a collaborative project between Newcastle University, Australia and Ottawa, Canada, was applied to assess the quality of non-randomized studies in meta-analysis.[21]

Outcome Measures

Data extracted for the meta-analysis included IOP, CSFp, TLPD, and CSFp measurements and glaucoma type.

Definitions

Validated CSFp measurements were both invasive (lumbar puncture) and non-invasive (formula,[8,9,10,11] transcranial Doppler[12]). TLPD was defined as IOP - CSFp.[3]

Statistical Analysis

The data were analyzed using RevMan 5.3 (Cochrane Collaboration). A random effects model was employed to calculate effect size due to the heterogeneity of the studies. A p value less than 0.05 was considered statistically significant.

Results

We found 471 results through database searches. After removing duplicated records, we screened 90 studies. Of these screened studies, 25 abstracts met the selection criteria for full-text assessment; 15 of them were excluded with reasons shown in Figure 1, leading to a final inclusion of 8 articles (Table 1).[5,9,10,11,22,23,24,25] Quality assessment and extracted data for meta-analysis of the included studies can be found in Supplementary Tables 1 and 2.

Glaucoma patients in the HTG group had significant higher IOP (Z=2.65, p=0.008), lower CSFp (Z=5.9, p<0.0001), and higher TLPD (Z=3.9, p<0.0001) than the healthy participants (Figure 2A, B, C). Similarly, the NTG group also had significant higher IOP (Z=93.89, p<0.00001), lower CSFp (Z=2.06, p=0.04), and higher TLPD (Z=2.41, p=0.02) compared to controls (Figure 2D, E, F). Table 2 includes studies supporting the correlation between TLPD and glaucoma progression in terms of structure and function.

Discussion

At the time of the first review in 2015, only 3 prospective studies were available for analysis. Since then, additional prospective studies have been carried out to explore the potential relationship between TLPD and glaucoma risk and progression. Our study found significant differences between glaucoma patients and healthy people in terms of IOP, CSFp, and TLPD in both the HTG and NTG groups. These findings are consistent with the meta-analysis of Siaudvytyte et al.[20] as well as most of the included studies, and further contribute to our knowledge of this topic.

In our study, the NTG group had a higher mean IOP than healthy controls (p<0.00001), which was similar to a recent study of Deimantavicius et al.[26] This could be because the studies by Ren et al.[5] and Lee et al.[9] included NTG patients whose IOP was higher on average than in other studies in this systematic review.

Our results also showed that CSFp was significantly lower in both the HTG (p<0.0001) and NTG (p=0.04) groups compared to control groups. According to Wang et al.[27], NTG patients had the narrowest orbital optic nerve subarachnoid space (SAS) on magnetic resonance imaging (MRI), suggesting a lower CSFp in comparison to POAG patients and healthy participants. Employing computed tomographic cisternography, Pircher et al.[28] indicated that contrast-loaded CSF gradually decreased along the optic nerve of NTG patients while no similar reduction was found in normal subjects. Boye et al.[29] measured the flow-range ratio between the intracranial cavity and SAS of the optic nerve in MRI diffusion images and demonstrated that this ratio was significantly lower in NTG compared to healthy people, indicating abnormal CSFp in NTG. In the study by Deimantavicius et al.[26], CSFp determined by two-depth transcranial Doppler (TCD) ultrasonography was lower in both the HTG and NTG groups than in healthy participants.

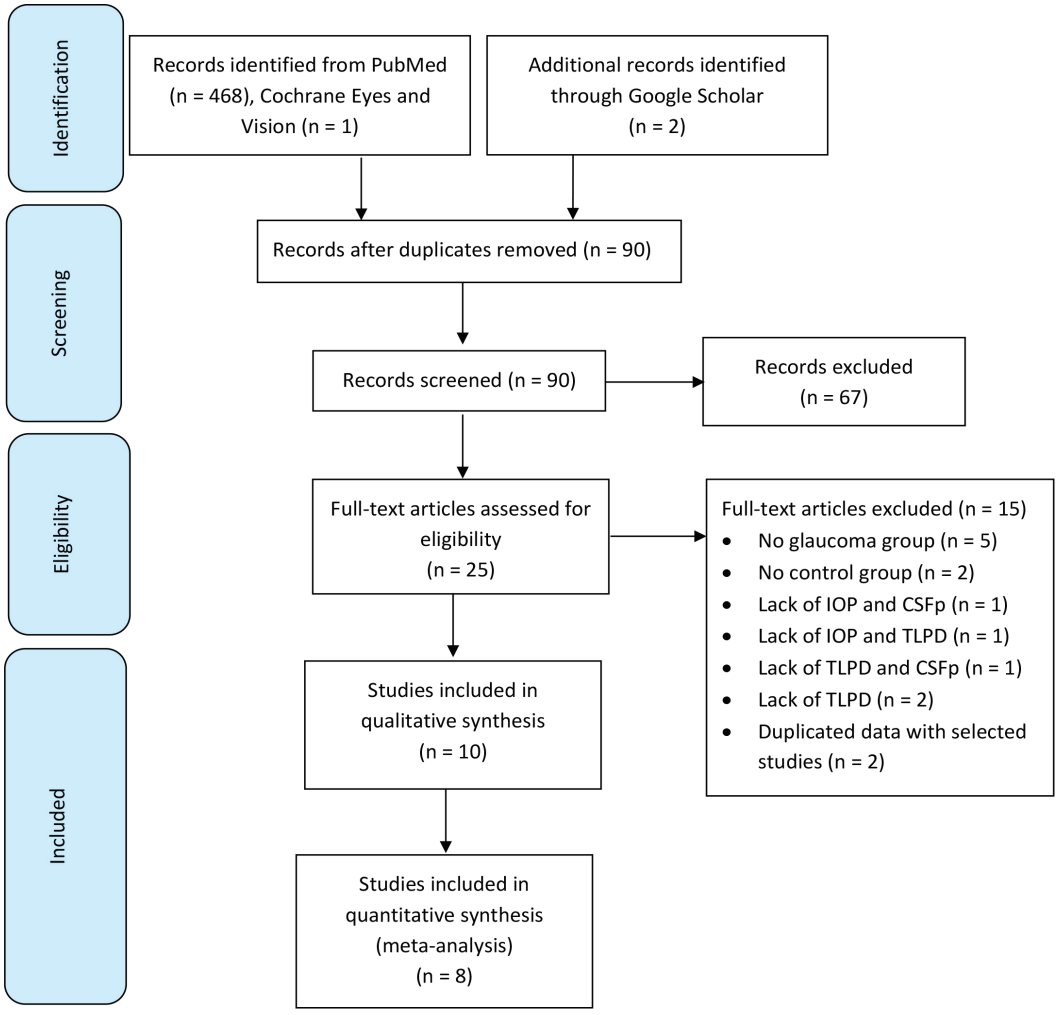

Figure 1. Systematic review flow diagram
IOP: Intraocular pressure, CSFp: Cerebrospinal fluid pressure, TLPD: Translaminar pressure difference

Table 1. Selected studies

Study	CSFp measurement	Research design	Number of patients	Glaucoma type
Ren et al.[5] 2010	Lumbar puncture	Cross-section (prospective)	114	NTG, HTG
Siaudvytyte et al.[22] 2014	Two depth TCD	Cross-section (prospective)	27	NTG, HTG
Jonas et al.[23] 2015	Formula	Cross-section (population-based)	3468	HTG (POAG, PACG)
Jonas et al.[24] 2015	Formula	Cross-section (population-based)	4711	HTG (POAG, PACG)
Lee et al.[9] 2016	Formula	Cross-section (population-based)	12743	NTG
Landi et al.[10] 2019	Formula	Cross-section (prospective)	43	HTG (POAG)
Matuoka et al.[11] 2021	Formula	Cross-section (prospective)	75	HTG (POAG)
Lindén et al.[25] 2018	Lumbar puncture	Cross-section (prospective)	24	NTG

CSFp: Cerebrospinal fluid pressure, NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, POAG: Primary open-angle glaucoma, PACG: Primary angle-closure glaucoma, TCD: Transcranial Doppler

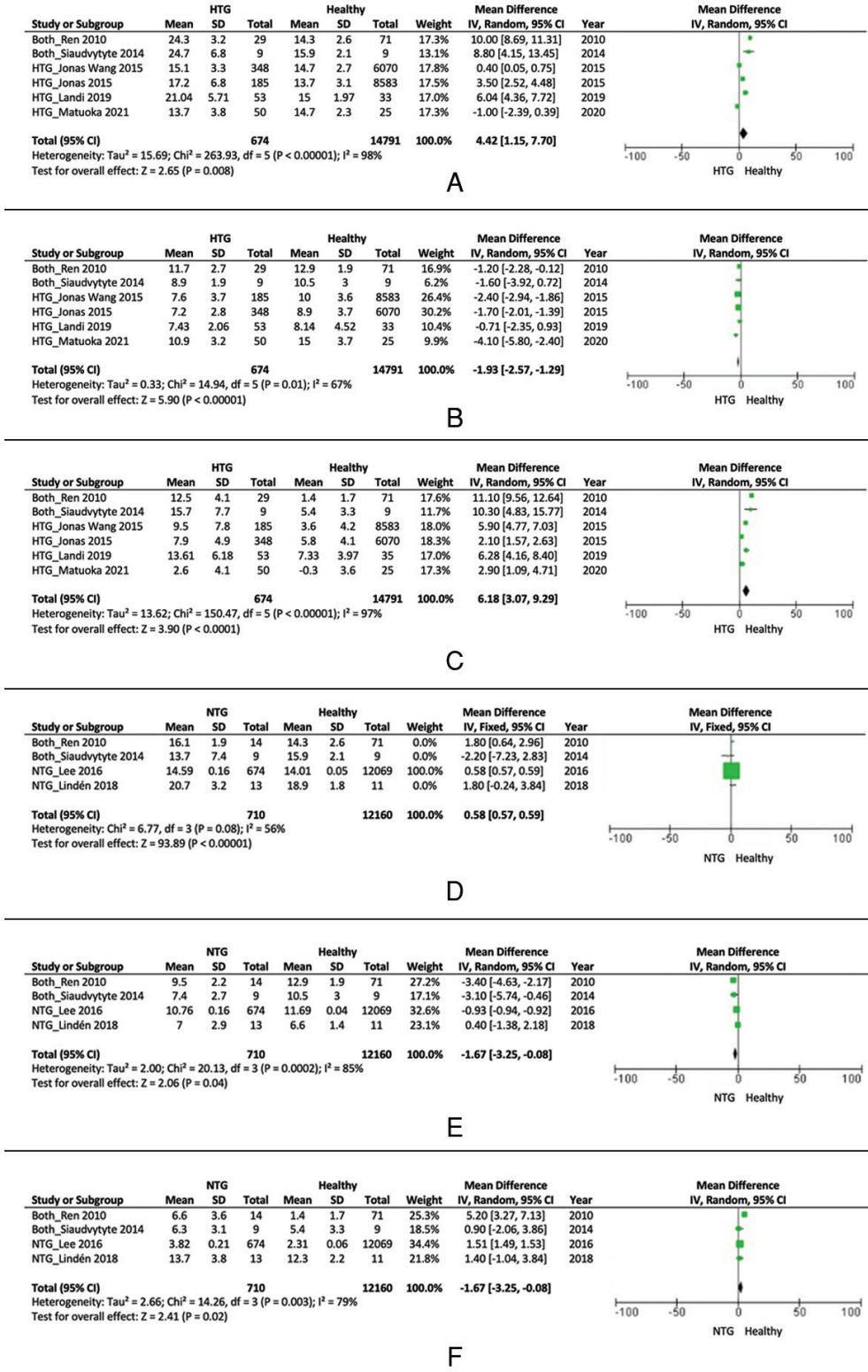

Figure 2. Meta-analysis results between high-tension glaucoma (A. Intraocular pressure, B. Cerebrospinal fluid pressure, C. Translaminar pressure difference), normal-tension glaucoma (D. Intraocular pressure, E. Cerebrospinal fluid pressure, F. Translaminar pressure difference), and healthy subjects

HTG: High-tension glaucoma, NTG: Normal-tension glaucoma, SD: Standard deviation, IV: Weighted mean difference, CI: Confidence interval, df: Degrees of freedom, I²: I-square heterogeneity statistic

Table 2. Correlation between translaminar pressure differences and glaucoma progression

Study	Number of patients	Groups	Outcome measures	Methods	Correlation
Ren et al.[5] 2010	114	NTG, HTG, control	MD	HFA	r=0.69, p=0.005
Ren et al.[31] 2011	52	HTG, NTG, OH	NRA MVFD	HFA HRT	r=-0.38, p=0.006 r=0.38, p=0.008
Siaudvytyte et al.[22] 2014	27	NTG, HTG, control	NRA	HRT	r=-0.83, p=0.01
Zhang et al.[32] 2018	6830	POAG, control	NRA	HRTII	B=-0.002, p=0.028
Landi et al.[10] 2019	43	POAG, control	MD Inferior RNFL Superior RNFL	HFA SD OCT SD OCT	r=-0.31, p<0.05 r=-0.29, p<0.05 r=-0.27, p<0.05
Matuoka et al.[11] 2021	50	POAG, control	OPP	Formula	r=-0.58, p<0.0001

NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, POAG: Primary open-angle glaucoma, OH: Ocular hypertension, MD: Mean deviation, MVFD: Mean visual field defect, NRA: Neural rim area, RNFL: Retinal nerve fiber layer, OPP: Ocular perfusion pressure, HFA: Humphrey field analyzer, HRT: Heidelberg retinal tomogram, SD-OCT: Spectral domain optical coherence tomography

An analysis of 30-year clinical data performed by Knier et al.[30] also demonstrated that patients with open-angle glaucoma had significantly lower CSFp compared to the control group.

We did not include the studies of Ren et al.[31] (2011) and Xie et al.[8] (2018) despite the fact that IOP, CSFp, and TLPD were presented because they did not include any glaucoma patients. Interestingly, Ren et al.[31] found that patients with ocular hypertension had higher CSFp than healthy participants. The authors hypothesized that this could be a physiologic compensation to prevent significant imbalance at the level of the lamina cribrosa and subsequent glaucoma progression. This finding was later confirmed by Xie et al.[8], who proposed a pre-glaucoma stage in which there were only changes in TLPD with no structural or functional damage. This paved the way for further studies to investigate the TLPD threshold that differentiated normal from the pre-glaucoma stage.

Our findings showed that the TLPD was significantly higher in both the HTG and NTG groups, which was consistent with the findings of Deimantavicius et al.[26] The lamina cribrosa is exposed to both IOP and CSFp, so this finding further supports the potential relationship between TLPD and glaucoma mentioned in numerous studies.[5,10,11,22,32,33,34,35]

Study Limitations

There are some limitations related to the measurement of IOP, CSFp, and TLPD. IOP is an indirect estimation, depending on the biomechanical characteristics of cornea, and is assessed with the person in an upright position (Goldmann applanation tonometry, rebound tonometry and pneumotonometry) except for less-frequently used tonometers such as the Schiotz (indentation) or Maclakov (applanation), which can assess IOP in the supine position. CSFp is normally measured by lumbar puncture in the prone or left lateral decubitus position, and because of gravitational effects, CSFp is higher in either of these positions than in the upright position in which IOP is measured. Simplified formulas for TLPD also assume that intraorbital CSFp is similar to intracranial CSFp. However, some previous studies suggested that the orbital SAS does not communicate freely with the intracranial SAS due to trabeculae and septate structures. Therefore, CSFp measured by lumbar puncture might not represent the true CSFp behind the laminar cribrosa.[3] Recently, a study by Pircher et al.[36] demonstrated an enlarged optic nerve sheath diameter without any increase in lumbar CSFp in NTG patients, suggesting a disrupted connection between intraorbital and intracranial SAS. Our review included studies with different methods of assessing CSFp (lumbar puncture, formula and transcranial Doppler). Hence, a random effects model was used in statistical analysis to account for this heterogeneity. Additionally, TLPD was not an empirical measurement, but instead a calculation based on two variables that were assessed for significance at the same time.

Lindén et al.[25] filled this gap in the literature data by measuring CSFp in different positions and found no statistical difference in CSFp between NTG patients and healthy people. However, despite using standardized and specialized equipment for CSFp recording in the study, the study assumed a direct connection between the two SAS compartments.[25] Pircher et al.[37] was also unable to confirm either a lower lumbar CSFp or higher TLPD in NTG compared to other studies, but their retrospective study did not include a control group. For this reason, this study was not included in our meta-analysis.

Further studies are needed to investigate the communication between the two SAS compartments as well as to evaluate the interaction between IOP and CSFp in different positions, especially in the upright position as suggested by Lindén et al.[25] and Pircher et al.[37] Two-depth TCD is a non-invasive method with better reliability and stronger relationship with lumbar CSFp than optic nerve sheath diameter and CSFp measured close to the optic nerve, and as such might offer a promising approach to fill the abovementioned gaps.[26,38] Discovering the correlation between TLPD and glaucomatous optic neuropathy might enhance the current understanding of NTG pathogenesis and the natural course of glaucoma progression despite well-controlled IOP, leading to future therapeutic interventions in glaucoma.

Conclusion

Our analysis validated that a significantly lower CSFp and higher TLPD is seen in both HTG and NTG patients in comparison with healthy groups, revealing the potential

relationship between glaucoma and TLPD suggested in previous population and prospective studies.

Ethics

Authorship Contributions

Concept: V.A.B., Design: V.A.B., P.S., T.T.H., Data Collection or Processing: V.A.B., T.T.H., Analysis or Interpretation: V.A.B., T.T.H., Literature Search: V.A.B., P.S., T.T.H., Writing: V.A.B., P.S., T.T.H.

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

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Supplementary Table 1. Newcastle-Ottawa scale assessing the quality of selected non-randomized studies

Study	Selection	Comparability	Exposure
Ren et al.[5] 2010	-*-*	*-	-*-
Siaudvytyte et al.[22] 2014	-*--	--	-*-
Jonas et al.[23] 2015	-**-	--	-*-
Jonas et al.[24] 2015	-**-	--	-*-
Lee et al.[9] 2016	-***	*-	-*-
Landi et al.[10] 2019	-*-*	--	-*-
Matuoka et al.[11] 2021	-*-*	--	-*-
Lindén et al.[25] 2018	**-*	--	-*-

Supplementary Table 2. Extracted data from selected studies

Study	Glaucoma type (number of eyes)	IOP (mmHg)	CSFp (mmHg)	TLPD (mmHg)
Ren et al.[5] 2010	NTG (n=14)	16.1±1.9	9.5±2.2	6.6±3.6
	HTG (n=29)	24.3±3.2	11.7±2.7	12.5±4.1
	Control (n=71)	14.3±2.6	12.9±1.9	1.4±1.7
Siaudvytyte et al.[22] 2014	NTG (n=9)	13.7±7.4	7.4±2.7	6.3±3.1
	HTG (n=9)	24.7±6.8	8.9±1.9	15.7 ±7.7
	Control (n=9)	15.9±2.1	10.5±3.0	5.4±3.3
Jonas et al.[23] 2015	HTG (n=348)	15.1±3.3	7.2±2.8	7.9±4.9
	Control (n=6070)	14.7±2.7	8.9±3.7	5.8±4.1
Jonaset al.[24] 2015	HTG (n=185)	17.2±6.8	7.6±3.7	9.5±7.8
	Control (n=8583)	13.7±3.1	10.0±3.6	3.6±4.2
Landi et al.[10] 2019	HTG (n=53)	21.04±5.71	7.43±2.06	13.61±6.18
	Control (n=33)	15.00±1.97	8.14±4.52	7.33±3.97
Matuoka et al.[11] 2021	HTG (n=50)	13.7±3.8	10.9±3.2	-0.3±3.6
	Control (n=25)	14.7±2.3	15.0±3.7	2.6±4.1
Lee et al.[9] 2016	NTG (n=674)	14.59±0.16	10.76±0.16	3.82±0.21
	Control (n=12069)	14.01±0.05	11.69±0.04	2.31±0.06
Lindén et al.[25] 2018	NTG (n=13)	20.7±3.2	7.0±2.9	13.7±3.8
	Control (n=11)	18.9±1.8	6.6±1.4	12.3±2.2

NTG: Normal-tension glaucoma, HTG: High-tension glaucoma, IOP: Intraocular pressure, CSFp: Cerebrospinal fluid pressure, TLPD: Translaminar pressure difference

Management of Contact Lenses and Visual Development in Pediatric Aphakia

Tomris Şengör*, Tuğba Gençağa Atakan**

*Private Practice, İstanbul, Türkiye
**University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Eye Ophthalmology, İstanbul, Türkiye

Abstract

Congenital cataract is among the main causes of treatable vision loss in childhood. The first weeks and months of life are a critical time for the development of vision. Therefore, early cataract surgery and effective multifaceted treatment of the resulting aphakia in the early stages of life are of great value for the management of vision development. Among the treatment models, contact lenses (CL) have an important place in infancy and early childhood up to the age of 2 years. Although good visual gains were not considered very likely, especially in unilateral aphakia, important steps have been taken in the treatment of pediatric aphakia thanks to the surgical techniques developed over time and the increasing experience with optical correction systems, especially CLs. This review examines current developments in the types of CL used in pediatric aphakia, their application features, comparison with other optical systems, the features of amblyopia treatment in the presence of CL, and the results obtained with family compliance to CL wear and occlusion therapy in the light of existing studies.

Keywords: Congenital cataract, pediatric aphakia, contact lens, visual rehabilitation, persistent fetal vasculature

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Address for Correspondence: Tomris Şengör, Private Practice, İstanbul, Türkiye
E-mail: tomris.sengor@gmail.com **ORCID-ID:** orcid.org/0000-0002-9436-5582
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Introduction

Congenital cataract (CC) is rare worldwide (2.2-13.6/10,000 births) but is one of the leading causes of vision loss in children.[1,2] It can be bilateral or unilateral and can be associated with systemic diseases or congenital abnormalities of the eye such as persistent fetal vasculature (PFV).[3] Aphakia resulting from penetrating eye injuries, which are fairly common in the pediatric age group, often leads to treatment challenges because of the accompanying irregular astigmatism.[4,5,6]

Cataract surgery should be performed as early as possible, as the presence of dense, vision-impairing cataract in the neonatal period and infancy causes amblyopia due to the lack of stimulation.[7] On the other hand, especially in unilateral cataract, the high anisometropia that occurs after surgery carries the risk of amblyopia and secondary strabismus.[8,9] To promote visual development, it is important to provide appropriate optical correction as soon as possible following surgery, implement effective patching treatment, and perform regular follow-up for changes that occur in the growing eye, as well as potential complications.[10]

Glasses, contact lenses (CL), and intraocular lenses (IOL) are options that can be selected for the optical rehabilitation of aphakia in infancy. CLs are one of the most suitable treatment tools because they eliminate aniseikonia, can be used immediately after surgery, can be modified according to the changing refractive power of the eye of the growing child, are available in all dioptric powers, and are low-risk and highly effective.[11,12]

Historically, a good visual gain was considered impossible 40-50 years ago, especially in unilateral CC.[13] With increasing knowledge about the development of the optical system and developments in CL technology, it has been shown that visual acuity (VA) can be improved in unilateral infantile cataract through early surgery, successful CL fitting, and effective patching, without leading to permanent and deep amblyopia.[7,14]

CL fitting and the management of vision development in

pediatric aphakia is one of the most challenging and unique areas of study and includes many components. In this review, the types of CL used in pediatric aphakia, their characteristics, comparison with other optical systems, the features of patching treatment for amblyopia in the presence of CLs, and the results obtained with family adherence to CL wear and patching therapy are examined in the light of existing studies.

Non-contact Lenses Optical Options

Glasses are optical devices that are often preferred for visual rehabilitation in bilateral aphakia because they provide visual improvement comparable to other optical options and are easy to use and obtain.[15] However, high-diopter (D) aphakic glasses are quite heavy and difficult to apply to the infant face. In addition, spectacle lenses have the effect of increasing the image size and narrowing the visual field, which can cause difficulties in children's adaptation to the real world. In unilateral aphakia, they may not be a successful treatment option due to the anisometropia resulting from the high dioptric difference between the two eyes.[10,11]

IOL implantation is a current treatment method with a growing area of use because of certain important advantages such as providing immediate optical correction and not requiring parent or child adherence. However, refractive predictability is low due to the rapid increase in axial length and changes in the corneal curvature that occur in the first two years of life. They may also increase the need for additional intraocular surgeries because of risks such as fibrin reaction, posterior capsule fibrosis, and VA opacification.[7,10] In recent years, comparing CLs with IOLs for the treatment of unilateral or bilateral infantile aphakia in terms of VA and complications has been one of the leading research topics.[7,15]

A meta-analysis study by Chen et al.[16] suggested that VA was better in eyes that underwent primary IOL implantation compared to those with CLs, while there was no increase in risk of complications. However, many previous studies on the subject (summarized in Table 1) demonstrated no difference in VA between high-compliance CL use and IOL implantation, while IOLs were associated with greater differences in change in axial length and astigmatism and higher prevalence of adverse events and risk of reoperation.[18,19,20,22,23,28,29] The results of the studies indicated that CL wear is more advantageous in infancy, IOL implantation is safer after 2 years of age, and secondary IOL surgery at later ages will result in less refractive error.[17,18,19,20,21,22,23,24,25,26,27,28,29]

Table 1. Comparative studies of CLs and IOLs in pediatric aphakia

Authors	Year	Study	Number of patients/ eyes	Follow-up (years)	Outcomes	Comments
Plager et al.[17]	2002	Comparison of complications in CC patients who received an IOL or were left aphakic	Group 1: 13 (15 eyes), surgery at age <6 months, IOL implanted Group 2: 16 (16 eyes), surgery at age >10 months, IOL implanted Group 3: 33 (33 eyes) left aphakic	1	Group 1: 86% surgery for secondary opacification Group 2: No opacification Group 3: 12% surgery for opacification	Early IOL implantation during infancy was associated with increased complications
Birch et al.[18]	2005	Prospective evaluation of VA in infants with unilateral CC who received a primary IOL, were left aphakic, and underwent secondary IOL implantation	Primary IOL implantation: 5 Good-to-excellent CL compliance: 36 Moderate-to-poor CL compliance: 11	4	Mean VA: 20/54 with primary IOL 20/50 with good-excellent CL compliance 20/135 with moderate-poor CL compliance	VA outcome with IOL placement was similar to that in the high CL compliance group but better than in the low CL compliance group
Autrata et al.[19]	2005	Evaluation of VA, reoperation, and ocular development in unilateral CC patients that underwent IOL implantation or were left aphakic	Primary IOL: 18 Received CL: 23	5	0.33 logMAR in IOL group 0.39 logMAR in CL group Reoperation: 78% in IOL; 35% in CL	VA outcomes were similar with IOL and CL, but the need for reoperation was greater in the IOL group
Infant Aphakia Treatment Study Group et al.[20]	2010	VA and complications were evaluated in patients with CL or IOL implantation	114 (57 CL + 57 IOL)	1	VA: 0.80 in the CL group, 0.97 in the IOL group. Reoperation: 12% in CL, 63% in IOL	There was no difference in terms of VA, while the risk of reoperation was higher in the IOL group
Lambert et al.[21]	2012	Axial lengths were compared between unilateral CC patients who received CL or IOL	114 (57 CL + 57 IOL)	1	Axial length changed 0.17 mm in the CL group and 0.24 in the IOL group. Eyes with cataract were 0.6 mm shorter than fellow eyes	Axial length was found to be higher in the IOL group than in the aphakic group

Table 1. Continued

Authors	Year	Study	Number of patients/ eyes	Follow-up (years)	Outcomes	Comments
Magli et al.[22]	2013	Long-term VA and adverse effects were evaluated in bilateral CC patients who underwent primary IOL and secondary IOL implantation	66 (30 IOL + 36 CL)	10	In the primary IOL group, VA at 79 months was 0.53; in the group who underwent secondary IOL implantation after 32 months of CL use, VA at 109 months was 0.54	VA and adverse effects were similar in the primary and secondary IOL groups, but myopic shift was greater in the primary IOL group
Infant Aphakia Treatment Study Group et al.[23]	2014	VA outcomes were compared in infants who underwent vision rehabilitation with CL or primary IOL	114 (57 CL + 57 IOL)	5	Mean VA in both groups: 0.9 logMAR. Postoperative adverse events: 56% in the CL group, 81% in the IOL group. Reoperation: 21% in the CL group and 72% in the IOL group	While there was no difference between the two groups in terms of VA, the need for reoperation was higher in the IOL group
Wall et al.[24]	2014	Surgical factors associated with postoperative astigmatism were examined in the IOL and CL groups	114 (57 CL + 57 IOL)	1	Mean astigmatism changed from 1.92 to 1.62 D in the CL group and from 2.00 to 2.09 D in the IOL group	There is a significant decrease in corneal astigmatism in the CL group compared to the IOL group No other surgical factor had a significant effect
Kruger et al.[25]	2015	Treatment costs were evaluated in the IOL and CL groups	114 (57 CL + 57 IOL)	5	At 5 years, need for at least one reoperation: 21% in the CL group and 72% in the IOL group	IOL implantation was found to be 7% more costly than CL wear
Solebo et al.[26]	2018	Prospective evaluation of outcomes in patients who received a primary IOL before the age of 2 years	102 bilateral and 56 unilateral CC; 88 received an IOL (50 bilateral) and 70 received CL/glasses (52 bilateral)	5	VA was 0.34 logMAR in bilateral and 0.70 logMAR in unilateral patients. Primary IOL implantation increased the risk of reoperation 5-fold in the bilateral and 20-fold in the unilateral cataract group	VA was similar in both groups but there were more complications in the IOL group
Plager et al.[27]	2020	10-year adverse effects, complications, and reoperation were examined in the IOL and CL groups	110	10	In the first year, 7 reoperations were required in the CL group and 36 in the IOL group	Complications were quite low between 6-10 years, while VA was the same. Aphakia for the first 7 months was recommended
Lambert et al.[28]	2020	VA was compared between the IOL and CL groups after unilateral lensectomy	114 (57 CL + 57 IOL)	10	At 10.5 years of age, 12 children in the IOL group (22%) and 15 children in the CL group (27%) had good VA (20/40 or better). However, 25 patients in both groups had low VA (20/200 and worse)	VA results were highly variable in both groups. IOL implantation time was not a determinant of VA outcome
VanderVeen et al.[29]	2021	VA, refractive outcomes, and adverse effects were investigated in the IOL and CL group after 10 years	114 (57 CL + 57 IOL)	10	Mean VA at age 10.5 years was 0.9 logMAR (0.2-1.7) in the IOL group and 0.8 logMAR (0.1-2.9) in the aphakic group. Mean refraction at age 10.5 years was 3.20±2.70 D in the secondary IOL group and -5.50±6.60 D in the primary IOL group	Delayed IOL implantation provides more predictable refraction results

IOL: Intraocular lens, CC: Congenital cataract, VA: Visual acuity, CL: Contact lens, logMAR: Logarithm of the minimum angle of resolution, D: Diopters

Contact Lenses Options

Current CL options that can be used during infancy are rigid gas permeable contact lenses (RGPCLs), silicone elastomer (SE) lenses, and soft hydrogel and silicone hydrogel (SiH) lenses. High DK/t lenses that can be worn continuously (day and night) are needed for aphakic infants because of high hyperopia and the need for long sleep periods. While SE lenses are the first choice for this purpose, RGPCLs, SiH lenses, and less commonly hydrogel lenses are important options that can also be used in the right circumstances.[30]

Rigid Gas Permeable Contact Lenses

As RGPCLs can be produced with the desired base curve (BC) and power, they have the advantage of being available in a wide range of parameters. In addition, being able to apply a lens with the needed dioptric power and the ability of rigid lenses to mask corneal astigmatism also offer the opportunity to achieve high visual quality.[31] Furthermore, RGPCLs carry a lower risk of hypoxia and infection because they can be produced from a highly oxygen-permeable material (fluorosilicone acrylate), allow for adequate tear exchange, and have low water content.[10] However, drawbacks that limit the preference for these lenses are discomfort caused by the rigid material, difficulty during wear, having to remove them every night, and the need for more experience and expertise to determine the appropriate lens.[10,12,30]

The BC refers to the posterior surface slope of the CL, and a BC value 1.0-1.5 mm steeper than the flattest keratometry value is generally preferred.[30,31] Lens diameters vary from 7.8 to 9.5 mm and can be determined according to the diameter of the infant's cornea. Lenses can be manufactured with a lenticular design to reduce edge thickness and thus increase lens comfort.[30,31] After inserting a trial lens, its position and movement on the ocular surface and the relationship of the lens to the cornea is checked by fluorescein staining (Figure 1). Many retrospective studies have investigated vision quality and risk of adverse events with corneal and intralimbal RGPCLs (Table 2). The results of these studies indicated that despite problems such as discomfort from the rigid material, application difficulties, and the requirement of daytime use, RGPCLs are safe and effective lenses that can be used successfully in all pediatric aphakia patients, including infants.[32,33,34,35,36,37]

In addition, RGPCLs are especially used in trauma cases with irregular and high corneal astigmatism. With their good VA and ease of use, these lenses are reported to be successful options that can be preferred for pediatric traumatic aphakia.[38] Piggyback CL systems that utilize an RGPCL on top of a high oxygen permeability SiH CL can also be applied in eyes with irregular corneas and other cases where RGPCLs alone are not tolerated (Figure 2).[39] In addition, two separate studies conducted in recent years reported that mini-scleral and scleral lenses can also be used as safe and effective options in aphakic children.[40,41]

Silicone Elastomer Lenses

SE lenses are among the most preferred CL options in pediatric aphakia. One of the main reasons for this is that SE lenses have very high oxygen permeability (Dk: 340, Dk/t: 58/0.61 mm) and low water content, and thus can remain on the eye without any problems for 15 days or even up to 1 month.[30] The fact that SE lenses do not need to be removed every day increases the safety and comfort of CL wear in infancy, a period in which CL insertion and removal difficulties may be encountered. Other superior features are that they provide high VA, are easy to insert and remove due to their lenticular design and minimal flexibility, and their material is resistant to bacterial colonization (Figures 3, 4).[30,42,43,44] On the other hand, SE is an extremely hydrophobic material, which may result in the formation of excessive lipid and mucus deposits on the lens surface. Special coating methods are used to improve its surface properties. However, gradual deterioration of these surface coatings and deposit accumulation can lead to lens

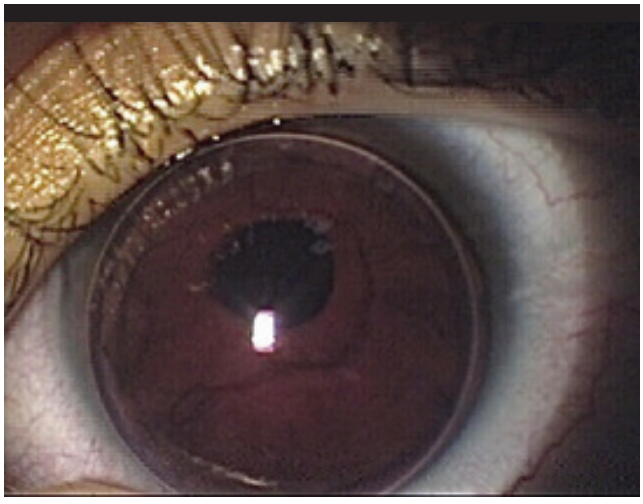

Figure 1. Optimum gas permeable rigid contact lens fitting; the lens is centered, with no slipping or tight adhesion

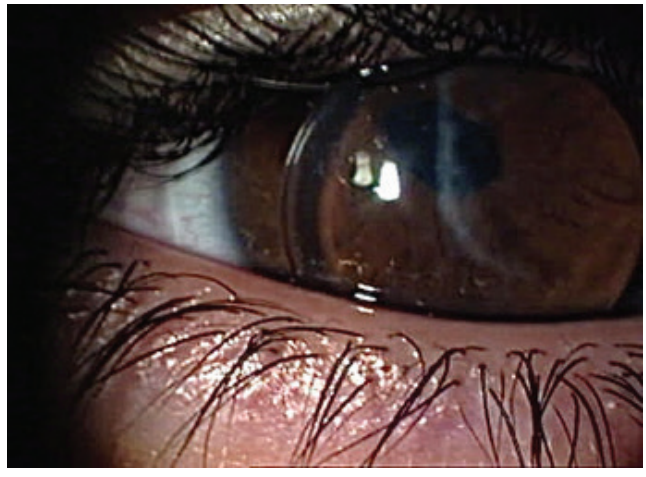

Figure 2. Piggyback contact lens fitting in a 7-year-old patient with aphakia due to trauma. A scar caused by a penetrating corneal wound passes through the center of the pupil

Table 2. Studies investigating the safety and efficacy of RGPCLs

Authors	Year	Number of patients/ eyes	Lens/power/wear schedule	Age at surgery/ follow-up period	Outcomes, VA	Adverse effects	Comments
Amos et al.[32]	1992	CC, 10 patients (15 eyes)	FluoroPerm 92 (Paragon Vision Sciences) 22-43 D Daily use	22.7 months/16 months follow-up	VA: >0.5 in 40%	1 lens dislocated to the superior fornix Lens loss rate: 2.4/year	The RGPCL is well tolerated and easily applied
Saltarelli et al.[33]	2008	CC, 10 patients (16 eyes)	Menicon Z (Menicon Co.) Intralimbal lens 23-32 D Continuous use	3 week-2 years/6 months follow-up	Well tolerated in continuous use (day and night) for 1 week.	Not reported	The RGPCL is easy to apply, effective, and safe
Loudot et al.[34]	2012	CC, 17 patients (23 eyes)	Menicon Z (Menicon Co.) Intralimbal lens	3.5 months (3 days-36 months) 1 year follow-up	VA: >0.3 in 9/12 eyes Good results in bilateral CC	3 patients discontinued CL wear Infection in 1 eye	RGPCLs are effective and reliable in the treatment of infant aphakia
Chen et al.[35]	2019	CC and PFV, 49 unilateral aphakic eyes	RGPCL Daily use	3 years (1-11 years) 4 years follow-up	Marked increase in VA if no additional pathology and good compliance to occlusion	Conjunctival hyperemia in 1 eye	The RGPCL is effective and safe in unilateral aphakia
Zhang et al.[36]	2019	CC, 36 unilateral aphakic eyes	OCUVIQ (Oculus) 23.9±4.2 D Daily use	7 months (5-13 months) 5 years follow-up	VA: 1.2±0.7 logMAR 69% continued CL use	Moderate conjunctivitis in 1 patient Difficulty applying and irritation	They are effective and safe lenses that can be well tolerated
Kooshki et al.[37]	2022	CC, 76 unilateral aphakic eyes	RGPCL	3 years	VA: 0.98±0.62 logMAR 8 children were diagnosed with suspected glaucoma.	27.6% of parents did not comply with occlusion therapy	It is a safe and effective method that can be well tolerated by children and parents

RGPCL: Rigid gas permeable contact lens, CC: Congenital cataract, PFV: Persistent fetal vasculature syndrome, D: Diopters, VA: Visual acuity, logMAR: Logarithm of the minimum angle of resolution, CL: Contact lens

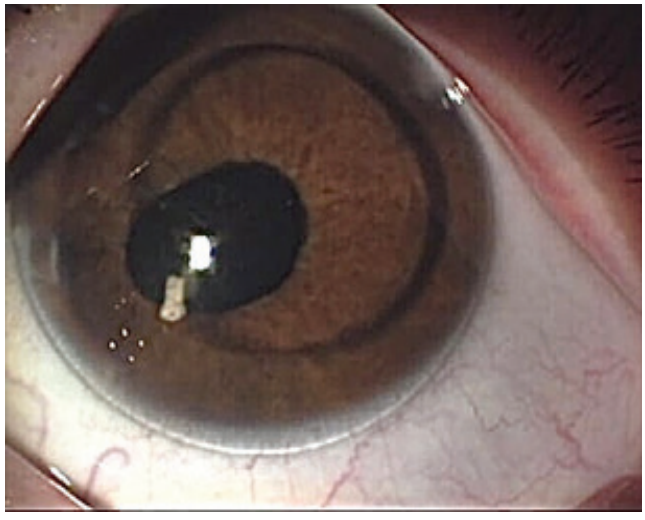

Figure 3. Optimum Silsoft contact lens fitting in a 4-year-old child with unilateral aphakia

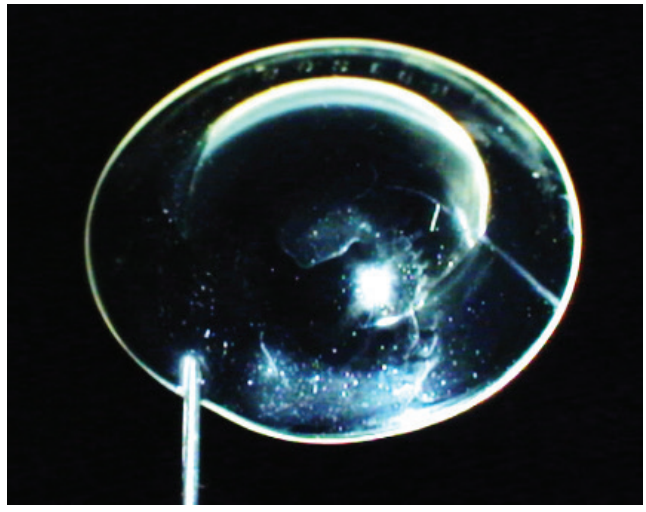

Figure 4. The lenticular design of the Silsoft contact lens with a thick 7-mm thick optic zone in the center and a thin periphery provides easy insertion and comfortable wear

wetting problems and visual disturbances (Figures 5, 6).[45,46] In addition, silicone is a waterproof material and the lens frequently adheres to the eye.[47] In addition to their surface issues, SE lenses usually need to be replaced every 3-6 months due to rapid refractive changes associated with infant development. As a result, the need to frequently replace these lenses increases the financial burden on families, and production and supply problems in recent years necessitated a search for different lens options.[42]

Currently produced and available SE lenses are the Silsoft® and Silsoft® Super Plus (Bausch & Lomb Incorporated, Bridgewater, NJ, USA). Silsoft® Super Plus lenses are often used in early infancy in parallel with the development of the child. These lenses come with BC options of 7.5, 7.7, and 7.9 mm, their diameter is 11.3 mm, and their power values range from +23.00 to +32.00 D in 3.00-D steps (+23.00, +26.00, +29.00, and +32.00). In addition, Silsoft® aphakic lenses for use at older ages are available with 5 BC options (7.5, 7.7, 7.9, 8.1, and 8.3 mm), 2 diameters (11.3 and 12.5 mm), and power options ranging from +11.50 to +20.00 D in 0.50-D steps.[30,43]

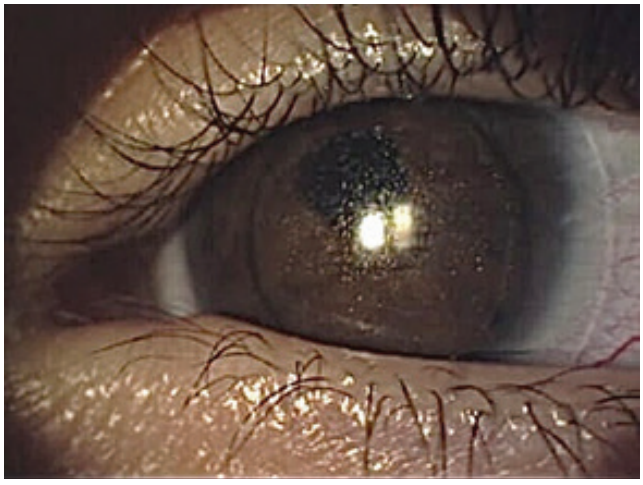

Figure 5. Surface irregularity and deposits on a Silsoft contact lens

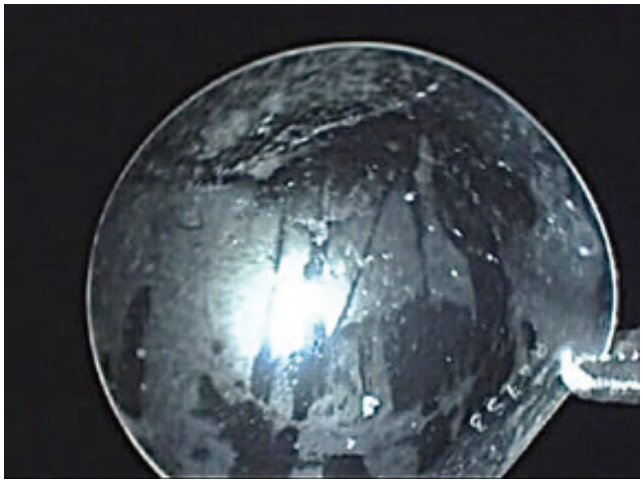

Figure 6. Emergence of the hydrophobic structure and blurring of a Silsoft contact lens due to deterioration of surface coating

The efficacy and safety of SE lenses have been investigated in many studies, both as a first-line choice and in comparison to RGPCLs (Table 3).[48,49,50,51,52] The common conclusion reached in these studies was that SE lenses can be used safely and effectively in the pediatric age group due to their ease of use, the advantages of extended wear, and the low rate of adverse events.[48,49,50] Additionally, the multicenter, prospective, randomized Infant Aphakia Treatment Study (IATS) examined the 1-year and 5-year results of unilateral aphakic children who underwent optical rehabilitation with SE lenses and RGPCLs. At the end of the 1-year period that was the first part of the study, it was reported that regardless of the lens type, successful VA results (+0.80 logarithm of the minimum angle of resolution [logMAR]) could be achieved with few adverse effects.[51] According to 5-year follow-up data from the same study, VA better than 20/40 could be reached in 33% of those using RGPCLs and 20% of those using SE lenses, there was no significant difference in visual prognosis between the two lens types, and few adverse events were observed.[52]

Soft Lenses: Hydrogel Lenses and SiH Lenses

Hydrogel lenses can be used in infancy and later childhood for pediatric aphakia. The low oxygen permeability of the hydrogel material may cause an increased risk of various complications such as corneal edema, neovascularization, endothelial polymegathism, and infective keratitis. Although lenses with high water retention can be used in aphakia to reduce the hypoxic complications of these lenses, oxygen permeability is reduced in high plus power lenses because of the thick central zone (i.e., the Dk/t ratio is still low). For this reason, daily insertion and removal is considered safe and effective.[53,54]

In contrast, SiH lenses have high oxygen permeability and provide an important advantage in preventing corneal complications associated with hydrogel lenses. However, since the increased lens thickness required for high power also reduces Dk/t (i.e., oxygen transmission), SiH aphakic lenses are mostly used for daily use in infancy and early childhood. In addition, they offer low water content, ease of use, and the opportunity for frequent replacement.[55,56] Custom-made SiH lenses are also available now.[57] In our country, CLs produced from SiH material (Definitive 74: Filcon V3, water content: 74%, Dk [Fatt; mmHg]: 60) and replaced every 3-6 months can be used (Figure 7). As CL dioptric power decreases with age, children can be switched to SiH and hydrogel lenses, which are available within the production parameter ranges and can be applied in a daily use/monthly replacement regimen (Figure 8). There are also domestically produced aphakic CL options made of materials suitable for daily use (NL64: MMA-N-vinyl-pyrrolidone copolymer, water content: 67%, Dk/t: 36 @ -3.00 D).

The efficacy and safety of soft CLs have been investigated in various studies over the years. In their prospective 3-year follow-up study of 141 eyes of 83 infants, Amaya et al.[58] shared the results of daily use of hydrogel CLs with water content

Table 3. Studies of SE (first-line choice) and SE/RGPCL (comparative)

Authors	Country/year	Number of patients/ eyes	Age at surgery/ follow-up period	Lens specifications/ wear schedule	Outcomes VA	Complications	Conclusion
Aasuri et al.[48]	India/1999	74 patients (106 eyes) with CC	9 months (1 month-12 years)/5 years follow-up	Silsoft® Super Plus (Bausch+Lomb) Continuous use (replacement after ≥1 week)	Increased in 45%	23 mild adverse events 2 microbial keratitis 3 scar	SE lenses are reliable and easy to use
de Brabander et al.[49]	Netherlands/2002	17 CC patients (26 eyes: 8 unilateral, 18 bilateral)	Infancy / 6 years follow-up	Silsoft® Super Plus (Bausch+Lomb) Continuous use	0.1-0.3 in 15 eyes 0.3-0.5 in 10 eyes >0.5 in 1 eye	No major complications Deposit formation was frequent	SE lenses are easy to use, logical, and safe
Ozbek et al.[50]	Turkey/2002	51 CC patients (83 eyes)	19±18 months	Silsoft® Super Plus (Bausch+Lomb) Initial lens power +29.0 D,	VA increased in 58 eyes (70%), was unchanged in 25 eyes	2 redness, itching 1 recurrent corneal infiltration	Safe for prolonged wear, easy to use, low rate of lens discontinuation
Russell et al.[51]	Multicenter/2012	57 CC patients, all unilateral	1-6 months 1 year follow-up	42 (74%) SE (Silsoft® Super Plus; Bausch+Lomb) 12 (21%) RGPCL (Boston XO2; X-Cel Specialty Contacts) 3 (5%) SE + RGPCL Wear schedule: SE: Continuous (7-21 nights) RGPCL: Daily	VA increased in 95% VA was +0.80 logMAR for both groups Measured with Teller Acuity Cards	SE: 1 corneal abrasion, 1 bacterial keratitis, 1 corneal opacity RGPCL: None	Successful outcomes were achieved in unilateral aphakia with few adverse effects, regardless of CL type
Russell et al.[52]	Multicenter/2017	52 eyes continued CL use	1-5 years follow-up	24 (46%) SE (Silsoft® Super Plus; Bausch+Lomb) 11 (21%) RGPCL (Boston XO2; X-Cel Specialty Contacts) 17 (33%) SE + RGPCL Wear schedule: SE: Continuous, RGPCL: Daily	VA: Better than 20/40 in 33% of RGPCL users and 20% of SE users	SE: 6 keratitis, 3 recurrent corneal opacities, 2 corneal abrasions RGPCL: 1 in situ broken lens	CLs yielded successful results with relatively few adverse effects

SE: Silicone elastomer, RGPCL: Rigid gas permeable contact lens, CC: Congenital cataract, D: Diopters, VA: Visual acuity, logMAR: Logarithm of the minimum angle of resolution, CL: Contact lens

that was initially high and decreased with age. The authors reported that 85% of the patients continued CL use, but 46 eyes had significant complications such as bacterial conjunctivitis, hypoxic corneal ulcer, corneal edema, and pannus formation.

Chen et al.[59] retrospectively examined factors affecting VA in 5 infants with unilateral idiopathic CC and 10 infants with cataract secondary to PFV who received various daily use hydrogel CLs after cataract surgery. Successful VA outcomes (20/50 or better) were obtained in 50% of unilateral aphakic children over the age of 5 years. Surgical or ocular complications were found to negatively affect VA in the PFV group. The authors concluded that compliance with CL and patching was directly related to VA. In addition, they reported that the most common CL-related complications were corneal pannus (26.66%) and giant papillary conjunctivitis (20%), and 60% of the patients were switched to an RGPCL for this reason.

In their study examining 205 patients, 173 (84.4%) with RGPCLs and 32 (15.6%) with soft CLs, Subramanian[60] found that only half of the children successfully continued CL use, the highest VA achieved was 0.2 logMAR in a 4-year-old successful CL user, and visual success depended on correct CL selection and close follow-up.

The results of these studies conducted over approximately 30 years indicate that complications associated with daily use soft CLs have decreased over time, VA can reach fairly high levels, and correct CL selection and compliance with patching are directly related to visual success.[58,59,60]

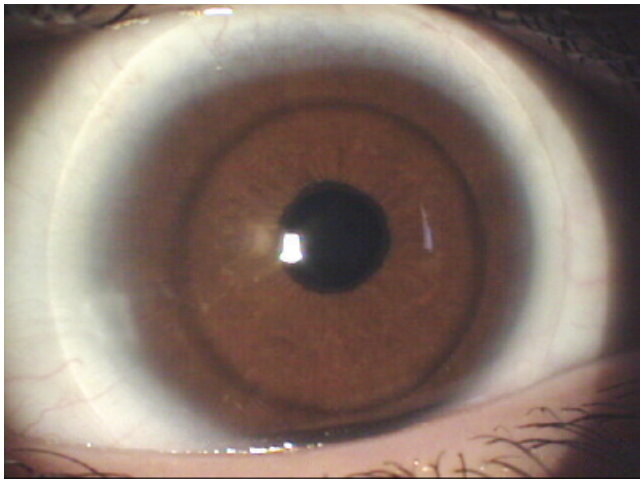

Figure 7. Fitting of a daily silicone hydrogen contact lens in a 4-year-old child with unilateral aphakia

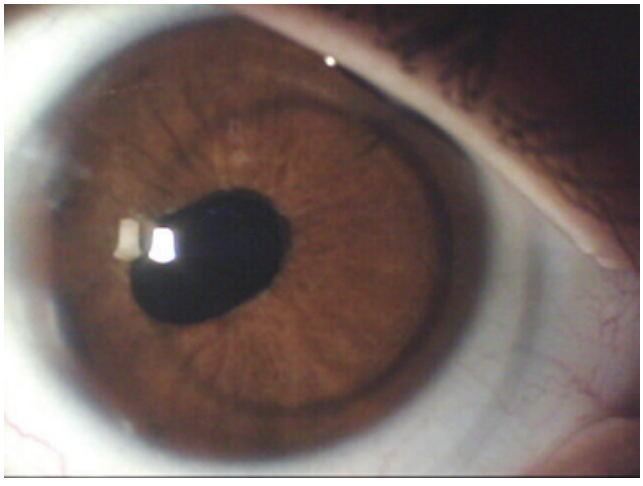

Figure 8. A 10-year-old child with unilateral aphakia fit with an 18-D, daily use hydrogel contact lens (Omafilcon A, water content: 62%, Dk/t: 42 @ -3.00 D) replaced every 15 days

Contact Lenses Fitting and Patient Compliance

Dioptric power, BC, and diameter are important parameters in CL fitting, and among their determining factors, axial length, keratometric values, corneal diameter, and aphakic refractive error vary with age, especially in infancy (Table 4).[61,62] However, eye development differs in pediatric aphakia. Axial elongation may be affected by surgery, visual deprivation, optical defocus, or various potential pathologies associated with cataract (e.g., glaucoma, PFV).[63] Therefore, CL parameters should be determined by evaluating each child within the framework of these specific changes, as well as the natural developmental process of the eye.

Base curve and diameter selection: It may not always be possible to determine corneal keratometric values during infancy. Therefore, the BC value and diameter of the initial lens are often determined according to the infant's age. When fitting Silsoft CLs, a 7.5 mm BC and 11.3 mm diameter are preferred as a rule because the infant cornea has a steep anterior surface slope and small diameter. As the corneal curvature will flatten by the age of 2 years, most children are switched to a 7.7 mm BC. However, in some children the cornea can maintain its steep slope and an SE lens with 7.5 BC can be used into later childhood. A steep fitting incompatible with the corneal anterior surface slope causes the lens to become immobile, while a flat fitting can lead to keratitis due to the central mechanical effect (Figure 9).[30,31,57]

The basic principles of soft CL fitting are similar to those in adults. The BC should generally be 0.5 mm flatter than the corneal slope (which is ~6.9-7.1 mm at birth), which corresponds to about 7.4 mm. Moreover, the diameter of soft CLs should be 2.5-3.0 mm greater than the entire corneal diameter (i.e., 12.5 or 13.00 mm) to ensure lens stability and prevent dislocation. Again, these values are modified as the patient grows.[57]

Determination of contact lenses power: Realistically, determining the dioptric power is more difficult than selecting the BC value. For this reason, the IATS working group protocol recommended that in cases where refractive error cannot be measured precisely, the initial lens power should usually be +32 D for Silsoft lenses and then modified as necessary as early as possible.[63] In their study with 50 patients who underwent

Table 4. Axial length, keratometry, and aphakic refractive error values according to age group*

Age range (years)	Axial length (mm)	Keratometry (D)	Aphakic refractive error (D)
0-1	19.2	45.2	18.77
1-2	20.2	44.9	16.87
2-3	21.4	44.1	15.00
3-4	21.8	43.7	14.51
4-5	22.3	43.2	13.92
5-6	22.7	43.7	12.84
6-7	22.9	43.4	12.69
7-9	22.6	44.2	12.67
10-15	23.8	43.5	11.02

*Axial length and keratometry cited from a study by Gordon and Donzis[61]; aphakic refractive errors from McClatchey and Hoffmeister[62]
D: Diopters

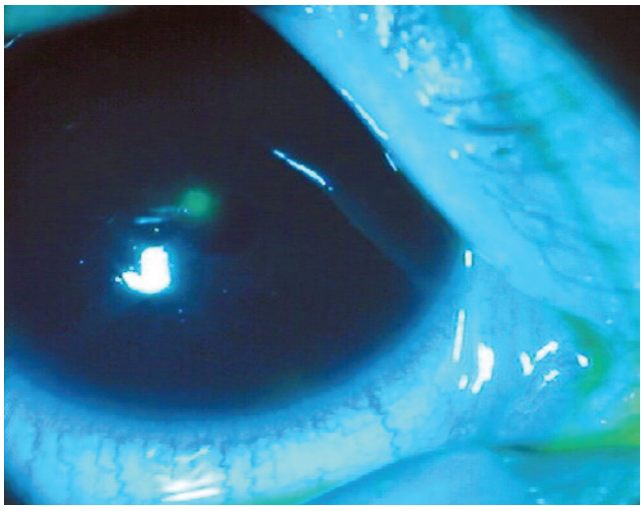

Figure 9. Central keratitis in a 5-year-old unilateral aphakic child caused by the mechanical effect of a flat-fitting silicone elastomer contact lens

cataract surgery at 2.4±1.7 months of age, Trivedi and Wilson[64] determined the mean refractive error was 29.6±4.4 D in the corneal plane and showed that lens replacement may be required in 22 of the 50 patients (44%) if a +32 D CL were used. Other researchers have reported that postoperative refraction examination may be difficult in infants and that estimating the CL power before surgery with the help of preoperative biometrics may reduce the need for lens change. On the other hand, the infant's refractive error can change rapidly in the first year after birth, after which this rate of change gradually decreases. Therefore, it is important to verify CL dioptric power and compliance monthly for the first 18 months and then every 3 months for the next 3 years.[53,54,55,56,57]

Contact lenses fitting and evaluation: While a CL can be inserted immediately after surgery, it is usually preferrable to have it applied at postoperative 1 week by an ophthalmologist in office conditions, after the infant is laid supine in the examination room, with head and arm movements minimized by the parents. The family is taught about CL insertion and removal in every detail and in practice. Fifteen minutes after CL insertion, lens movement and centration are evaluated, as well as fluorescein staining patterns for RGPCLs and SE lenses. SE lenses can be relatively easily applied to the small infant eye due to their thickness and design.[65] SiH lenses can also be applied more easily than hydrogel lenses due to their high modulus of rigidity.[57] The infant is examined at 1 day, 1 week, 1 month, and 3 months after fitting, after which follow-up can be recommended at least 4 times a year depending on the condition of the case. Corneal complications and pathologies such as glaucoma and retinal problems are evaluated. Surface problems specific to SE lenses can frequently occur. Due to these surface problems and dioptric changes parallel to eye growth, most patients may require lens replacement in 3-6 months.[30,65]

Contact lenses wear time: SE lenses are fitted immediately or within the first week after surgery and can remain in the eye for up to 30 days unless there is a problem. However, most practitioners prefer that SE lenses are removed every 1 or 2 weeks and inserted the next morning after a night of rest.[30] Although parents initially have difficulty with the process of inserting and removing the lenses, they gradually gain experience and can often do it more easily while the infant is feeding or falling asleep. These lenses can be cleaned and disinfected with multi-purpose soft CL solutions. The recommended time for adequate disinfection is reported as 8 hours. In the early years, eye rubbing commonly results in ejection of a CL from the infant's eye, and it may be found in their bed or among their toys.[30,52]

Calculation of spectacle power over the contact lenses: Although measurements can be made with a pediatric autorefractometer, the retinoscope is primarily used in all circumstances. If over 1.5-2 years of age, spectacle correction over the CL for near vision (+2.0/+2.50 D) can be provided as monofocal, bifocal, or progressive according to the patient's age.[50,53]

Contact lenses compliance: As both the child's reaction to CL wear and the parent's adherence play a role in CL compliance, they can be evaluated together. All infants initially react to CL insertion, but with time their reactions to this process decrease, or contrariwise, they may reject lens use as they grow. The CL adherence of the family should be assessed according to their success in inserting and removing the lens and the continuity of wear.[66]

Amblyopia Risk and Occlusion Therapy

The first weeks and months of life are a critical time for the development of amblyopia. An inadequate retinal image during this sensitive period hinders the formation of good visual perception in the occipital cortex and negatively impacts vision development.[67] However, if amblyogenic risk factors are reduced or eliminated in the early period, vision loss can be avoided thanks to the plasticity of the brain. Therefore, unilateral or bilateral cataracts detected in the neonatal period should be operated as soon as possible, refractive correction should be provided with the most appropriate CL and/or glasses immediately afterwards, and patching treatment for amblyopia should be initiated, especially in unilateral aphakia. In addition, attention should be paid to the risk of occlusion amblyopia that may occur in the other eye with excessive patching.[68] In bilateral cataract, the risk of amblyopia may be less and occlusion therapy may not be required if there is no strabismus. In acquired cataracts, the risk decreases but can continue until 5 years of age or later.[69,70,71,72,73]

The duration of patching treatment is determined according to the patient's age, unilateral or bilateral involvement, and their fixation and deviation status. This procedure is done using adhesive patches or patching tapes suitable for infants and children and requires complete occlusion of the well-sighted eye. The child is asked to play with near objects during the

patching period, and as they grow they are asked to identify and track pictures and shapes in a book or digital environment while wearing near-glasses.[74,75]

There are different patching regimens, such as patching methods tailored according to the VA of the fixating or treated eye, but none has been shown to be superior over the others.[76,77] Lambert et al.[78] from the IATS group started patching treatment 2 weeks after cataract surgery and defined the patching duration as 1 hour per day for each month of age for the first 8 months, then half of their waking hours each day or their entire waking time every other day.

Adherence to patching is one of the factors that has the greatest impact on vision development in unilateral aphakia.[79,80] To enable an objective evaluation, the information conveyed by parents in phone calls or written logs can be used as a primary source.[81,82] However, these practices require years of attention and dedication and are a significant source of tension and anxiety for children and families.[83] Several studies have shown that pediatric cataract significantly impairs the social and functional quality of life of the patient and their family.[84,85,86] As the stress experienced by families can have many important effects on children, from behavioral disorders to maladaptive parental approaches, it is important to evaluate this during the treatment of pediatric aphakia. Sources of stress and the factors influencing treatment adherence vary from the choice of treatment method to cost-related issues, and may change in severity as the child grows.[87,88]

Contact Lenses Fitting and Follow-up in the Presence of Additional Pathologies

Persistent fetal vascular syndrome: The anatomic involvement in PFV is diverse and can be classified based on location as anterior, posterior, or combined.[89,90] Although it has been reported that visual gain is likely to be low in these cases, many studies have suggested that successful visual outcomes can be achieved in anterior PFV through early diagnosis, carefully planned surgical treatment, appropriate optical correction, and effective amblyopia treatment.[91,92,93,94,95] Because PFV is often associated with microphthalmia, it may be difficult to obtain lenses with appropriate corneal BC, diameter, and dioptric power values. Such cases can be approached by first using glasses for optical correction and later switching to a CL when corneal parameters become suitable, or fitting can be attempted with different CL options.[30,35]

Glaucoma: Glaucoma is a common pathology in pediatric aphakia, reported to occur at rates of approximately 12% in the 1-year results of the IATS study and 30% in the 5-year study, independent of the treatment modalities applied. This emphasizes the importance of close follow-up and treatment in aphakic children regardless of the optical correction used.[96,97,98] In infants who develop glaucoma, SE lenses may be advantageous because their use is suitable for medical treatment.[54] In cases of buphthalmos, it may be more appropriate to continue with glasses, considering that the corneal diameter and keratometric values will change and the refractive error will decrease to lower values.[99,100]

Study Limitations

Apart from the IATS study, most previous studies have been retrospective and consisted of case series. Small patient samples and inadequate follow-up periods are limitations of these studies, as well as variability in many parameters that can affect vision, such as cataract type, surgical timing, timing of postoperative CL fitting, and family adherence to CL and patching treatment. Therefore, there is a need for long-term prospective studies that minimize these limitations to the evaluation of safety and efficacy and directly compare visual outcomes and quality of life with various CLs and amblyopia treatments in different patient groups.

Conclusion

Aphakia is an important problem that can affect a child's future, especially given the associated risk of deep amblyopia in the neonatal and infancy periods. Therefore, it is necessary to initiate treatment for vision development as soon as possible after cataract surgery. With their low risk and high efficacy, CLs have an important place in the treatment of aphakia in infants and young children up to 2 years of age. Although a wide range of lenses can be used in pediatric aphakia, SE lenses with high Dk/t values that enable continuous day and night wear are often preferred.[30] However, RGPCLs, SiH lenses, and more rarely hydrogel lenses are other important options that can also be used under the right conditions.[34,36,56] Despite this development and diversification in CL materials and technology, family adherence to CL use and occlusion therapy is the main factor affecting success.[79,80] With early diagnosis, early surgery, CL fitting as soon as possible after surgery, and full compliance with patching treatment, it is now possible to reach very high levels of vision.[7,14] However, there is still a lack of knowledge and experience related to the efficacy and safety of treatments being provided, and there is a need for more comprehensive scientific studies with long-term follow-up in which data can be standardized.

Ethics

Authorship Contributions

Concept: T.Ş., T.G.A., Design: T.Ş., T.G.A., Data Collection or Processing: T.Ş., T.G.A., Analysis or Interpretation: T.Ş., T.G.A., Literature Search: T.Ş., T.G.A., Writing: T.Ş., T.G.A.

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Case Report

Scleral Contact Lens to Preserve a Corneal Graft in Chronic Lagophthalmos

Zeynep Özbek, Işıl Kefeli

Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Abstract

Facial burns involving the periorbital region may lead to cicatricial ectropion and lagophthalmos, causing severe exposure keratopathy and eventually blindness if uncorrected. In these patients, it is critical to provide aesthetic and functional surgical correction to protect the ocular surface from chronic desiccation in addition to visual rehabilitation. Conventional methods may not be sufficient to provide visual rehabilitation in complex cases. Scleral lenses can be a multipurpose alternative for these patients. Herein, we present the challenging case of a patient who developed cicatricial lagophthalmos and exposure keratopathy after facial transplantation due to gasoline burns and received a scleral contact lens for visual rehabilitation.

Keywords: Cicatricial lagophthalmos, ectropion, exposure keratopathy, facial burn, scleral contact lens

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Address for Correspondence: Işıl Kefeli, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-mail: isilkefeli@gmail.com **ORCID-ID:** orcid.org/0000-0002-5540-848X
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Introduction

Severe burns involving the periorbital and facial area are infrequent but potentially devastating injuries. Facial burn lesions lead to physical and psychosocial morbidities.[1,2,3] Periorbital and ocular injuries are present in 20% of facial burns.[4] Injury to the globe, eyelids, orbit, and ocular adnexa predispose these patients to eyelid deformities, conjunctival scarring, and corneal disease, leading to visual impairment and blindness.[5,6,7]

Face transplantation is an effective reconstructive option aiming for functional and aesthetic results in extensive facial burns involving the periorbital region.[8,9] The majority of face transplantations performed to date have included periorbital components, and postoperative ocular and periocular complications are common. Therefore, ophthalmologists have an essential role in the long-term care of such patients.[6] These patients are predisposed to develop cicatricial ectropion and lagophthalmos due to burn contractures secondary to the original trauma as well as consequent surgical trauma. These conditions can lead to exposure keratopathy and corneal ulcers, resulting in serious consequences such as keratitis and even endophthalmitis.[6,7]

Therefore, it is critical to provide visual rehabilitation and protect the ocular surface by conventional methods or other options such as scleral lenses if conventional methods are insufficient.

Herein we present a case in which a scleral contact lens was used to protect the ocular surface and provide visual rehabilitation in a facial transplant recipient who underwent penetrating keratoplasty for fungal keratitis scar and tarsorrhaphy for cicatricial lagophthalmos.

Case Report

A 60-year-old woman presented in September 2018 to the Cornea Division of the Ophthalmology Department of Dokuz Eylül University Faculty of Medicine with complaints of pain

and redness in the left eye for 4 days. She had undergone face transplantation due to severe gasoline burns involving the entire face in 2000. Her medical history revealed that she had multiple revisional reconstructive procedures within 5 years, including blepharoplasty, canthopexy, and eyelid repair. Macroscopic examination of the patient revealed extensive scarring in the face and neck region. There was pronounced deformation due to previous surgeries and burn trauma. Periocular scars and related cicatricial ectropion and lagophthalmos were observed bilaterally, worse in the left eye (Figure 1). Best corrected visual acuity (BCVA) was 1.0 Snellen decimal in the right eye and counting fingers at 2 meters in the left eye. Slit-lamp examination of the left eye revealed bulbar conjunctival hyperemia, corneal edema, 5x7 mm white infiltration in the center of the cornea, and adjacent inferior temporal thinning (Figure 2). Intraocular pressure (IOP) was normal in both eyes. After obtaining smears, treatment with fortified ceftazidime (Orion Pharma, Bangladesh) and fortified vancomycin drops (Koçak Farma, Türkiye) (every 2 hours), cyclopentolate drops (Abdi İbrahim İlaç, Türkiye) (3 times daily), oral doxycycline (Deva İlaç, Türkiye) (100 mg twice daily), and vitamin C (Bayer, Germany) (1000 mg/day) was initiated for the diagnosis of infectious keratitis due to exposure keratopathy secondary to cicatricial lagophthalmos. Cultures revealed Aspergillus fumigatus; the fortified antibiotics were tapered rapidly and topical amphotericin B (Gilead Sciences, USA) and systemic intravenous amphotericin B (3 mg/kg) were ordered. The patient also received three intracorneal voriconazole (Polifarma İlaç, Türkiye) and amphotericin B injections 3 days apart. In order to prevent exposure and facilitate epithelialization after face transplantation due to gasoline burns, lateral tarsorrhaphy was performed in September 2018 (Figure 3a). Amniotic membrane transplantation was performed in November 2018 to support healing and revert thinning (Figure 3b). The infiltrate regressed and healed without complications, leaving a central scar. Penetrating keratoplasty was performed for the corneal scar in December 2018 (Figure 4). BCVA in the left eye was 0.5 decimal (-6.00 diopters sphere, -1.00 diopters cylinder x 95°) at 6 months. No recurrent infection or rejection was noted. IOP was normal and the graft remained transparent. The patient did not agree to keep the tarsorrhaphy, therefore persistent inferior corneal staining despite aggressive lubrication raised the concern for infection or keratinization during long-term follow-up. The right eye was emmetropic and considering the anisometropia and lagophthalmos,

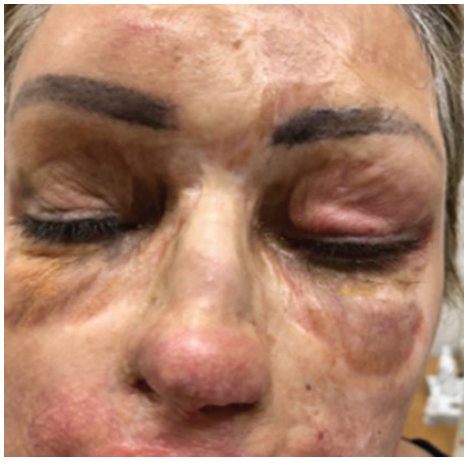

Figure 1. Multiple scars and deformation of the entire face due to previous surgery and burn trauma. Cicatricial ectropion and lagophthalmos were observed bilaterally, worse in the left eye

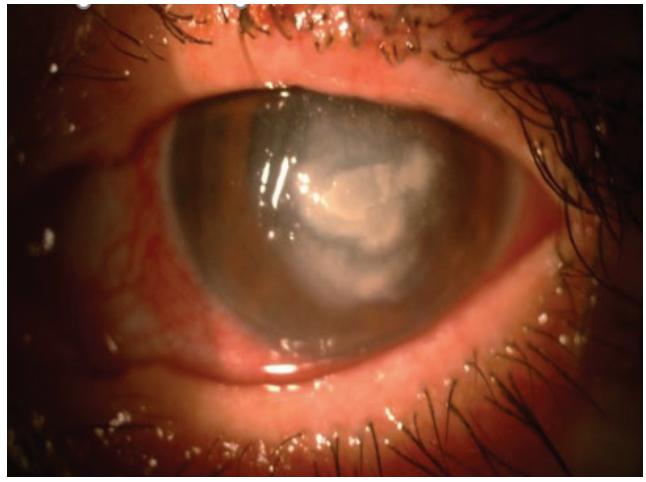

Figure 2. A 5x7 mm area of white infiltration in the center of cornea and adjacent thinning of the inferior temporal cornea in the left eye

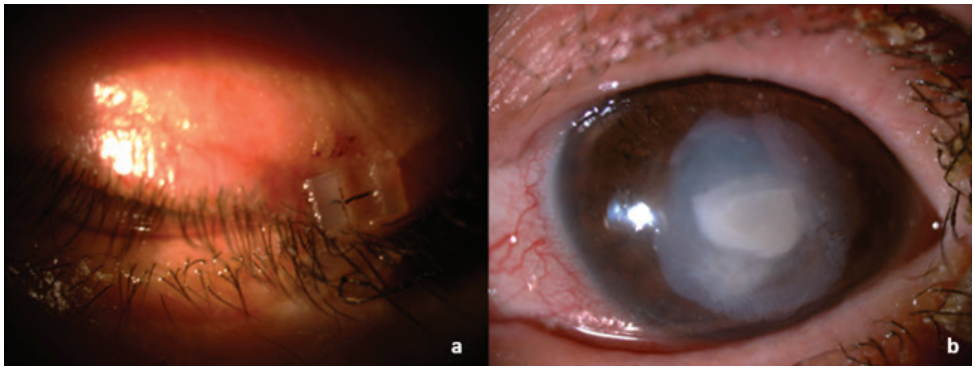

Figure 3. Lateral tarsorrhaphy (a) and amniotic membrane transplantation (b) in the left eye

we recommended a scleral contact lens. The left eye was fit with a Mini Misa® (Microlens, Netherlands) (base curve: 7.80 mm, diameter: 16.5 mm, vault: 400 µm, landing zone Z 12 N, power: -3.00 diopters) in 2019 (Figure 5) and BCVA increased to 1.0 decimal. The patient was encouraged to obtain and wear the lens for 4-6 hours a day. No complications were observed in the following year of use.

Discussion

Burns can directly or indirectly affect the face and periorbital region, causing significant acute morbidity of the lids and ocular surface with severe consequences. Contraction and deformation of the periorbital soft tissue can lead to eyelid dysfunction, trichiasis cicatricial entropion or ectropion, and lagophthalmos, which pose a serious threat to the cornea.[3,4] Chronic desiccation and epithelial trauma can give rise to serious infections and permanent scarring, resulting in visual impairment. Long-term follow-up is often mandatory due to potentially significant medical and psychological problems.[1,6] Goals in the treatment of periorbital burns are preserving vision, preventing future complications, and achieving an acceptable aesthetic result.

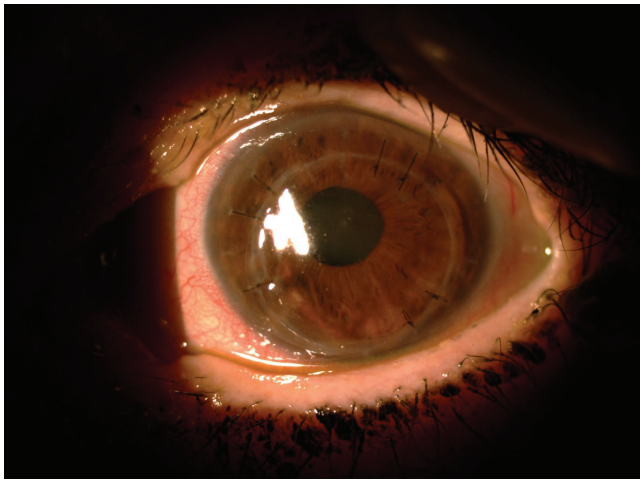

Figure 4. Penetrating keratoplasty in the left eye. Clear corneal graft after selective suture removal

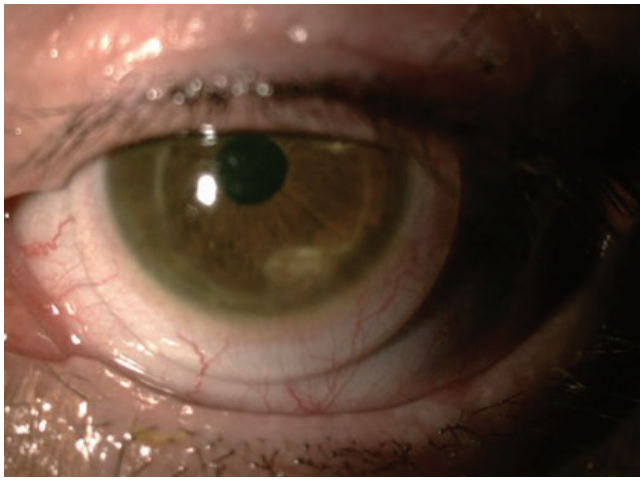

Figure 5. Scleral contact lens fitting in the left eye

Face transplantation can address facial and periorbital deformity with satisfactory functional and aesthetic outcomes in these patients. However, timely consideration and management of postoperative complications is critical to ensure a healthy ocular surface and optimal visual acuity. More than half of all face transplants performed to date involved periorbital components, and available data suggest that postoperative ocular and periorbital issues are common and frequently require revisional procedures, as in our patient.[2,5,6] Therefore, a multidisciplinary approach with closely scheduled ophthalmological follow-up examinations is recommended to manage possible complications in the postoperative period.[6]

Late complications of eyelid burns include ectropion and lagophthalmos as a result of secondary burn contractures. If left untreated, exposure keratopathy due to lagophthalmos can result in corneal thinning, scarring, and ulceration, potentially leading to corneal blindness as well as perforation and endophthalmitis.[1,2,3]

Our patient had fungal keratitis secondary to cicatricial ectropion and lagophthalmos. Our first aim was to control the corneal infection and prevent perforation or endophthalmitis. Lateral tarsorrhaphy and amniotic membrane transplantation were performed after aggressive topical and systemic antifungal therapy and intrastromal injections.

After restoring the integrity of the ocular surface, a penetrating keratoplasty was performed because of the corneal scar. A stable ocular surface is generally requisite to achieve a successful corneal transplant. One of the difficulties we encountered in our patient was poor wetting in the inferior temporal quadrant of the corneal graft. Readjusting the tarsorrhaphy or lid surgery was not an effective plan due to the tight scar in the lower lid. Therefore, we chose to apply a scleral lens to protect the corneal graft from the traumatic effect of the scarred upper lid, to improve vision and to provide ocular surface wetting.

The main purpose in the treatment of cicatricial lagophthalmos is to prevent exposure keratitis and restore eyelid function. There are various medical and surgical options to protect the ocular surface from the effects of exposure, such as ocular surface lubrication, amniotic membrane grafting, tarsorrhaphy, and upper eyelid reanimation techniques.[10,11] In addition to the exposure effect, the traumatic effect of the cicatrized eyelid with blinking may also cause conventional methods to be insufficient in these patients. Scleral lenses are another option that provide a barrier to trauma from the lid and a moist chamber to preserve the cornea.[11,12]

Medical and surgical conventional methods may not be sufficient to provide visual rehabilitation in complicated cases. Scleral lenses can provide constant hydration and protection of the ocular surface in addition to rehabilitation of vision, as in our patient.

Scleral lenses of various designs are currently used for the management of severe ocular surface diseases.[13,14] The Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) scleral lens (Boston Foundation for Sight, Needham, MA) is a large-diameter lens that ranges from about 17.0 to 23.0 mm, vaults the cornea and limbus, and holds a saline reservoir that can mask surface irregularities and create a moist ecosystem while acting as a liquid bandage.[13,14]

In the treatment of complex cases in which conventional therapies are not sufficient, PROSE treatment has been successfully used to maintain the integrity of the ocular surface while improving visual acuity at the same time.[10,12] PROSE treatment can also be used in conjunction with other medical and surgical interventions, as in our patient.

There are some reports in the literature showing the benefits of PROSE treatment in patients with lagophthalmos and exposure keratopathy. Chahal et al.[12] evaluated the utility of PROSE scleral lenses in 26 eyes of 18 patients with exposure keratopathy and found them to be effective in improving both visual acuity and function, as well as ocular surface integrity. Their results revealed that PROSE scleral lens therapy is effective in patients with exposure keratopathy who had failed conventional therapies and can serve as an alternative to lid surgery.

Another case report by Gire et al.[10] described four patients who were successfully treated for lagophthalmos and exposure keratopathy with the PROSE device.

Gervasio et al.[13] compared baseline characteristics and visual acuity outcomes in patients treated with PROSE versus other standard-of-care (SOC) treatments for postsurgical lagophthalmos and exposure keratopathy. They found that PROSE treatment provided rapid and substantial visual improvement within 1 month of use compared with SOC. Their findings in conjunction with previous studies support that PROSE is a viable alternative or adjunct therapy to SOC in the most severe cases of postsurgical lagophthalmos and exposure keratopathy.

Unfortunately, PROSE is not currently available in our country. Therefore, we opted to use the Mini Misa® in our patient. We selected a lens with a diameter of 16.5 mm because it offered good protection of the keratinization area in the lower limbus and was easier for the patient to use than large-diameter scleral lenses. Compared to large-diameter scleral lenses, scleral lenses in the 14-17 mm diameter range are classified as mini scleral lenses and offer more practical application in patients with corneal disorders.[15,16,17] As in our case, mini scleral lenses can be used to improve vision and protect the ocular surface in exposure keratopathy patients, similar to PROSE scleral lenses.[18]

Ocular surface disease resulting from periorbital burn scars is a challenging problem. Sequential surgical and medical treatment plans should be customized according to each patient's unique features. Especially complex cases require a multidisciplinary approach involving both a plastic surgeon and an ophthalmologist, who is crucial in every step of reconstructive procedures to restore ocular integrity and protect vision.

Ethics

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: Z.Ö., Concept: Z.Ö., I.K., Design: Z.Ö., I.K., Data Collection or Processing: Z.Ö., I.K., Analysis or Interpretation: Z.Ö., I.K., Literature Search: I.K., Writing: Z.Ö., I.K.

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

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Case Report

Vasoproliferative Tumor Secondary to Sarcoidosis-Associated Intermediate Uveitis

Sara Abdel Jalil, Tareq Jaouni, Radgonde Amer

Hadassah Medical Center, Department of Ophthalmology, Jerusalem, Israel

Abstract

We report the visual and clinical outcomes of a middle-aged woman who presented with exudative retinal detachment (ERD) secondary to a vasoproliferative tumor (VPT) in an eye with sarcoidosis-associated intermediate uveitis. A 55-year-old woman previously diagnosed with sarcoidosis presented with decreased vision in the left eye (LE). Visual acuity in the LE was counting fingers. She had active vitritis, and a peripheral retinal vascular mass was noted in the superotemporal periphery. The mass was associated with ERD involving the posterior pole. The patient was managed with systemic and intravitreal steroids, and cyclosporine was subsequently added as a steroid-sparing agent. Because of recurrence of ERD, the patient underwent pars plana vitrectomy, and cryotherapy and laser photocoagulation were applied to the VPT. Two months postoperatively, visual acuity in the LE improved to 6/10. There was marked regression of the VPT and total resolution of the ERD. In conclusion, we report a favorable visual and clinical outcome in a patient with VPT-associated ERD who responded to a combination of medical therapy and surgical intervention. VPT may lead to different remote complications, so timely diagnosis of these tumors and proper management of their complications is warranted.

Keywords: Vasoproliferative tumor, sarcoidosis, intermediate uveitis, pars planitis

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Address for Correspondence: Sara Abdel Jalil, Hadassah Medical Center, Department of Ophthalmology, Jerusalem, Israel
E-mail: dr.sara.jalil@gmail.com **ORCID-ID:** orcid.org/0009-0009-5150-3816

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Introduction

Vasoproliferative tumors (VPTs) are uncommon retinal lesions that may be primary or associated with other ocular conditions (secondary). Secondary VPTs most commonly occur in association with retinitis pigmentosa, pars planitis, and toxoplasmosis.[1]

VPTs can lead to different complications such as cystoid macular edema, exudative retinal detachment (ERD), and epiretinal membrane formation. Different modalities including surgery, cryotherapy, and radiotherapy have been used to treat these lesions.[1]

VPTs were also reported as one of the infrequent late complications in patients with intermediate uveitis (IU).[2]

Sarcoidosis is a systemic granulomatous inflammatory disease of unknown etiology. Its most common ocular manifestation is uveitis, reported in 25-50% of cases.[3]

Herein we report the clinical course and visual outcome of a middle-aged woman with inactive systemic sarcoidosis in whom chronic IU culminated in the development of VPT-induced ERD.

Case Report

A 55-year-old woman was referred to the uveitis clinic because of localized ERD in her left eye (LE). She was diagnosed with pulmonary sarcoidosis by transbronchial biopsy four years earlier and treated with oral steroids for a period of one year. Subsequently she was in remission for three years prior to presentation. On examination, best corrected visual acuity (BCVA) was 6/15 in her right eye (RE) and counting fingers at 1 meter in the LE. She was pseudophakic in both eyes. RE anterior and posterior segments were normal. LE biomicroscopic exam revealed clear cornea and +2 anterior chamber flare. On LE fundoscopy, there was vitritis that obscured the posterior pole and a peripheral yellow vascular retinal mass was noted in the superotemporal periphery (Figure 1A). Fluorescein angiography

(FA) demonstrated signs of diffuse retinal vasculitis, macular and optic disc leakage, as well as leakage from the peripheral retinal mass (Figure 2). There were adjacent hard exudates and ERD that involved the macula (Figure 3A). B-scan ultrasound revealed the presence of vitreous opacities and a homogenous hyperechogenic retinal lesion with a thickness of 1.5 mm (Figure 4).

The patient was diagnosed as having sarcoidosis-associated chronic IU with ERD secondary to VPT. Treatment was initiated with pulse intravenous methylprednisolone (Upjohn [now Pfizer], Pennsylvania, USA) (1 g/day for 5 days) in addition to intravitreal triamcinolone acetonide (Bristol Myers Squibb, New Jersey, USA) (4 mg/0.1 mL). Subsequently, she received prednisone (Jubilant Cadista Pharmaceuticals, Salisbury, USA) and cyclosporine (Sandoz, Basel, Switzerland). The ERD totally resolved (Figure 3B). However, the patient did not perceive any improvement because of the persistent dense vitreous opacities and low LE BCVA (counting fingers at 3 meters). Seven months later, during prednisone tapering (at the dose of 5 mg/per day), the patient experienced recurrence of ERD involving the posterior pole. Intravitreal triamcinolone acetate (2 mg/0.05 mL) was administered. Ten days later, she received a preoperative pulse of intravenous methylprednisolone (1 g/day for 5 days). She then underwent pars plana vitrectomy because of the dense vitreous opacities, and cryotherapy and laser photocoagulation were applied to the VPT. Intravitreal triamcinolone acetate (2 mg/0.05 mL) was injected at the end of the operation. Two months postoperatively, LE BCVA improved to 6/10. There was marked regression of the VPT and of the adjacent hard exudates with complete resolution of the ERD (Figure 1B).

Discussion

We herein report the clinical outcome of ERD secondary to VPT in a patient with sarcoidosis-associated chronic IU. The patient presented four years after the diagnosis of pulmonary sarcoidosis at a time when the systemic disease was quiescent. The patient had irregular follow-up prior to presentation and had not been properly treated for IU and ERD despite being previously diagnosed. Combined medical therapy and surgical intervention proved to be successful in the management of this case and yielded a favorable visual outcome. The presence of non-resolving vitreous opacities in the visual axis necessitated vitrectomy in addition to cryotherapy and laser photocoagulation.

The histopathological findings in IU-associated VPTs were first described by Henkind and Morgan[4] in 1964. They described them as lesions with a "Coats-like" phenotype in eyes that were enucleated due to malignant glaucoma. In 1983, Shields et al.[5] reported the presence of an unusual retinal vascular lesion in 12 eyes with ERD and called these tumors "presumed acquired non-familial retinal hemangioma". A decade later, Shields et al.[1] reported on 129 eyes with vascular lesions and suggested the term VPT. In their report, VPT was classified as secondary in 29 eyes, 8 of which were due to pars planitis. This vascular lesion

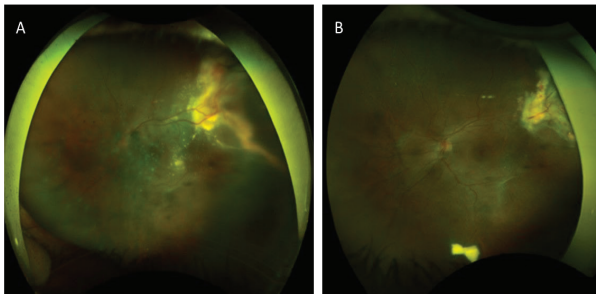

Figure 1. (A) Widefield pseudo-color fundus photograph (Optos Panoramic 200MA; Optos PLC, Dunfermline, Scotland, United Kingdom) of the left eye at presentation shows dense central vitritis obscuring the posterior pole and a peripheral temporal retinal vascular lesion with adjacent hard exudates. (B) Postoperatively, the vasoproliferative tumor is decreased in size, with marked resolution of the hard exudates. A clear view of the posterior pole is noted and the deposit of intravitreal triamcinolone acetonide is observed in inferior vitreous cavity

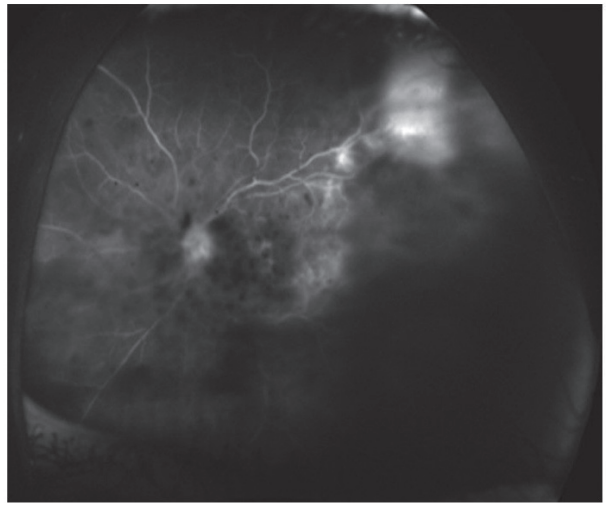

Figure 2. Fluorescein angiography of the left eye at presentation shows signs of vasculitis and leakage from the vasoproliferative tumor in the superotemporal periphery as well as from the optic disc and macula

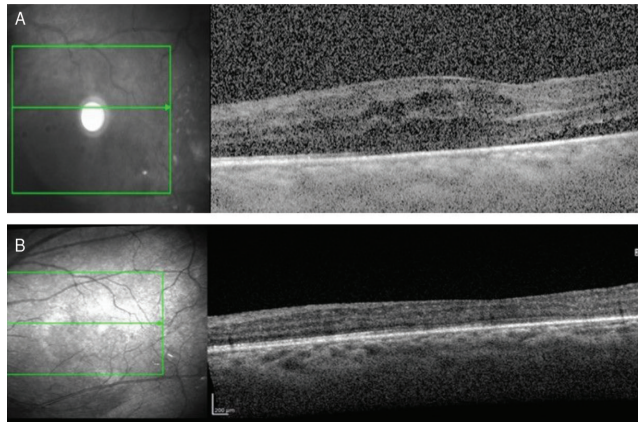

Figure 3. Upper panel A: optical coherence tomography (OCT) of the left eye at presentation shows subretinal and intraretinal fluid. Lower panel B: OCT of the same eye 3 weeks postoperatively shows resolution of the cystoid macular edema and exudative retinal detachment

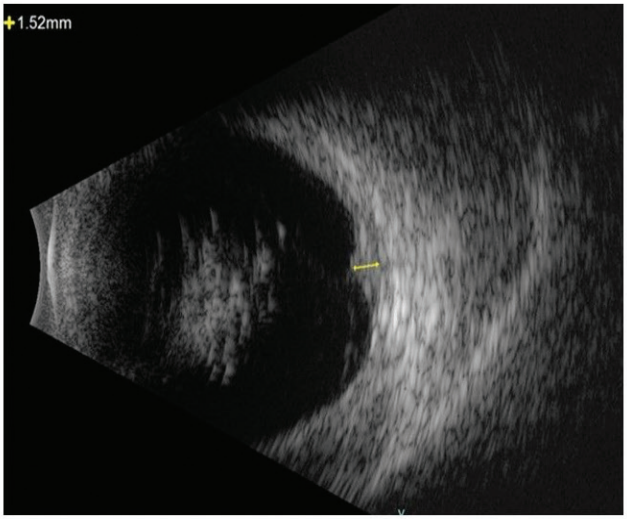

Figure 4. Ocular ultrasound (B-mode) of left eye at presentation revealed the presence of dense vitreous opacities and a homogenous hyperechogenic retinal lesion with a thickness of 1.5 mm (yellow mark)

was revealed to involve not only the retina, but infrequently the retinal pigment epithelium as well as choroid, so it was termed VPT of the ocular fundus.[1]

In 2013, Shields et al.[6] published a report of 275 patients with VPT (mean presenting age of 44 years). They reported that VPT predominantly affected females (59%) and was primary in 80% of patients and secondary in 20% of patients. The two most common causes of secondary VPT were retinitis pigmentosa (22%) and pars planitis (21%). Additional causes included Coats disease (16%) and previous retinal detachment surgery (12%).[6]

Although VPT is a benign lesion, it may lead to severe visual morbidity because of the distant effects of this tumor. According to the most recent report by Shields et al.[6], ocular complications include macular edema (32%), epiretinal membrane (20%) and vitreous hemorrhage (19%). Retinal exudation developed in 71% of cases (extramacular 48%, macular 23%).

IU is an inflammatory condition affecting predominantly young adults and children. It can affect either healthy individuals or it can occur secondary to other systemic diseases such as tuberculosis and multiple sclerosis. It is usually bilateral.[7] This type of uveitis is characterized by vitritis and a relatively quiet anterior chamber. IU may be associated with diverse ocular complications of the anterior and/or posterior segment.[2] Because of the wide spectrum of associated vision-threatening sequelae, it may lead to a potentially guarded prognosis.[7] A cohort study including 96 patients (174 eyes) with IU reported on its early and long-term complications.[2] VPT was among the late complications, described in 1% of eyes. The mean time between uveitis diagnosis and the development of secondary VPT was found to be 160 months.[6]

The pathogenesis of VPT in eyes with IU remains unknown. It was proposed that inadequately controlled inşammation, peripheral vascular leakage, and hypoxic alterations in the pars plana region may lead to retinal elevations and VPT. In a multicentric study, Pollack et al.[8] reported 13 eyes with pars planitis who also had peripheral retinal elevation. All of these eyes showed signs of chronic inflammation, including the presence of snow-banking, inferior fibrovascular abnormalities, and/or marked RPE hypertrophy.

A recent multicentric study of VPTs secondary to IU reported on 36 eyes of 34 patients (22 females).[9] The mean age at onset was 35 years. Twenty-nine patients were diagnosed with pars planitis, three patients had tuberculosis, and one had multiple sclerosis. The VPTs were unilateral in 93.7% of the cases. At the time of VPT diagnosis, all these eyes had active IU, which was defined by the presence of vitritis and/or vascular leakage on FA.[9]

Retinal VPTs secondary to IU are relatively rare tumors, which is the reason for the lack of an evidence-based consensus regarding the best way to treat these lesions. Pichi et al.[9] reported the results of local treatment in 22 of 36 eyes with VPT secondary to IU. Treatment consisted of cryotherapy (8 eyes), argon laser photocoagulation (10 eyes), intravitreal anti-VEGF (2 eyes), or a combination of anti-VEGF injections and cryotherapy (2 eyes). The other 14 eyes were observed without receiving any direct treatment for these tumors. During the follow-up period, the treated VPTs had a decrease in tumor thickness to 1.25 mm (mean initial thickness was 3.13 mm). In the untreated group, the final mean tumor thickness remained stable at 2.65 mm.

In conclusion, VPTs need to be managed with a variety of modalities, particularly in the setting of uveitis. Awareness and recognition of these tumors with proper management of their complications is needed.

Ethics

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: T.J., R.A., Concept: R.A., Design: S.A.J., R.A., Data Collection or Processing: S.A.J., Analysis or Interpretation: R.A., Literature Search: S.A.J., Writing: S.A.J., R.A.

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Case Report

Vitiligo in a Patient Receiving Adalimumab for Idiopathic Uveitis

Mehmet Fatih Kağan Değirmenci*, Fatime Nilüfer Yalçındağ**

*University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
**Ankara University Faculty of Medicine, Department of Ophthalmology, Clinic of Uvea, Ankara, Türkiye

Abstract

In recent years, adalimumab has been increasingly used in the chronic treatment of non-infectious uveitis. This case report aimed to describe a drug-induced adverse event in a 34-year-old man who presented with blurred vision and floaters in the right eye and was being treated for intermediate uveitis. The patient had started topical treatment with a diagnosis of uveitis at another center. Best corrected visual acuity at presentation was 0.8 (decimal) in the right eye and 1.0 in the left eye. On examination, the anterior chamber in the right eye was clear, with anterior vitreous cells and mild haze, and snow banking and vitreous opacities in the inferior periphery. Fluorescein angiography (FA) showed hyperfluorescence in the right disc and leakage in the inferior periphery. As the inflammation did not resolve with local treatment, systemic cyclosporine was administered, after which the patient exhibited vomiting and weakness. Cyclosporine was discontinued and adalimumab treatment was started. On examination 5 months later, bilateral vitreous cells and mild vitreous opacity were noted, and FA showed mild leakage in the inferior periphery bilaterally. In addition, a depigmented patchy vitiligo lesion was observed on the chin. Due to the persistence of intraocular inflammation and on the recommendation of the dermatology clinic, adalimumab treatment was continued and topical tacrolimus was started for the lesion. On examination 3 months later, the inflammatory findings had resolved and there was no progression of the vitiligo lesion. The patient's treatment was continued. Taken together with the previous literature findings, no pathology was found in the patient's systemic examination, suggesting that this lesion was a side effect of the treatment. Ophthalmologists should be alert for this side effect in patients receiving adalimumab.

Keywords: Adalimumab, pars planitis, vitiligo

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Address for Correspondence: Mehmet Fatih Kağan Değirmenci, University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
E-mail: mfkdegirmenci@ankara.edu.tr **ORCID-ID:** orcid.org/0000-0003-2358-9535
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Introduction

Tumor necrosis factor-α antagonists (anti-TNFα) are used in the treatment of dermatological, rheumatological, and gastroenterological diseases, as well as non-infectious uveitis.[1] Some case reports describe improvement of vitiligo in patients receiving anti-TNFα therapy for other conditions,[2,3] while others report patients who developed vitiligo after starting anti-TNFα therapy.[4,5,6] In cases of vitiligo subsequent to anti-TNFα use, the patients received the drug to treat systemic chronic inflammatory diseases. No previous study has described a patient developing vitiligo after using adalimumab for idiopathic uveitis.

In this case report, we aimed to report new-onset vitiligo in a patient receiving adalimumab therapy for pars planitis.

Case Report

A 34-year-old man with complaints of floaters and blurred vision for 3 weeks presented to another clinic where he was diagnosed with uveitis, prescribed topical steroid drops, and referred to our center. In the other clinic he was treated with topical dexamethasone (Maxidex, Novartis, Puurs, Belgium) 3 times daily for a week, followed by topical loteprednol drops (Lotemax, Bausch and Lomb, Rochester, NY, USA) 5 times daily. He presented to our center after 2 weeks of use. The patient's best corrected visual acuity (BCVA) at presentation was 0.8 (decimal) on the right and 1.0 on the left. Intraocular pressure (Goldmann applanation tonometry) was 13 mmHg on the right and 18 mmHg on the left. On anterior segment examination of the right eye, no cells or flares were observed in the anterior chamber, while cells and mild turbidity were observed in the anterior vitreous. The left eye was normal. On fundus examination, "snow banking" and vitreous opacities were observed in the inferior periphery of the right eye. Macular images obtained by optical coherence tomography were normal. Fluorescein angiography (FA) showed optic disc hyperfluorescence and peripheral vascular leakage in the right eye (Figure 1). Possible infectious causes

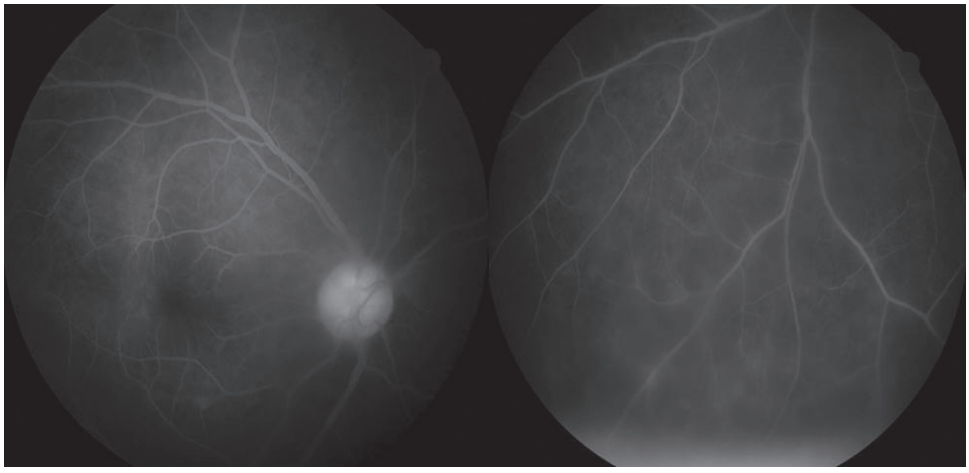

Figure 1. In the patient's initial examination, late fluorescein angiography of the right eye showed hyperfluorescence in the optic disc and vascular leakage in the lower periphery

of intermediate uveitis (tuberculosis, *Borrelia burgdorferi, Bartonella henselae,* syphilis, and toxocariasis) were ruled out. Consultations with the departments of neurology, rheumatology, and chest diseases were requested to investigate non-infectious causes (sarcoidosis, multiple sclerosis, inflammatory bowel disease, lymphoma, tuberculous interstitial nephritis and uveitis syndrome, and Sjögren's syndrome), but no systemic cause could be identified. With the diagnosis of pars planitis, three deep sub-Tenon injections of triamcinolone acetonide (Kenacort-A, Deva, Tekirdağ, Türkiye) were administered to the patient at 1-month intervals while topical steroid therapy was continued. As there was no regression in inflammatory findings with local treatment, systemic cyclosporine (Sandimmun Neoral, Novartis, Eberlach, Germany) treatment was initiated. However, due to complaints of fatigue and vomiting, it was discontinued and replaced with adalimumab (Humira, AbbVie, Ravensburg, Germany). Subcutaneous adalimumab injections were administered as a loading dose (80 mg) followed 1 week later by doses of 40 mg repeated at 2-week intervals.

Although the inflammation findings regressed, the development of a vitiligo lesion on the patient's lower jaw area was observed in month 5 of treatment (Figure 2). On examination, his BCVA was 1.0 (decimal) in both eyes and the anterior chamber was calm bilaterally. Sparse cells and minimal turbidity were observed in the vitreous of both eyes. Minimal peripheral vascular leakage was observed bilaterally on FA imaging (Figure 3). Ocular findings and examinations were reviewed for Vogt-Koyanagi-Harada (VKH) syndrome, but no additional pathology was detected. No side effects other than vitiligo were observed in the patient. Complete blood count and biochemistry test results were within normal limits. No pathology was detected in repeated consultations to investigate for both systemic diseases and extraocular findings of VKH syndrome. The dermatology clinic stated there was no contraindication to the continuation of adalimumab therapy. Tacrolimus (0.1%) pomade (Tacrolin, Farma-Tek, Sakarya, Türkiye) was started for the treatment of vitiligo as recommended by the dermatology clinic.

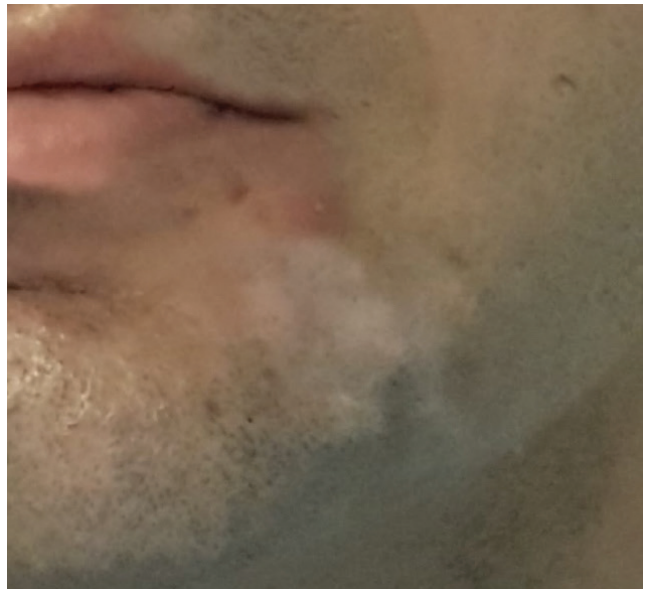

Figure 2. A vitiligo lesion is observed on the patient's left jaw

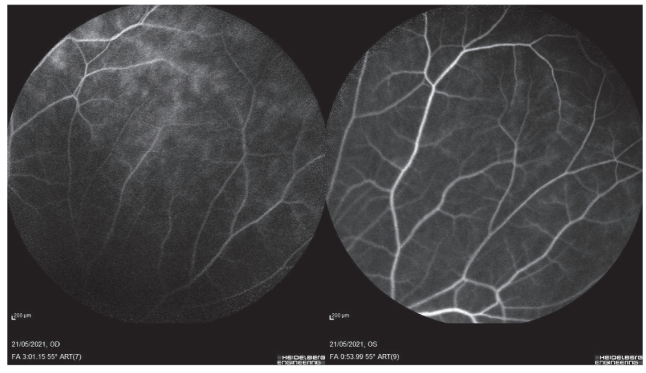

Figure 3. After 5 months of treatment, fluorescein angiography revealed persistent peripheral vascular leakage in the right and left eyes

No progression of the vitiligo lesion was observed at follow-up 3 months later. Treatment with adalimumab and topical tacrolimus was continued.

Discussion

Previous studies showed that TNF is an important mediator in various inflammatory diseases, leading to the development of various anti-TNF agents such as infliximab, etanercept, and adalimumab. Although anti-TNF therapy has been proven to be effective and safe in the treatment of chronic inflammatory conditions, the development of autoimmune diseases and conditions associated with anti-TNF therapy have also been reported.[7] These conditions include new-onset vitiligo or worsening of existing vitiligo.[4,5,6] However, anti-TNF drugs have also been shown to be beneficial in the treatment of vitiligo lesions, which are considered an autoimmune condition.[2,3]

TNF levels in vitiligo lesions have been shown to be increased and associated with disease activity.[8] Anti-TNF drugs were thought to be beneficial in the treatment of vitiligo and were reported to induce regression of the lesions in clinical studies.[2,3] In contrast, new vitiligo lesions may develop while receiving anti-TNF therapy for various autoinflammatory diseases.[4,5,6] Although several hypotheses have been put forward regarding the underlying cause of these contradictory findings, the most accepted of these hypotheses is that long-term TNF inhibition causes an imbalance in cytokine levels.[9] Studies on mouse models of vitiligo have shown that interferon (IFN) also plays a role in lesion formation,[10,11] and later reports also indicated that JAK inhibitors that inhibit IFN were effective in the treatment of vitiligo.[12,13] In an epidemiological study evaluating patients receiving anti-TNF and non-anti-TNF treatments for various autoinflammatory diseases, the risk of developing vitiligo was found to be twofold higher in patients receiving anti-TNF treatment than in patients undergoing conventional treatment.[14] In another case series, it was reported that anti-TNF agents both caused new-onset vitiligo and worsened vitiligo lesions that existed before treatment.[15] In our case, a detailed investigation for systemic disease was conducted both at first admission and after the development of the vitiligo lesion, and no underlying pathology that could cause uveitis was detected. When evaluated together with the previous literature, the fact that our case was under adalimumab treatment for idiopathic uveitis suggests that the development of vitiligo is a result of using adalimumab.

Continuing the anti-TNF agent with an additional topical treatment for the lesion is recommended for the treatment of new-onset vitiligo during anti-TNF therapy. In a multicenter retrospective study, it was reported that continuation of anti-TNF therapy was appropriate in patients with new lesions, but the prognosis was poor when anti-TNF therapy was continued in patients with worsening of existing lesions.[15] In the same publication, it was stated that while spontaneous regression was observed in some of the patients, others received additional topical treatments. Our case was also evaluated by the dermatology clinic, and because he had only a single lesion, continuation of anti-TNF and topical treatment were recommended.

Another point to keep in mind in our case is the exclusion of VKH syndrome in the differential diagnosis, as vitiligo and uveitis occurred together. Ocular signs of VKH syndrome include increased choroidal thickness, hyperemia and edema of the optic disc, multiple serous retinal detachments, and multiple early hyperfluorescent spots on FA.[16] After our patient developed vitiligo, we reassessed him for VKH syndrome. However, no suspicious findings were observed in our examinations, and there were no findings suggestive of VKH in the systemic investigations and evaluations made by the relevant clinics.

In summary, a review of studies in the literature documenting new-onset vitiligo after the use of various anti-TNFs shows that all patients were using these drugs because of systemic autoimmune diseases. In contrast, our patient was using adalimumab to treat idiopathic intermediate uveitis. Previous studies have not reached a definite conclusion on whether vitiligo occurs because of the underlying disease or the anti-TNF agents. However, the absence of an underlying systemic disease in our case supports the view that vitiligo lesions may be induced by adalimumab use.

In recent years, ophthalmologists increasingly prefer biological agents with high efficacy and reliability for the treatment of inflammatory eye diseases. Ophthalmologists should also be aware that vitiligo lesions may develop due to the use of adalimumab. In such cases, the patients should be re-evaluated in terms of systemic diseases, and treatment should be reviewed with the relevant departments using a multidisciplinary approach.

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Ethics

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: F.N.Y., Concept: M.F.K.D., Design: M.F.K.D., Data Collection or Processing: F.N.Y., M.F.K.D., Analysis or Interpretation: F.N.Y., M.F.K.D., Literature Search: F.N.Y., M.F.K.D., Writing: F.N.Y., M.F.K.D.

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Case Report

Unusual Metastasis to Eyelid from Extraocular Merkel Cell Carcinoma

Ahmet Özdemir, Volkan Yeter, Nurullah Koçak, Sultan Çalışkan

Ondokuz Mayıs University, Department of Ophthalmology, Samsun, Türkiye

Abstract

Merkel cell carcinoma (MCC) is an unusual skin tumor that has a significant rate of distant and local metastases. It is known that primary MCC of the eyelid usually occurs at the upper eyelid. Here we report an unusual case of MCC metastasis to the eyelid. A 63-year-old male was diagnosed with MCC three years earlier after initially presenting with a mass in his right thigh. After histopathological diagnosis, the patient received medical therapy. During treatment, he developed multiple distant metastases and a firm, purple, vascularized lesion on the upper eyelid. We confirmed the lesion was an eyelid metastasis of MCC by histopathological examination and imaging methods. This case shows that extraocular MCC can metastasize to the eyelids, particularly the upper eyelid, where primary periocular MCC usually appears.

Keywords: Merkel cell carcinoma, eyelid, metastasis

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Address for Correspondence: Ahmet Özdemir, Ondokuz Mayıs University, Department of Ophthalmology, Samsun, Türkiye
E-mail: dr_ahmet_ozdemir@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0728-6027
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Introduction

Merkel cells are deep epidermal cells that function as mechanoreceptors. They are essential for light touch sensation and are also capable of malignant transformation.[1] Merkel cell carcinoma (MCC) is a rare, destructive tumor that has a mortality rate of up to 40%.[2] MCC tumors are generally observed on sun-exposed skin areas in older whites and usually present as painless, bluish red, expansive nodules. Immunosuppression is an important risk factor, especially in people with solid organ transplants, chronic lymphocytic leukemia, or human immunodeficiency virus.[2]

A literature review of eyelid MCCs in 2019 reported nearly 200 published cases, which included 127 women (64.1%) and 67 men (33.8%), with a median age of 77 years.[2] As approximately 50% of the cases occurred on the head or neck, the cancer now ranks among the five most common malignant tumors found at these sites, preceded in frequency only by basal cell, squamous cell, and sebaceous carcinomas and melanoma.[3] After diagnosis, appropriate staging is necessary to develop a treatment course and effectively counsel patients.[3] Treatment usually includes wide local excision, commonly with the addition of radiotherapy for improved loco-regional disease control.[4] Adjuvant chemotherapy had been reserved for metastatic disease, but immunotherapy and targeted chemotherapies are currently being investigated for use in primary cases.[4]

There have been previous reports of metastases from the eyelid to the regional lymph nodes, parotid lymph nodes, preauricular nodes, submandibular nodes, and distant sites such as the lungs with larger tumors.[5] However, MCC of the ocular adnexa remains a very rare condition.

This is the first case report of the metastasis of MCC from an extraocular region to the eyelid. Another interesting feature of this case is the appearance of metastasis only on the upper eyelid, where primary eyelid MCC usually occurs, without any concomitant uveal or orbital metastasis.

Case Report

A 63-year-old man who underwent kidney transplantation nine years earlier and had diabetes and hypertension reported a history of a mass in the outer center of the right thigh that had first emerged about three years ago. The histopathological examination of the excisional biopsy was reported as malignant neuroendocrine tumor infiltration of MCC (grade 3). The first surgical (extensive) resection was then performed, and six cycles of chemotherapy (etoposide + carboplatin) were administered.

Nine months later, a new mass and lymph node involvement were detected, and surgical resection and lymph node dissection were performed again. After surgery, 31 radiotherapy sessions were administered. Positron emission tomography with computed tomography (PET/CT) performed four months after the second surgery revealed new and widespread metastatic lesions. Off-label pembrolizumab was initiated for immunotherapy. After four courses of this treatment, there was a decrease in the metabolic activity of the existing metastatic lesions on PET/CT, and this was accepted as a response to the treatment. However, a significantly low platelet count (PLT: 11,000 cell/mL) and tumor infiltration in the bone marrow biopsy were observed during this follow-up period. Chemotherapy (carboplatin + irinotecan) was started by the oncologist. After the patient received four cycles of this treatment, the oncologist discontinued immunotherapy and further chemotherapy was planned.

While the patient was hospitalized in the oncology unit, the ophthalmology department was consulted because of the onset of discharge and redness in the right eye. On examination, a mass in the form of a vascularized nodule approximately 1.5 × 1 cm in size was observed on the midline of the left upper lid (Figure 1). According to information received from the patient's relatives, the nodule had appeared in the last 15 days and was growing rapidly. A comparison of recent magnetic resonance images to those obtained six months earlier (Figure 2) revealed a new enhancing mass on the left upper eyelid and multiple intracranial metastases. Apart from the eyelid metastasis, PET/CT imaging from the same period also detected multiple metastases at sites including the C7, T3, T8, and T9 vertebrae, the bone marrow of the left femur, the fourth rib on the right and third rib on the left, the posterior left iliac bone, the left sacrum, right superior scapula, sternum, abdomen, and pelvis region. In addition, there were multiple hypodense lesions widespread in both lobes of the liver.

Total excision of the eyelid tumor and upper eyelid reconstruction were recommended but could not be performed because the patient's general condition was unsuitable for surgery. Approximately one day after the patient's ophthalmological consultation, a local incisional biopsy of the center of the upper eyelid lesion was performed bedside under sterile conditions for histopathologic evaluation. However, the patient's general condition deteriorated further and he died approximately two days after the biopsy. Histopathologic examination subsequently confirmed the upper eyelid lesion was a metastasis of MCC (Figure 3).

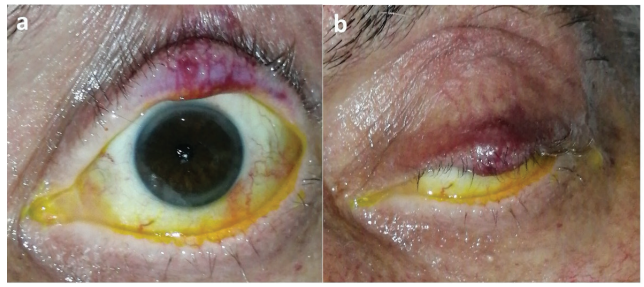

Figure 1. A vascularized, purplish nodule approximately 1.5 x 1 cm in diameter was observed in the center of the upper eyelid (a, b)

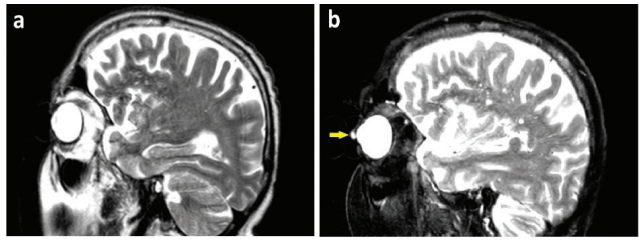

Figure 2. Comparison of magnetic resonance imaging performed 6 months ago (a) with recent scans (b) confirmed the development of a well-confined hyperreflective nodule (yellow arrow) in the left eyelid, as well as multiple intracranial metastases

Discussion

MCC of the eyelid is a rare and extremely malignant tumor with distinctively rapid progression, a high recurrence rate after resection, and early local or metastatic spread.[2] It usually appears in the upper eyelid (76%) as a solitary, painless, multilobulated, violaceous (bluish-purple) nodule near the lid margin (Figure 1).[6] Ulcerations, madarosis, abnormal vascular configuration, and local invasion are often associated with MCC of the eyelid.[6] The eyelid mass may be accompanied by early regional lymph node metastasis in the initial presentation of MCC. MCC of the eyelid may be misdiagnosed as a dermal cyst, chalazion, or hemangioma, and differentiation from other similarly presenting cancerous masses, such as basal cell carcinoma, lymphoma, keratoacanthoma, or metastases, may be difficult in some cases.[6] Thus, a biopsy for histopathologic evaluation should be performed to confirm the clinical diagnosis.

Several risk factors have been identified, such as Merkel cell polyomavirus (MCPyV) infection, sun (ultraviolet light) exposure, acquired immunodeficiency syndrome, chronic lymphocytic leukemia, and immunosuppression.[7] In 2008, Feng et al.[8] detected genomic integration of polyomavirus DNA in 40% of patient samples, leading to the conclusion that MCPyV may be involved in the etiology of MCC. High rates of local recurrence (27-60%), lymph node involvement (45-91%), and distant metastasis (18-52%) have been reported in groups infected with the virus.[8] Recently, Komatsu et al.[7] evaluated the MCPyV status of 10 cases of MCC arising from the eyelid and elucidated the clinical and histopathological characteristics of MCPyV-positive MCC in a literature review.

MCC occurs more commonly on sun-exposed skin. Half of cases are located on the head and neck, 40% on the extremities,

and 10% on the trunk.[7] However, some exceptional tumor sites that are not exposed to sunlight have also been reported, such as the vulva, penis, pharynx, oral mucosa, and thigh, as in our patient.

Poor prognostic factors of MCC are a tumor diameter larger than 2 cm, male sex, immunosuppression, and location on the lower extremities.[5] The average survival time is about eight months from diagnosis in patients with widespread disease. Regional metastases are quite common, and distant metastases do sometimes arise, especially in the liver, bones, lungs, and brain. In the literature, there are no cases of MCC metastasizing to the eyelid from extraocular tissues; this is the first case that showed metastasis of MCC from another region to the eyelid.

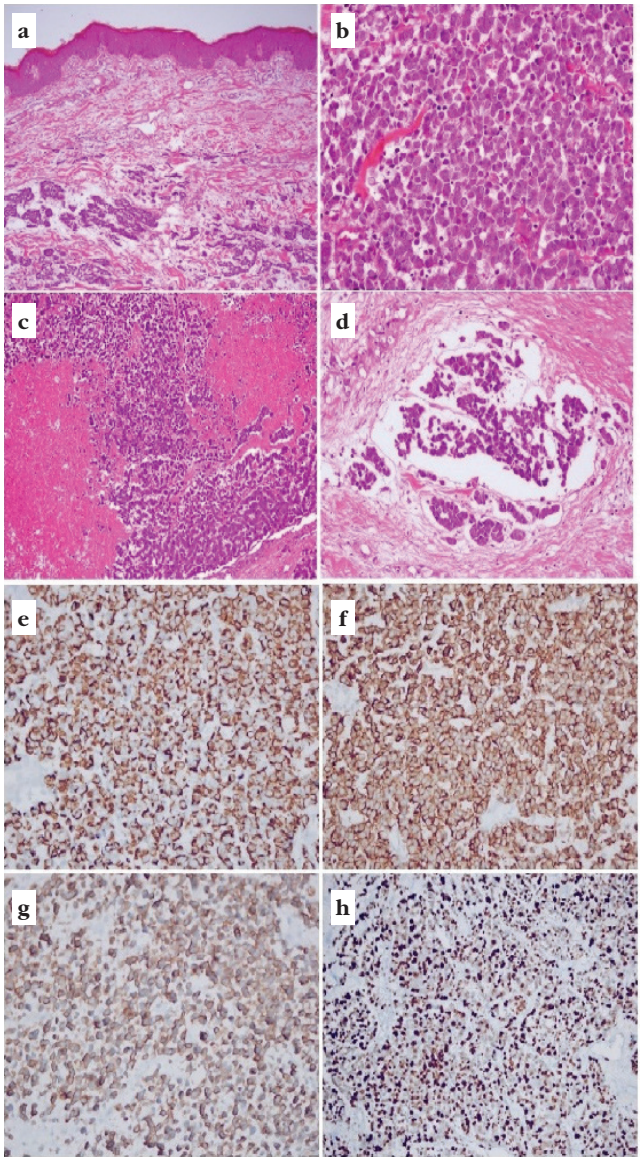

Figure 3. At low magnification, the tumor is seen to be localized to the dermis, unrelated to the epidermis, and arranged as cords and islands (hematoxylin-eosin [H&E], x100) (a). High magnification shows the nuclear features of the tumor cells: neuroendocrine cells with a uniform round nucleus, scant cytoplasm, nuclear molding, and salt and pepper chromatin; mitoses and apoptotic bodies are present (H&E, x400) (b). Areas of necrosis in the tumor (H&E, x200) (c). Tumor cells with lymphatic invasion (H&E, x200) (d). Immunohistochemical features of tumor: cytoplasmic staining with CK20 (e), chromogranin (f), and synaptophysin (g). The proliferative index is very high with Ki-67 (h)

The National Comprehensive Cancer Network Guidelines propose that baseline imaging with CT or whole-body PET/CT may be useful for MCC, especially in cases of lymph node-positive disease.[9] Eyelid metastasis of MCC can occur in various clinical circumstances and should be considered in patients with systemic cancer. These patients usually have multiple metastatic lesions of an ocular and extraocular nature.[10] In our patient, PET/CT imaging revealed multiple extraocular metastases concurrent with the eyelid metastasis in areas such as the vertebral bodies, bone marrow, ribs, iliac bone, sacrum, scapula, sternum, abdomen, pelvis region, liver, and brain.

Metastases from distant primary sites to the eyelids are very rare and comprise less than 1% of all malignant eyelid lesions.[10] The most common primary tumors that metastasize to the eyelids are breast carcinoma, followed by skin melanoma, gastric carcinoma, and lung carcinoma.[10] Half of these metastatic lesions have concomitant ocular sites, which include the uvea and orbit.[10] In the present case, MCC metastasized to multiple body sites, while the only ocular metastasis was to the upper eyelid, the site where primary eyelid MCC frequently arises.

In conclusion, MCC is a rare skin tumor with a significant rate of distant and local metastasis. This case shows that the eyelids are also a possible site for the metastasis of extraocular MCC.

Ethics

Informed Consent: Written consent was obtained from the patient's relatives.

Authorship Contributions

Surgical and Medical Practices: A.Ö., Concept: V.Y., Design: V.Y., N.K., Data Collection or Processing: A.Ö., V.Y., S.Ç., Analysis or Interpretation: A.Ö., N.K., V.Y., Literature Search: A.Ö., V.Y., Writing: A.Ö.

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