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Editorial

Systems Biology Approach for Identification of Essential Growth Factors in Retinal Regeneration

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J Ophthalmic Vis Res 2021; 16 (1): 1–2

Tissue engineering may be considered as a potential treatment modality for various types of retinal diseases. Retinal regeneration depends on an optimal combination of scaffolds, cells, and growth factors. Growth factors play a fundamental role in a variety of cellular processes such as proliferation, migration, differentiation, and multicellular morphogenesis.[1] Growth factors expedite tissue growth/regeneration by providing the right signals to the cells.[2] Systems biology-related approaches help us understand the mechanisms underlying retinal tissue engineering and investigate the effect of growth factors through protein–protein interaction network analyses. Network centrality analysis using different criteria has the potential to reveal growth factors important for retinal regeneration.

In the current issue of *Journal of Ophthalmic and Vision Research*, Beheshtizadeh *et al* report an *in-silico* study which was aimed to determine the most important growth factors in retinal tissue engineering.[3] Gene ontology (GO) and degree centrality analysis were used to identify the most effective proteins for retinal regeneration. Despite the remarkable results presented in the study, it should be stressed that the growth factors were determined only by degree centrality analysis. Numerous studies have established that low connectivity growth factors may also be considered critical in biological processes and for network integrity.[4, 5]

There are several types of centrality which include degree, closeness, between-ness, centroid value, bridging, eccentricity, and eigenvector centrality. Degree centrality is used to evaluate the regulatory importance of immediate neighboring nodes. Nodes with high degree centrality interact with different proteins and therefore usually play a key regulatory role in the network. The short average distance of a distinct node to the entire network of proteins is represented by the closeness index. Proteins with high closeness index (compared to the network) impose a fundamental regulatory effect on other proteins and will be significantly affected by changes in the network. Between-ness index represents the number of times that a specific node (via the shortest path) is used to hold communicating proteins together. The coherence and functionality of the network are likely maintained by the betweenness centrality index. To determine the functional ability of a distinct node to orchestrate discrete clusters of proteins, centroid value is used in the network. Nodes with high centroid values coordinate the activity of other clusters to regulate a distinct cell function. Bridging centrality index is employed to distinguish nodes that link clusters or densely connected regions. Eccentricity index is used to distinguish nodes which are easily reachable by all other proteins. Therefore, a protein with high eccentricity index affects, or gets more easily affected by, other proteins. To determine nodes with a central super-regulatory role or those that serve as key targets of a regulatory pathway, the eigenvector centrality index is used.[6]

In summary, to comprehensively understand the importance of each node in any given network, different kinds of centrality analyses should be performed. Moreover, integration of centrality analyses results helps one correct selection of the most important nodes in the network. It is highly recommended to use web servers such as DAVID (Database for Annotation, Visualization, and Integrated Discovery; https://david.ncifcrf.gov/) or Enrichr (https://maayanlab.cloud/Enrichr/) which have been specifically developed for gene ontology (GO) and enrichment analyses.[7, 8] Moreover, there exists a need for developing a

software which integrates servers that test for GO category enrichment via recruiting the output and provide the resources for summarizing and visualizing data.

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Original Article

Multiplex PCR for Detection of Herpes Simplex Viruses Type-1 and Type-2, Cytomegalovirus, Varicella-zoster Virus, and Adenovirus in Ocular Viral Infections

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Abstract

Purpose: Most common viruses causing ocular infections are Herpes Simplex Viruses (HSV) type 1 and type 2, Cytomegalovirus (CMV), Varicella-zoster Virus (VZV), and few strains of Adenovirus. Diagnosis of these infections through clinical manifestations and using conventional methods has a number of limitations. The purpose of this study was to develop a multiplex Polymerase Chain Reaction (PCR) for simultaneous detection of all pathogenic viruses from ocular infections.

Methods: Ten uniplex PCRs were standardized, two each for HSV type 1 (HSV-1) and type 2 (HSV-2), CMV, VZV, and Adenovirus. Various multiplexing combinations of above PCRs were put to finalize targets and reaction conditions enabling diagnosis of all in a single reaction. The uniplex and multiplex PCRs were run for known positive and negative controls, and samples from clinically suspected patients and healthy controls.

Results: Out of the 170 samples from suspected ocular infections, 24.7% were positive by uniplex PCR and 22.9% were correctly identified by multiplex PCR. None of the samples negative by uniplex PCRs was positive by the multiplex PCR. The sensitivity and specificity of multiplex PCR compared to the commonly used uniplex PCRs as gold standard was 92.86% and 100%, respectively. The prevalence of different viral pathogens was 13.5% for HSV-1, followed by 5.9% for Adenovirus, 2.4% for VZV, 1.8% for HSV-2, and 1.2% for CMV.

Conclusion: The establishment of multiplex PCR has found immediate application in diagnosing ocular viral pathogens in a single reaction, thus saving time, manpower, and resources by fivefold.

Keywords: Adenovirus; Cytomegalovirus; Herpes Simplex Virus; Multiplex Polymerase Chain Reaction; Varicella-zoster Virus

J Ophthalmic Vis Res 2021; 16 (1): 3–11

INTRODUCTION

It is estimated that by the year 2020, the blind population in India will grow to 15 million and ocular infections will account for 15% of the total burden.[1] Viruses can cause a variety of ocular infections including conjunctivitis, keratitis, keratoconjunctivitis, uveitis, chorioretinitis, iridocyclitis, and acute retinal necrosis syndrome.[2–7] Unattended/late treated ocular infections especially with members of *Herpesviridae* family, including Herpes Simplex Virus-1 (HSV-1), Herpes Simplex Virus-2 (HSV-2), Cytomegalovirus (CMV), Varicella-zoster Virus (VZV), and few serotypes (1–4, 7, 8, 11, 19, 37, 53, and 54) of Adenovirus can lead to loss of vision.[8, 9] It is often challenging to determine the causative agent, as there could be significant overlap between the clinical features especially in the early stages of the disease leading to misdiagnosis. There is therefore a need to establish a prompt diagnostic testing that is both rapid and sensitive for an early detection and to determine the choice of treatment.[4] The conventional methods used for diagnosing ocular viral infections are either less sensitive and/or specific, require sophisticated equipment and infrastructure and/or explicit expertise, or have a long turnaround time. In recent decades, focus has been on molecular diagnostics for such infections, in which Polymerase Chain Reaction (PCR) has proven to be a valuable technique. In this technique, the target gene of interest, called nucleic acid template, is amplified in a thermo-cycling reaction. From a single template, billions of copies are produced, which can then be identified by post-amplification analysis. It overcomes the lower sensitivity of conventional laboratory techniques while maintaining specificity. In addition, it can also be performed on limited patient-derived ocular specimen and is less time consuming, inexpensive, and rapid.[2]

Multiplex PCR is a variant in which all viruses in the differential can be diagnosed in a single PCR, thus saving time and cost. The technique works on the principle that different pairs of primers are unique to different infectious agents and their amplicon size varies in length so that the visual difference is observed when PCR reaction product is resolved on an agarose gel. It has an enormous clinical value as it allows simultaneous detection of multiple target organisms in a single reaction; thus, it is more informative and requires very less starting patient specimen. Further, there are various technical advantages of using multiplex PCR including rapid diagnosis, less cumbersome procedure, cost effectiveness, and less time taken to obtain results than conventional diagnostic methods. It has increased accuracy of data normalization and is subject to fewer human pipetting errors.[10]

Standardization and establishment of multiplex PCR for the diagnosis of ocular viral infection has immense clinical and technical advantage. Hence, this study was planned to standardize and establish a multiplex PCR targeting all common ocular viral pathogens for accurate and rapid laboratory confirmation, thereby aiding in the implementation of correct and timely treatment and to determine the prevalence of different viruses as ocular pathogens in our patient cohort.

METHODS

Ethics

Approval of the Institute Ethics Committee was taken, and the procedures were done in accordance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients and controls.

Study Design

The current prospective case–control study was conducted over a duration of 21 months (July 2016

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to March 2018) in the Ocular Microbiology section of an apex healthcare institute of North India, which caters to the tertiary healthcare requirements of Delhi and nearby six to seven states.

Selection and Description of Participants

A total of 170 samples, clinically guided to undertake laboratory diagnostic tests for viral infections, were included as test samples. The patients had various clinical manifestations. Vitreous and aqueous aspirates were collected in sterile Eppendorf tubes; and samples like scrapings, tears, swabs, etc. were collected in sterile Eppendorf tubes containing 1 ml of phosphate buffered saline (PBS, pH 7.2). Maximum numbers of samples received were corneal scrapings (54), conjunctival swabs (45), and tears (33). Fifty tear samples from individuals devoid of any clinical symptoms of ocular infections were included as controls.

DNA Extraction

DNA extraction was done using the QIAamp DNA extraction kit (QIAGEN, Qiagen Str. 1, 40724 Hilden, Germany), strictly following the manufacturer's instructions. As the quantity of ocular specimens was very little, elution of DNA was done in 60 µl of elution buffer. Extracted DNA samples were stored at 0–4°C until processed.

Standardization of Multiplex PCR

Published primers unique and highly specific for HSV-1, HSV-2, CMV, VZV, and Adenovirus were used for standardizing uniplex PCRs. A total of 10 uniplex PCRs were standardized, two each for HSV-1, HSV-2, CMV, VZV, and Adenovirus.[11–13] Results of uniplex PCRs were checked in control strains of all viruses, non-ocular stored clinical specimens positive for different study viruses, and also in extracted DNA from cultures of *Staphylococcus*, *Pseudomonas aeruginosa*, *Acanthamoeba species*, *Aspergillus flavus*, and *Fusarium species*.

The uniplex PCRs were then run at different annealing temperatures and with some variations of cycle conditions to obtain the annealing temperature and cycle conditions suitable for all five study viruses. Various multiplexing combinations of above PCRs were put to make it possible to diagnose all the above five viruses in a single reaction. The five targets, annealing temperature, and reaction conditions which were giving best results for all viruses in a single reaction were finalized. The multiplex reactions were run with control strains of all viruses, non-ocular clinical specimens positive for different study viruses, and DNA extracted from the cultures of *Staphylococcus*, *P. aeruginosa*, *A. species*, *A. flavus,* and *F. species*. All the results of uniplex and multiplex PCRs were finally verified in stored DNA of ocular specimens with known results.

Subsequently, for all clinical samples and controls, five uniplex PCRs (one for each virus) and one multiplex was run. DNA of ATCC-VR-539D, HSV-1 strain McIntyre; ATCC-VR-734D, HSV-2 strain G; OKA vaccine strain of VZV; and pooled extracted DNA positive for CMV and Adenovirus from clinical samples were used as positive controls in each run. Autoclaved MilliQ water controls were used as negative controls in each run. ATCC strains were purchased through LGC Promochem India Private Limited, Bangalore, India.

The details of primers for the five selected targets for the multiplex PCR are shown in Table 1. Both the uniplex and multiplex PCR amplification reactions were conducted in 25 µl volumes. The reaction mixture consisted of dNTPs (200 mM) – 0.5 µl, 10X buffer – 2 µl, MgCl2 – 1.2 µl, forward primer – 1 µl, reverse primer – 1 µl, Taq DNA polymerase 1U – 0.2 µl, test DNA – 2 µl, and autoclaved MilliQ water – 12.1 µl made up to 25 µl. The amplification profile chosen was as follows: initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing at 55°C for 35 sec, extension at 72°C for 40 sec, and final extension at 72°C for 10 min.

Electrophoresis and Documentation

Following the PCR, the amplicons were resolved on a 1.5% agarose gel. Visualization was done with the aid of ethidium bromide (0.5 µg/ml) under ultraviolet illumination using gel documentation system – Biospectrum R 810 Imaging System – UVP (2066 W. 11th St., Upland, CA 91786, USA). Figures 1a, 1b, and 1c show the gel images of positive controls and positive test samples by multiplex PCR.

Results of uniplex and multiplex PCRs were entered in Microsoft Excel sheets (Microsoft^R Office

Table 1. Details of primers for the five selected targets for the multiplex PCR

Name	Primers	Region	Sequence (5'-3')	Size
HSV 1	HSV 1-F	RL-2	TGGGACACATGCCTTCTTGG	147 bp
	HSV 1-R	RL-2	ACCCTTAGTCAGACTCTGTTACTTACCC	
HSV 2	HSV 2-F	gp-D	GTCGGTGTGGTGTTCGGTCATAAGCT	276 bp
	HSV 2-R	gp-D	GGCTGAATCTGGTAAACACGCTTC	
CMV	CMV-F	pol and gp-B	CACGGCCGCCACCAAGGT	392 bp
	CMV-R	pol and gp-B	AGTGGTTGGGCAGGATAAA	
VZV	VZV-F	gp	ATCGCGGCTTGTTGTTTGTCTAAT	355 bp
	VZV-R	gp	GGGCGAAATGTAGGATATAAAGGA	
Adenovirus	Adenovirus-F	Hexon	GCCGCAGTGGTCTTACATGCACATC	308 bp
	Adenovirus-R	Hexon	CAGCACGCCGCGGATGTCAAAGT	

RL, long repeat region; gp, glycoprotein region; pol, DNA polymerase gene

Table 2. Results of uniplex and multiplex PCRs in test samples

Pathogenic virus	Numbers identified by uniplex PCR	Numbers identified by multiplex PCR
HSV-1	23	22
HSV-2	03	03
CMV	02	02
VZV	04	03
Adenovirus	10	09
Total Positive	**42**	**39**
Negative	**128**	**131**

Excel^{R} 2007 [12.0.4518.1014] MSO [12.0.4518.1014]). Sensitivity, specificity, positive and negative predictive values, and accuracy of multiplex PCR was calculated with uniplex PCRs as gold standard.

RESULTS

Controls

Both uniplex and multiplex PCRs were correctly able to identify the viruses from stored DNA of positive ocular and non-ocular samples. None of the DNA from non-viral ocular pathogens – *Staphylococcus*, *P. aeruginosa*, *A. species*, *A. flavus* and *F. species* – was positive for any of the viruses by uniplex or multiplex PCR. None of the 50 control samples from healthy eyes were positive for any of the viruses by uniplex or multiplex PCR.

Clinical Samples

Over the duration of 21 months, 170 specimens from clinically suspected ocular viral infections were received. Uniplex and multiplex PCRs for HSV-1 and HSV-2, CMV, VZV, and Adenovirus were performed for all patients' specimens.

Table 2 shows the results of uniplex and multiplex PCRs in test samples. Out of the 170 samples from cases of suspected ocular infections, 42 (24.7%) were positive for some of the five viruses tested by uniplex PCR. Multiplex PCR was able to correctly detect 39 out of 42 positives of uniplex PCRs (22.9% of 170). None of the samples were positive for more than one virus. None of the samples negative by uniplex PCRs was positive by the multiplex PCR. Thus, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the multiplex PCR was 92.86%, 100%, 100%, 97.71%, and 98.24%, respectively.

Table 3. Results of uniplex and multiplex PCRs from patients with different clinical diagnosis

Clinical diagnosis	Number of specimens received	Positive by uniplex PCR	Positive by multiplex PCR
Conjunctivitis	41	17	16
Keratitis	81	12	11
Blepharitis	3	0	0
Lid and periocular vesicles	5	4	3
Uveitis	5	2	2
Chorioretinitis	5	2	2
Endophthalmitis	3	0	0
Others	27	5	5
Total	**170**	**42**	**39**

The prevalence of different viral pathogens causing ocular infections as determined by the PCR was found to be 13.5% for HSV-1 (23 out of 170 cases positive), followed by 5.9% (10 positive) for Adenovirus, 2.4% (four positive) for VZV, 1.8% (three positive) for HSV-2, and 1.2% (two positive) for CMV (Table 2).

Table 3 and Figure 2 show the distribution of samples received from patients with different clinical diagnoses. Maximum samples were from patients having keratitis, followed by conjunctivitis. Viral infections could be diagnosed using multiplex PCR in 60% of patients having lid and periocular vesicles. Viral etiology could also be clinched in 39% of conjunctivitis and 40% each of uveitis and chorioretinitis patients using the multiplex PCR.

Maximum positivity was observed in vesicle fluid and scrapings (60%), followed by lid scrapings (33.3%), conjunctival swabs (31.1%), and vitreous tap (30%). The positivity in tear samples was found to be 24.2% (Figure 3).

DISCUSSION

Ocular viral infections can range from simple self-limiting discomfort to possibly vision challenging manifestations. The clinical manifestations of such infections are not specific for a particular virus; frequently, the differential includes a number of viruses. There often is an overlap of signs and symptoms with non-viral infections and some non-infective conditions. This is more common in tertiary care centers where the patients often come after partial treatment performed outside, have some underlying immune-compromise, or have some complications of the infection. Most common viruses causing ocular infections are HSV-1, HSV-2, CMV, VZV, and Adenovirus, which are difficult to differentiate by clinical findings alone; nevertheless, the differentiation is important as it determines the choice of treatment.[2] Late or inappropriate treatment of such infections due to delayed diagnosis can compromise the vision of the patient. PCR is now a popular diagnostic test for viral infections; however, its application is limited in clinical situations where the differential diagnosis takes account of several pathogens. Running a PCR for each pathogen in the differential is a time- and resource-consuming process; moreover, each extra reaction has its own share of errors; and sometimes it is not possible to do many reactions as the specimen size is minute in ocular infections. There is a dearth of an accurate, rapid, and cost-effective diagnostic test which can be undertaken on limited ophthalmic sample volume.

A multiplex PCR was thus standardized targeting HSV-1, HSV-2, CMV, VZV, and Adenovirus. This enabled the diagnosis of all five common ocular viral pathogens in a single reaction. The sensitivity and specificity of the multiplex PCR was found to be 92.5% and 100%, respectively. The multiplex PCR was made sensitive for diagnosing ocular viral infections by multiplexing the five most common pathogenic viruses. Specificity was established by simultaneously using uniplex PCRs in all clinical specimens and controls; also, the multiplex PCR did not show any false positivity in DNA from non-viral pathogens. The multiplex PCR was found to be useful in tear samples, which are the least invasive

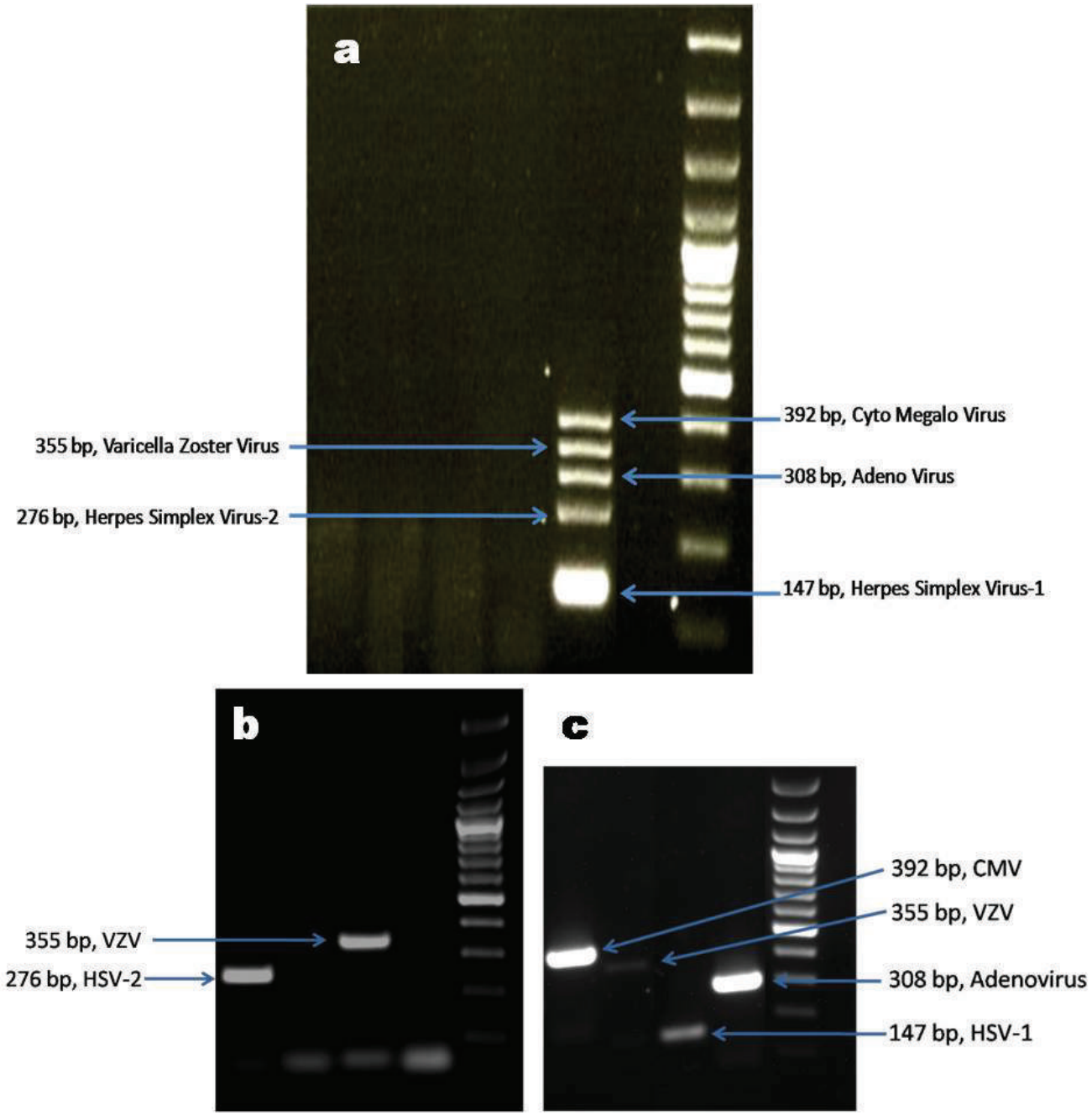

Figure 1. Gel images of positive controls and positive test samples by multiplex PCR. (a) Multiplex PCR simultaneously detecting all five viruses, (b) Ocular specimens positive for HSV-2 and VZV by multiplex PCR, and (c) Ocular specimens positive for CMV, VZV, HSV-1, and Adenovirus by multiplex PCR.

of ocular specimens, showing viral detection in 24.2% of tear samples received. Furthermore, the test was able to clinch diagnosis in 40% of uveitis and chorioretinitis cases, establishing the etiology of which is otherwise very difficult and time-consuming.

In the current study, we also looked for the prevalence of different viruses as ocular pathogens in our patient cohort, and for any asymptomatic carriage in control group.

The overall positivity for viral pathogens in clinically suspected ocular viral infections as detected by uniplex PCR was 24.7% with HSV-1 being the most common (14.4%), followed by Adenovirus (5.9%). None of the healthy controls were positive for any of the viruses.

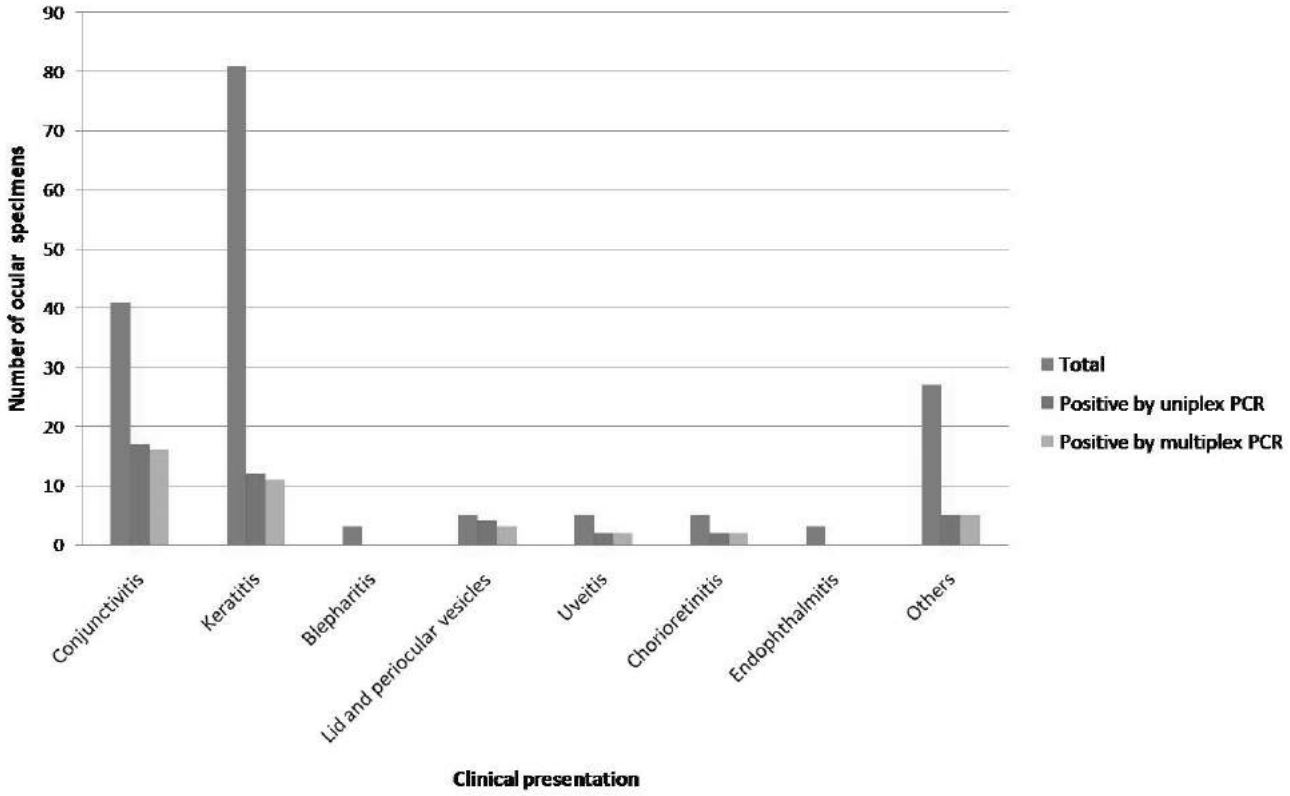

Figure 2. Distribution of specimens received and results of uniplex and multiplex PCRs from patients with different clinical diagnosis.

Our results are comparable to similar studies done in India and abroad.

A study from Japan utilizing multiplex PCR for the detection of HSV-1, HSV-2, CMV, and VZV in different ocular infections has reported the multiplex PCR to be as good as uniplex PCRs for each of the viruses. They have reported a positivity of 57.6% in clinically suspected ocular viral infection cases. Amongst the positives, HSV-1 was the most common (68.4%), followed by VZV (31.6%).[13] Sugitha *et al* from Japan have recently described the results of utilization of a multiplex PCR for the detection of eight herpes viruses and the parasite *Toxoplasma gondii* in cases with uveitis and endophthalmitis. They reported sensitivity and specificity of 91.3% and 98.8%, respectively. The positivity in their study group was 34%, with CMV and VZV being the most common viral pathogens.[14]

Elnifro *et al* in their study in United Kingdom tested a multiplex PCR for detecting HSV, Adenoviruses, and *Chlamydia* in eye swabs. Although they observed a 10-fold fall in the sensitivity of detection limit using multiplex PCR, there was no significant difference in the diagnostic sensitivity of multiplex PCR when compared to that of individual uniplex PCRs.[15]

Another similar study from India reported multiplex PCR for HSV, VZV, and CMV in ocular specimens. The authors have not compared their results with uniplex PCRs in all samples; however, they have established detection limits of multiplex PCR using several dilutions of standard strains. The sensitivity of uniplex PCR for HSV, VZV, and CMV was 4, 4, and 6 PFU/ml, respectively, while that of multiplex PCR was 4, 4, and 12 PFU/ml, respectively. The authors have also established specificity using diverse DNA samples derived from non-viral infections and non-infectious conditions of the eyes. The most common viral infections found were HSV (83.6%), followed by VZV (2%) and CMV (1.4%).[12]

The most recent study is from United States, in which Bizpo *et al* have reported results of a qualitative multiplex real-time PCR for the

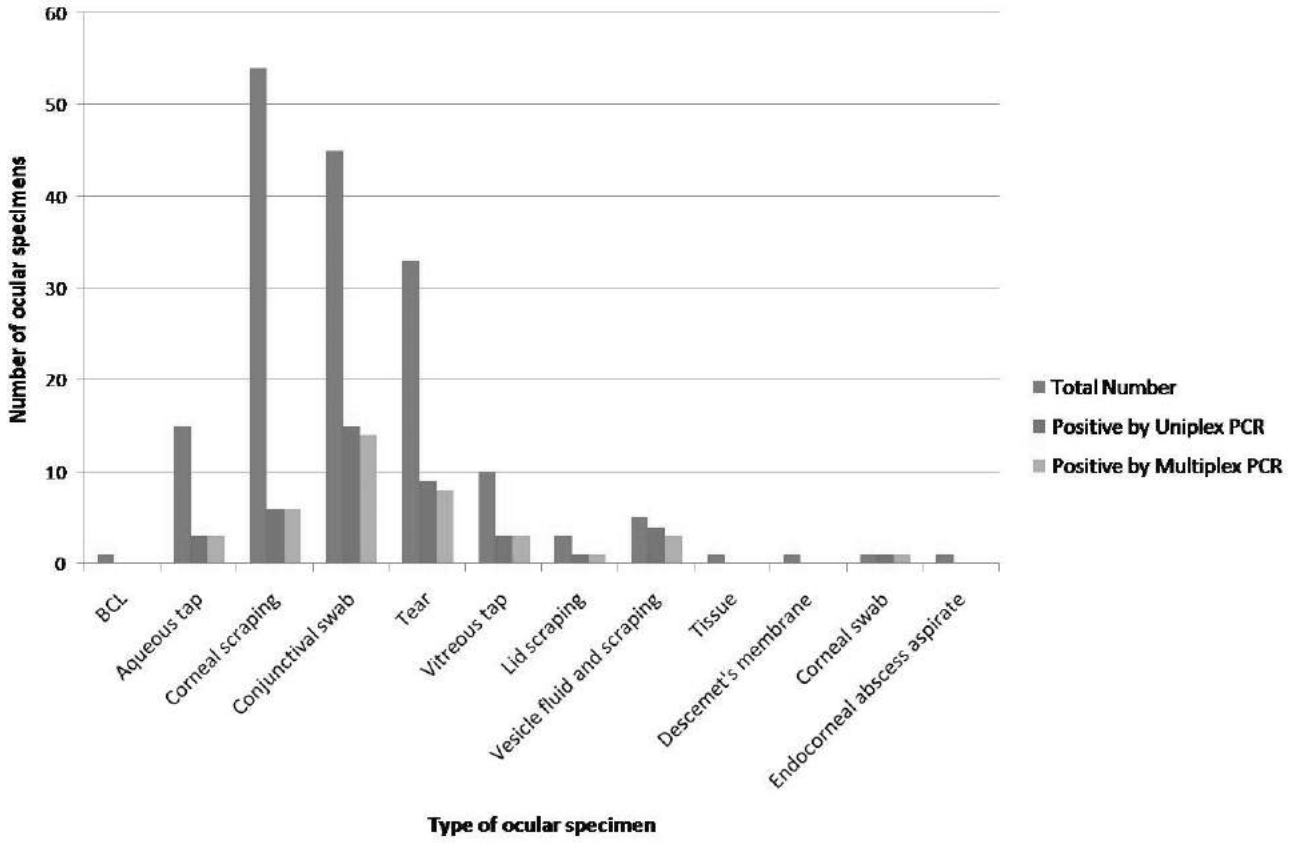

Figure 3. Sample-wise distribution of results of uniplex and multiplex PCRs.

identification of common pathogens causing uveitis. They have targeted viruses HSV-1, HSV-2, VZV, CMV and parasite *T. gondii* and have found the multiplex real-time PCR to be highly specific with a limit of detection of 20 genome copies for viral pathogens and 200 genome copies for *T. gondii*.[16]

There are a few limitations of the study. We have not found the detection limit in terms of genome copy number of uniplex and multiplex PCR for each virus, which would be a better marker of sensitivity of the test. Also, involvement of samples from other ophthalmic centers and inclusion of bioinformatics and in silico analysis would have added weight to the results of the present study.

To conclude, the present study has shown that the multiplex PCR targeting five common viral infections can serve as a valuable diagnostic tool for ophthalmic viral infections. It reduces the turnaround time to diagnose specific viruses, and also the chances of errors associated with putting multiple reactions; at the same time saving on hands on work and cost of diagnosis. The study has also thrown light on current epidemiology of ocular viral infections.

The understanding of current pattern of ocular viral infections and utilization of multiplex PCR for diagnosis can go a long way in improving the management of patients having viral infections of the eyes.

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Conflicts of Interest

There are no conflicts of interest.

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Original Article

Secondary Piggyback Intraocular Lens for Management of Residual Ametropia after Cataract Surgery

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Abstract

Purpose: To investigate the indications, clinical outcomes, and complications of secondary piggyback intraocular lens (IOL) implantation for correcting residual refractive error after cataract surgery.

Methods: In this prospective interventional case series, patients who had residual refractive error after cataract surgery and were candidates for secondary piggyback IOL implantation between June 2015 and September 2018 were included. All eyes underwent secondary IOL implantation with the piggyback technique in the ciliary sulcus. The types of IOLs included Sulcoflex and three-piece foldable acrylic lenses. Patients were followed-up for at least one year.

Results: Eleven patients were included. Seven patients had hyperopic ametropia, and four patients had residual myopia after cataract surgery. The preoperative mean of absolute residual refractive error was 7.20 ± 7.92, which reached 0.42 ± 1.26 postoperatively ($P < 0.001$). The postoperative spherical equivalent was within ±1 diopter of target refraction in all patients. The average preoperative uncorrected distance visual acuity was 1.13 ± 0.35 LogMAR, which significantly improved to 0.41 ± 0.24 LogMAR postoperatively ($P = 0.008$). There were no intra- or postoperative complications during the 22.4 ± 9.5 months of follow-up.

Conclusion: Secondary piggyback IOL implantation is an effective and safe technique for the correction of residual ametropia following cataract surgery. Three-piece IOLs can be safely placed as secondary piggyback IOLs in situations where specifically designed IOLs are not available.

Keywords: Residual Ametropia; Intraocular Lens Implantation; Piggyback IOL Implantation

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INTRODUCTION

Cataract surgery currently plays a pivotal role in achieving the best possible postoperative

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refraction, resulting in patients' independence from spectacles. Despite the advances in surgical techniques and intraocular lens (IOL) power calculation, residual refractive error and refractive surprise occasionally occur and cause both patients' and surgeons' dissatisfaction.[1]

Inaccurate estimation of postoperative IOL position, incorrect biometry measurements, and error in IOL power selection are among the main causes of residual refractive error. Additionally, patients with high ametropia are more prone to residual refractive error, mainly due to the limitations of IOL calculation formula and imprecision of IOL manufacturing in these extreme conditions.[2]

There are multiple surgical techniques used to correct residual refractive error. Various factors affect proper method selection, including the amount of residual refraction and experience of the surgeon, while laser refractive surgeries are considered for lower amounts of residual errors. IOL exchange or piggyback lens implantation is required to correct higher amounts of residual errors.[3, 4]

Piggyback IOL implantation was first introduced in 1993 by Gayton and Sanders[5] and involves the placement of another IOL in the bag or more recently, in the sulcus.[6] Higher safety profile, easier technique, and the potential for removing the second lens are the advantages of piggyback IOL implantation over IOL exchange.[4, 7] However, the increased risk of glaucoma, iris pigment release, and intralenticular opacification make this procedure controversial for many surgeons.[8–11]

Piggyback IOL implantation is considered primary when the refractive error is higher than can be corrected with one IOL and secondary when the residual refractive error is corrected. In secondary piggyback IOL implantation, in which the second IOL is placed in the ciliary sulcus, different IOL designs and types are used, including monofocal, multifocal, and toric.[2]

The present study aimed to investigate the clinical outcomes and complications of secondary piggyback IOL implantation in a tertiary referral eye center.

METHODS

In this prospective interventional case series, all patients who underwent secondary piggyback IOL implantation at Labbafinejad Medical Center from June 2015 to September 2018 were included. The study protocol was approved by the Ethics Committee of the Ophthalmic Research Center, which is the equivalent of the Institutional Review Board at Shahid Beheshti University of Medical Sciences, and adheres to the tenets of the Declaration of Helsinki. Patients who had hyperopic or myopic residual refractive errors following uneventful cataract surgery and had no compliance with spectacle correction were included in the study. The amount of refractive error required for surgery was individualized for each patient and did not have an exact cut-off. Patients with ocular inflammation, iritis, glaucoma, significant guttate or corneal edema, and any complications in the previous surgery that precludes well-centered IOL in the bag were excluded from the study. Informed consent was obtained from all participants.

Preoperative Assessment and Piggyback IOL Power Calculation

An experienced optometrist measured the patients' uncorrected distance visual acuity (UDVA) and best-corrected distance visual acuity (BCVA) using the Snellen chart. Subjective refraction was measured and recorded for all patients. In patients with hyperopic residual refractive error, the power of the piggyback IOL was calculated by multiplying the desired spherical equivalent by 1.5. In myopic patients, the power of the IOL was similar to the desired spherical equivalent. This method was described by Gayton et al.[12]

The type of IOL selection was individualized for each patient based on their refractive error, IOL availability, and surgeon's experience (Table 1).

Surgical Technique

The minimum required interval between the first surgery and piggyback IOL implantation was three months. All procedures were performed by one experienced cornea surgeon (M.J.). Young and uncooperative patients underwent general anesthesia. In other patients, topical tetracaine 0.5% (Anestocaine, Sinadarou, Tehran, Iran) was instilled and coupled with intracameral

lidocaine 2%. Using a 2.8-mm keratome, a clear corneal incision was made on the steep meridian. After the formation of the anterior chamber and area behind the iris with the use of viscoelastic, the IOL was inserted into the ciliary sulcus. OVD (Ophthalmic Viscosurgical Devices) was thoroughly washed using an irrigation and aspiration probe. The incision was made watertight using stromal hydration or a nylon 10-0 suture. Subconjunctival antibiotics were injected at the end of surgery.

On postoperative day 1, topical 0.5% chloramphenicol (Chlobiotic®, Sina Darou, Tehran, Iran) was started four times a day, and 0.1% betamethasone (Betasonate, Sinadarou, Tehran, Iran) was applied eight times a day. Antibiotics were continued for one week, and betamethasone was tapered off for six weeks based on the postoperative degree of inflammation. The patients were closely monitored in terms of wound leakage, intraocular pressure (IOP), and inflammation.

Postoperative Assessment

The patients were followed-up on days 1, 3, 7, and 21, and after three and six months postoperatively, and then yearly. Complete ophthalmic examinations, including UDVA, BCVA, slit-lamp biomicroscopy, and funduscopy were repeated at each visit. Any complication was recorded during the patients' follow-up.

Statistical Analysis

Frequency (%), mean ± SD, median, and range were used to describe the data. To evaluate the difference between the two sets (before and after the surgery for spherical equivalent and UDVA), paired *t*-test was used. All statistical analyses were performed using SPSS (IBM Corp. Released 2017; IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

Eleven eyes of 11 patients were enrolled in the present study. The mean age of the patients was 39.27 ± 29.28 (range, 0.5 to 71) years, and 72.7% of the patients were male (Table 2). The absolute mean deviation from emmetropia in the entire cohort was 7.20 ± 7.92 diopters (D), with a median of 4.25 (–9.50 to +14.00 D). In seven patients who had hyperopic ametropia, the mean SE before surgery was 6.85 ± 4.06 (+2 to +14) D. In myopic patients, the mean SE was –7.81 ± 2.01 (–9.50 to –5.00) D.

Indications for Surgery and Type of IOL

Seven patients with residual hyperopic ametropia and four patients with residual myopia underwent secondary piggyback IOL implantation.

In general, the inability to achieve accurate keratometric data was the most common cause of residual ametropia. The exact causes of inaccurate keratometric data are summarized in Table 3. Other causes include biometric error secondary to chorioretinal coloboma in one patient, biometric error secondary to silicone oil in another patient, and myopic shift following congenital cataract surgery in three patients (Table 4). Three-piece, 6-mm optic, foldable acrylic IOL (AcrySof MA60AC, Alcon Laboratories, Inc.) was placed in seven patients. The main reasons for choosing a three-piece IOL in these patients did not include the availability and cost. In four patients, Sulcoflex piggyback IOL (Sulcoflex; Rayner Intraocular Lenses Ltd, East Sussex, UK) was placed in the ciliary sulcus. The properties of the two IOLs are summarized in Table 1.

Refractive Outcome and Complications

UDVA improved in all participants. The mean duration of follow-up was 22.4 ± 9.5 months. The average preoperative UDVA was 1.13 ± 0.35 LogMAR, which significantly improved to 0.41 ± 0.24 LogMAR postoperatively ($P = 0.008$) (Table 2).

Postoperative SE was within ± 1 diopter of target refraction in all patients (Figure 1). There was no significant difference between pre- and postoperative IOP (14.09 ± 2.5 mmHg vs 14.27 ± 1.67 mmHg, respectively, $P = 0.54$).

There were no intraoperative complications, including primary IOL and vitreoretinal complications, immediate pupillary block, hyphema, intraocular hemorrhage, and postoperative IOP spike. Similarly, no complications, such as pupillary block, glaucoma, pigment dispersion syndrome, postoperative uveitis, postoperative endophthalmitis, or

Table 1. Comparison of two types of intraocular lenses

Variable	Acrysof	Sulcoflex
Generic Name	MA60AC	Sulcoflex Aspheric
Country	Switzerland	United Kingdom
Company	Alcon	Rayner Intraocular Lenses
Pieces	Three-pieces	One-piece
Overall diameter	13 mm	14 mm
Optic diameter	6 mm	6.5 mm
Other properties	Sharp optic edges	Aspheric, Round edged optic
Lens material	Hydrophobic acrylic	Rayacryl hydrophilic acrylic
Haptic angle	10°	10°

Table 2. Patients demographic

		Mean ± SD	Median (range)
Age	Years	39.27 ± 29.28	47 (0.5,71)
Sex, *N* (%)	Male	8 (72.7%)	
	Female	3 (27.3%)	
Eye, *N* (%)	OD	5 (45.5%)	
	OS	6 (54.5%)	
Type of ametropia, *N* (%)	Hyperopia	7 (64%)	
	Myopia	4 (36%)	

OD, right eye; OS, left eye; SD, standard deviation; N, number

Table 3. Postoperative clinical outcome of the study participants

		Mean ± SD	Median (range)	*P*-value
Preoperative ARRE (SE)	Diopter	7.20 ± 7.92	4.25 (–9.5,14)	<0.001
Postoperative ARRE (SE)	Diopter	0 ± 0.97	0.42 (–1,2)	
Preoperative UDVA	logMAR	1.13 ± 0.35	1.31 (0.52,1.48)	0.008
Postoperative UDVA		0.41 ± 0.24	0.3 (0.1,0.7)	
Preoperative BDVA	logMAR	0.41 ± 0.21	0.4 (0.1,0.7)	
Preoperative SE	Hyperopic	6.85 ± 4.06	6.5 (2, 14)	<0.001
Postoperative SE		0.28 ± 0.8	0 (–0.5,2)	
Preoperative SE	Myopic	–7.81 ± 2.01	–8.37 (–9.5,–5)	<0.001
Postoperative SE		0.06 ± 2.43	–0.62 (–2 to 3)	
Preoperative IOP		14.09 ± 2.5	14 (11,17)	0.54
Postoperative IOP		14.27 ± 1.67	15 (11,16)	
Complications		None		

ARRE, absolute residual refractive error; UDVA, uncorrected distance visual acuity; BDVA, best-corrected distance visual acuity; SE, spherical error; IOP, intraocular pressure

Table 4. Indications, clinical outcome, and type of implanted IOL in the study participants

Patient	Age/Sex	Possible Causes	Pre-op UCVA	Pre-op BCVA	Post-op UCVA	Post-op BCVA	Targeted SE	Pre-op SE	Post-op SE	Diff SE (Post-op & Targeted)	IOL Type/power
1	6 Mo M	Incorrect keratometry	–	–	–		+3.00	+14.00	+2.00	+1.00	3-piece/ +21.00
2	4 Y F	Known case of PHPV pseudophakic myopic shift	20/800	3/10	2/10	3/10	0.00	-9.50	0.00	0.00	1-piece/ –10.00
3	41 Y F	Biometric error due to chorioretinal coloboma	20/600	5/10	5/10	5/10	0.00	+10.0	0.00	0.00	3-piece/ +15.50
4	71 Y M	Keratometric error due to corneal nebule	2/10	8/10	8/10	8/10	0.00	+5.00	0.00	0.00	3-piece/ +7.50
5	65 Y F	Keratometric error due to KCN	1/10	7/10	7/10	7/10	0.00	+6.50	–0.50	0.00	3-piece/ +10.0
6	70 Y M	Biometric error due to SO	20/400	2/10	2/10	2/10	0.00	+7.00	+0.50	+ 0.50	3-piece/ +10.00
7	47 Y M	(known case of RP) Acceptable RE	3/10	4/10	5/10	4/10	0.00	+2.00	0.00	0.00	3-piece/ +3.00
8	15 Mo M	Known case of PHPV myopic shift	–	–	–	–	+4.00	–500	+3.50	–0.50	1-piece/ –9.00
9	57 Y M	Wrong IOL power, Human error	20/400	4/10	5/10	4/10	0.00	+3.50	0.00	0.00	3-piece/ +5.00
10	11 Y M	Hx of congenital cataract sx, Myopic shift	20/800	2/10	2/10	2/10	0.00	–9.00	0.00	0.00	Sulcuflex/ –10.00
11	64 Y M	Keratometric error due to PMD	1/10	4/10	4/10	4/10	0.00	–7.75	–1.00	–1.00	Sulcoflex/ –8.00

BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity; SE, spherical error; PHPV, persistent hyperplastic primary vitreous; RP, retinitis pigmentosa; SO, silicon oil; RE, refractive error; sx, surgery; KCN, keratoconus; PMD, pellucid marginal degeneration; IOL, intraocular lens; op, operative; Diff, difference; M, male; F, female; Hx, history of; Mo, month; Y, year

interlenticular opacification (ILO), were observed during the follow-up period. In follow-up examinations, all IOLs were well centered, and no cases of IOL tilt or capture were observed. In the last follow-up, all patients were satisfied with their quality of vision, and none of them were dependent on spectacles for distance vision.

Patients undergoing either type of IOL had comparable refractive outcomes and complications (Table 4). Postoperative complications such as endophthalmitis and cystoid macular edema did not occur.

Description of a Presenting Case

A 41-year-old female patient with irido-choroidal coloboma in the left eye was referred to Labbafinejad Medical Center with the complaint of poor vision. She had a history of uneventful cataract surgery and IOL implantation at another

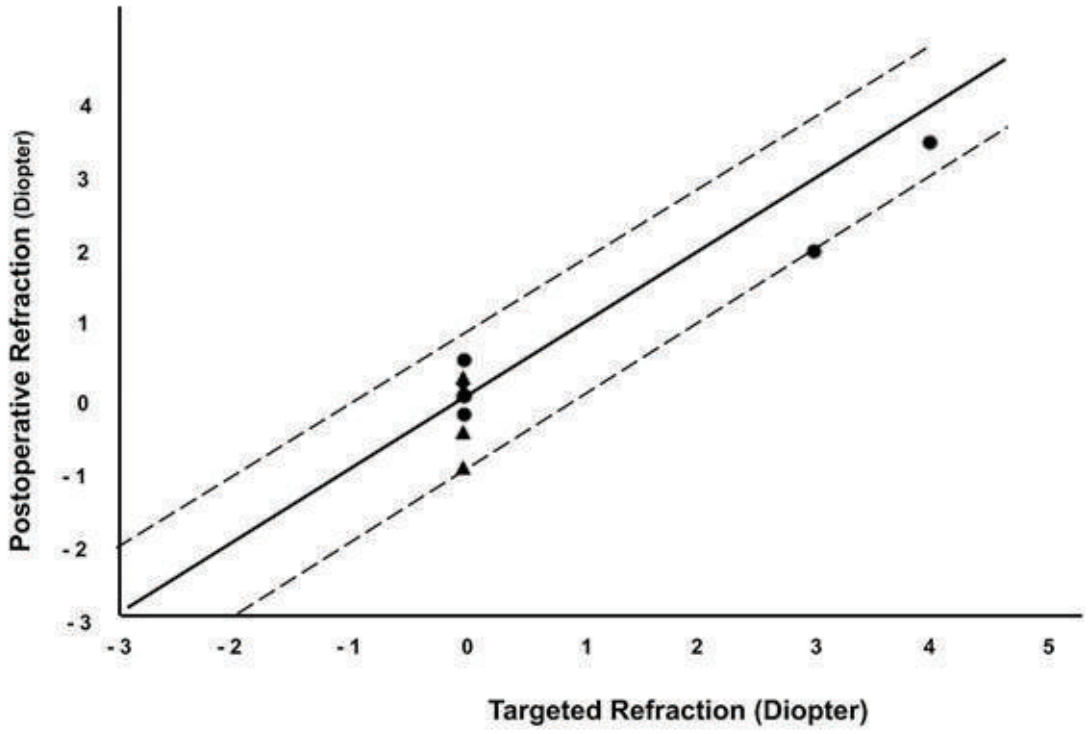

Figure 1. Target refraction plotted against achieved refraction. Triangles depict myopic patients and bullets represent hyperopic patients. All patients were within ± 1 diopters of target refraction.

eye center three weeks before her presentation to us. Her UDVA was 20/400 in the left eye with the Snellen chart. Her acuity increased to 20/40, with a refraction of +10.50 –1.50 × 150. Slit-lamp biomicroscopy revealed iris and choroidal coloboma in both eyes; it was more severe in the left eye, in which the posterior pole was involved. The cornea was clear. The IOP was within normal limits, and the IOL was well centered in the capsular bag. A review of her previous surgery records revealed implantation of a three-piece acrylic IOL (Acrysof, SA60AT, Alcon, Inc.) with 7.5 diopters calculated based on SRK-T formula. Axial length was measured using a Lenstar LS 900 non-contact biometer (Haag-Streit AG, Switzerland).

An immersion A-scan ultrasound was used to repeat the biometry. A B-scan was also achieved simultaneously. Using the SRK/T formula, the power of IOL was calculated to be 23 diopters, which had a large difference compared with the implanted IOL (15.50 diopters). To calculate the power of the piggyback IOL, the SE was multiplied by 1.5, and the power was calculated to be 15.5 diopters, which was exactly the same as the difference value calculated by biometry.

The patient underwent a piggyback IOL implantation of a three-piece foldable IOL of +15.50 D (MA60AC, AcrySof, Alcon, Inc.) in the ciliary sulcus. Postoperatively, her UDVA reached 20/50. The SE of the residual refractive error was –0.25 D.

DISCUSSION

The present study reviewed the indications and clinical outcomes of secondary piggyback IOL implantation at a tertiary referral center over a five-year period. The results revealed that patients with both myopic and hyperopic ametropia following cataract surgery achieved excellent refractive outcomes after the implantation of piggyback IOL in the ciliary sulcus.

Various surgical modalities have been proposed to correct residual ametropia following cataract surgery.[13] Laser refractive procedures, IOL exchange, and secondary IOL implantation are available strategies.[3] Selection of the best

one depends on many factors, including the magnitude of residual error and the surgeon's preferences and experience. Laser refractive surgery is an effective and safe method for residual refractive error correction; however, it can create potential complications that may be more common in older patients secondary to concomitant ocular morbidities, such as dry eye and deteriorated wound healing processes.[14] Considering other alternatives, IOL exchange with a new IOL is a very difficult procedure, which requires a high level of expertise, and would impose excessive surgical risk to patients, even if it is performed by an experienced surgeon.[15] Furthermore, this procedure achieves the best results when performed soon before the formation of capsular adhesions, which is not feasible in all patients.[4, 7, 10]

Recently, secondary piggyback IOL implantation has received more attention due to its promising safety profile and easier surgical techniques.[6, 15–18] Additionally, there are many studies reporting predictable refractive outcomes with the application of power calculation of the second IOL, which is not very complicated.[19] Another advantage of a secondary piggyback IOL over IOL exchange is that the implantation of a secondary IOL is a reversible procedure, and if complications such as ILO, pupillary optic capture, pigment dispersion syndrome, or pigmentary glaucoma occur, the removal of piggyback IOL can be considered.[13]

The present findings are in line with other studies reporting piggyback IOL implantation. Gayton et al reported an excellent refractive outcome in patients who underwent piggyback IOL implantation.[16] Similarly, they chose a minus-power IOL equal to the patient's residual spherical error. This amount was multiplied by 1.5 in hyperopic patients, regardless of keratometry or axial length.[12] However, there are various methods to calculate secondary IOL power with comparable or even superior results.[20, 21]

Our patients did not experience any intra- or postoperative complications. Complications of secondary piggyback IOL implantation include ILO, pupillary optic capture, pigment dispersion syndrome, pigmentary glaucoma, and other adverse events that occur generally in ocular surgeries, such as retinal detachment, postoperative endophthalmitis, or uveitis.[8–11, 22] ILO is a unique complication in piggyback implantation, which occurs mainly due to retained regenerative cortical material similar to posterior capsular opacification.[8, 23]

Recently, the application of different IOL materials and placement of secondary IOL in the ciliary sulcus, which increases the distance between two IOLs, have reduced the incidence of ILO.[24] Accordingly, no ILO was observed in our study series because all secondary IOLs were placed in the ciliary sulcus.

A similar outcome was observed among patients with Sulcoflex IOL compared to patients who underwent three-piece IOL implantation. Secondary piggyback IOLs are available as monofocal, multifocal, toric, and multifocal models.[1, 15, 17, 18] There are three types of IOLs specifically designed for secondary implantation in the ciliary sulcus to correct pseudophakic ametropias or presbyopia: Sulcoflex (Sulcoflex; Rayner Intraocular Lenses Ltd., East Sussex, UK),[19] Add-on (Human optics, add-on IOLs, Germany),[1] and 1st Add-on (1st Gmblt, Mannheim, Germany).[25] In addition, implantable collamer lens and Artiflex phakic IOL are reported to be safely implanted as secondary IOLs.[18–20, 26] The Sulcoflex, Add-on, and 1st Add-on IOLs were designed to reduce complication rates; no significant difference was observed in our series.[12] These specifically designed IOLs with different powers are not always available, especially in developing countries and countries with a transitional economy. Their cost can also be a concern in these situations. Three-piece IOLs are reported to be safely placed in the ciliary sulcus and capsular bag and are the preferred types of IOL in situations where ciliary sulcus implantation is needed.[27?] To our knowledge, the use of three-piece IOLs as secondary piggyback implantation has not been previously reported. Herein, we reported their safety and efficacy as secondary piggyback IOL implantation during an approximately two-year follow-up.

Additionally, we described in more detail one of our patients with choroidal coloboma who had refractive surprise after an uneventful cataract surgery. This case highlights the rare possibility of postoperative refractive surprise due to incorrect measurements of the axial length by optical devices, or A-scan without accompanying B-scan,

in eyes with posterior pole retinal coloboma or staphyloma.

Although all patients were satisfied with their visual outcomes, the small sample size, lack of matched control group, and relatively short follow-up duration are the important limitations of the current study.

The present study reported the indications and clinical outcomes of a series of patients who underwent secondary piggyback IOL implantation for residual ametropia correction following cataract surgery. This strategy is recommended as an effective and safe technique, especially in extreme ametropia, in the presence of corneal or systemic diseases that exclude laser refractive procedures, or when excimer laser platforms are not available.

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Nil.

Conflicts of Interest

The authors have no proprietary or commercial interest in any materials discussed in this article.

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Original Article

Longitudinal Growth Differentiation Factor 15 (GDF15) and Long-term Intraocular Pressure Fluctuation in Glaucoma: A Pilot Study

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Abstract

Purpose: Growth Differentiation Factor 15 (GDF15) was previously identified as a molecular marker of retinal ganglion cell stress in rodent models of glaucoma and was elevated in the aqueous humor (AH) of patients with primary open-angle glaucoma as a possible risk factor for glaucoma progression. The purpose of this study was to determine whether changes in the AH GDF15 levels were associated with intraocular pressure (IOP) changes in eyes undergoing glaucoma surgery.

Methods: Here, we performed a prospective, longitudinal pilot study in nine patients to determine whether changes in AH GDF15 levels from surgery to post-surgery follow-up were associated with IOP fluctuation. An initial AH sample was taken from the peripheral corneal paracentesis during planned glaucoma surgery, and a second sample was taken during an outpatient follow-up visit, approximately six months later.

Results: There was a statistically significant correlation between GDF15 fold change and IOP standard deviation (r = 0.87, P = 0.003), IOP range (r = 0.87, P = 0.003), and maximum IOP (r = 0.86, P = 0.003). There was no correlation between the GDF15 fold change and baseline IOP (r = 0.50, P = 0.17), final IOP (r = 0.038, P = 0.92), or mean IOP (r = 0.40, P = 0.28).

Conclusion: Our findings in this pilot study suggest that longitudinal changes in AH GDF15 may be associated with IOP fluctuation during the postoperative period. Further studies are necessary to corroborate these findings in a larger patient population and to explore the possibility that AH GDF15 may be used not only to improve treatment algorithms but also as a surrogate endpoint in clinical trials.

Keywords: GDF15; Glaucoma; Neurodegeneration; Molecular Markers

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INTRODUCTION

Glaucoma is a neurodegenerative disease characterized by progressive death of retinal

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ganglion cells (RGCs). Although it is currently the second leading cause of blindness worldwide,[1] the molecular pathogenesis of RGC death remains elusive. Therefore, interventions are currently centered on lowering intraocular pressure (IOP), a risk factor for disease progression.[2] Most clinical decision-making is based upon measuring IOP and surrogates of glaucomatous neurodegeneration, such as Humphrey visual field, cup-to-disc ratio, and nerve fiber layer thickness. Unfortunately, these surrogate metrics are imprecise in their ability to quantify disease severity and, in some cases, are subjective and unreliable. Therefore, there is a clinical need for molecular markers that measure RGC health and stress prior to cell death to guide optimal medical and surgical management of glaucoma patients.

It was previously reported that Growth Differentiation Factor 15 (GDF15), a member of the Transforming Growth Factor beta (TGF-β) superfamily, is a molecular marker of RGC stress in rodent models of glaucoma.[3] Validation studies in well-characterized human patients showed that GDF15 levels not only were elevated in the aqueous humor (AH) of primary open-angle glaucoma (POAG) patients compared to control patients without glaucoma but also increased stepwise with increasing visual field loss by Hodapp-Parrish-Anderson staging.[3] However, because of the cross-sectional study design, they were unable to determine whether changes in AH GDF15 levels were associated with IOP changes, which have been reported as possible risk factors for progression. To explore this possibility, we performed a prospective, longitudinal pilot study to determine whether changes in AH GDF15 levels over a follow-up period of approximately six months are associated with IOP changes in eyes undergoing glaucoma surgery.

METHODS

We recruited nine participants from one large academic institution. All patients gave written informed consent. This study was approved by the Institutional Review Board (IRB) of the Human Research Protection Office (HRPO) of the local Ethics Committee. All procedures adhered to the tenets of the Declaration of Helsinki. Patients were included if they had any form of glaucoma, including POAG or secondary glaucoma, and were determined to be candidates for Molteno® glaucoma implant (Molteno Ophthalmic Limited, Dunedin, New Zealand) or Ahmed® glaucoma valve (New World Medical, Rancho Cucamonga, CA) surgery. Eyes were excluded if there was active inflammatory eye disease, any retinopathy, or any optic nerve degeneration from non-glaucomatous causes. To determine appropriate sample size, we performed a power analysis using G*Power 3.1.9.2.[15] Estimating an effect size of $r = 0.75$ based on previous data, we calculated a sample size of $N = 9$ to achieve 80% power at a two-tailed alpha of 0.05.

Two AH samples were obtained from each patient. The first AH sample was obtained in the operating room during planned glaucoma surgery. Briefly, a blunt cannula attached to a tuberculin syringe was inserted into the initial peripheral corneal paracentesis and used to remove 50–100 µl of AH. The second AH sample was obtained during a clinic visit, approximately six months after the initial surgery. Briefly, using sterile technique, a needle on a syringe was used to enter the anterior chamber temporally, anterior to the limbus, to gently aspirate AH, with care taken to not deform the anterior chamber. In both cases, AH samples were immediately placed on dry ice and then stored at –80°C until further analysis. We measured GDF15 levels of all AH samples at the same time using the commercially available human GDF15 Quantikine enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems), as described previously.[3] The individual performing GDF15 measurements (XXX) was masked to demographic and clinical information to minimize bias.

Demographic information, clinical information, and IOP measurements were obtained by retrospective chart review. All IOP values were measured by Goldmann Applanation Tonometry, performed by ophthalmologists or optometrists who were masked to the study data. Participants had IOP measurements taken as a part of routine clinical care at postoperative day 1, postoperative week 1, postoperative month 1, and additional follow-up visits as clinically indicated. The primary variables of interest were measures of IOP fluctuation that have been previously reported as risk factors for glaucoma progression, such as IOP standard deviation, IOP range, and maximum IOP. We also analyzed baseline IOP (measured at the clinic visit prior to glaucoma surgery), final IOP (measured at the same clinic visit during which the

second AH sample was collected), and mean IOP over the follow-up period.

We performed statistical analysis and data visualization with R Version 3.6.2 and RStudio Version 1.2.5003. To compare means between two groups, we used the Mann–Whitney U test due to small sample size. To compare pre- and post-surgery number of medications, we used the Wilcoxon signed-rank test. To determine associations between continuous variables, we calculated Pearson product-moment correlation coefficients. Because of relatively small sample sizes, we also calculated Kendall rank correlation coefficients to confirm our results. We considered $P < 0.05$ to be statistically significant.

RESULTS

Demographic and clinical characteristics of the participants are shown in Table 1. There were four male and five female participants. The mean age was 71.0 years (standard deviation: 9.6 years). Eight patients had POAG, while one patient had glaucoma secondary to presumed herpes simplex uveitis/trabeculitis, which had been inactive for greater than three months. Three patients underwent placement of a Molteno® glaucoma implant; six patients underwent placement of an Ahmed® glaucoma valve. Three patients underwent surgery in their left eye; six in the right eye. The mean follow-up duration was 183.4 days (standard deviation: 28.0 days, minimum: 131 days, maximum: 215 days). Patients were on significantly fewer classes of medications after surgery compared to before surgery ($P = 0.013$).

There was no significant correlation between baseline AH GDF15 and baseline IOP, mean IOP, or final IOP ($P > 0.05$). Similarly, there was no significant correlation between follow-up AH GDF15 and baseline IOP, mean IOP, or final IOP ($P > 0.05$). Of the nine participants, six had increased AH GDF15 levels over the follow-up interval, while three had decreased AH GDF15 levels at follow-up approximately six months later [Figure 1]. All participants had between four to nine IOP measurements during the follow-up period [Figure 2]. When dichotomizing participants into those who had increased ("GDF15 Up"; $N = 6$) versus decreased ("GDF15 Down"; $N = 3$) AH GDF15 levels, there were no statistically significant differences in the baseline IOP, final IOP, mean IOP, IOP standard deviation, IOP range, or maximum IOP ($P > 0.05$ by Mann–Whitney U tests). GDF15 fold change from baseline to follow-up was not correlated with baseline IOP, final IOP, or mean IOP [Figures 3A–C]. In contrast, GDF15 fold change was strongly correlated with IOP standard deviation, IOP range, and maximum IOP [Figures 3D–F] with statistical significance achieved with both parametric and non-parametric tests.

DISCUSSION

In this prospective, observational pilot study, we analyzed whether changes in AH GDF15 levels from baseline to follow-up at approximately six months were associated with IOP fluctuation. Our findings suggest that AH GDF15 fold change is indeed associated with IOP fluctuation. IOP fluctuation that occurs over months to years has been reported as a risk factor for visual field progression in glaucoma in the Advanced Glaucoma Intervention Study (AGIS),[4, 5] the Collaborative Initial Glaucoma Treatment Study (CIGTS),[6] and the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG).[7] Thus, our findings suggest that increases in AH GDF15 measurements may be associated with increased risk of glaucoma progression. Although not all studies have corroborated IOP fluctuation as a risk factor for glaucoma progression, Kim and Caprioli previously hypothesized that this discrepancy may be due to higher mean IOP in some study populations that could potentially mask the effect of IOP fluctuation.[8]

Given this possible role of IOP fluctuation in glaucoma progression, especially for patients who show progression despite having IOPs near goal, the ability to use a molecular marker such as GDF15 as a marker of long-term IOP fluctuation is highly desirable. Routine IOP measurements to assess for fluctuation is time-consuming given the need for repeated clinic visits and is rarely performed outside of clinical trials due to demands not only for the clinician but also for patients and their families. Home tonometer devices such as the Icare® HOME tonometer (Icare USA, Raleigh, NC) are available but have uncertain reliability. Additionally, devices such as the Triggerfish® Contact Lens Sensor (SENSIMED, Lausanne, Switzerland) can measure changes in ocular dimensions thought to be related to IOP but is typically used for only a 24-hr period and is still experimental, as studies investigating

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Value
Age, Mean ± SD[a]	71.0 ± 9.6
Sex, *N*[b] (%)	
Male	4 (44.4)
Female	5 (55.6)
Type of Glaucoma, *N* (%)	
Primary open-angle glaucoma	8 (88.9)
Glaucoma secondary to inflammation	1 (11.1)
Type of Procedure, *N* (%)	
Molteno® glaucoma implant	3 (33.3)
Ahmed® glaucoma valve	6 (66.7)
Study Eye, *N* (%)	
OS	3 (33.3)
OD	6 (66.7)
Pre-surgery Medication Classes, Median (Range)	4 (2 – 4)
Post-surgery Medication Classes, Median (Range)	2 (0 – 3)[c]

[a]SD: standard deviation; [b]N: number of participants; [c]There is a significant difference between pre- and post-surgery number of medication classes by the Wilcoxon signed rank test: $P = 0.013$

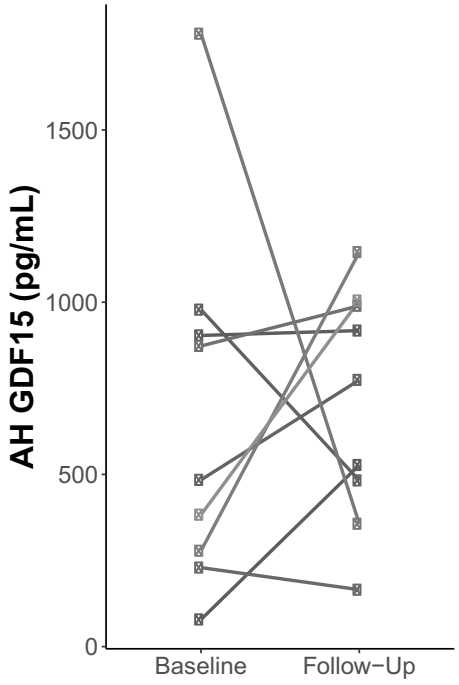

Figure 1. Of the nine participants, six had increased aqueous humor (AH) Growth Differentiation Factor 15 (GDF15) from baseline to follow-up at approximately six months (shades of red), while three had decreased AH GDF15 (shades of blue). Circles denote patients who received the Ahmed® glaucoma valve; squares denote patients who received the Molteno® glaucoma implant.

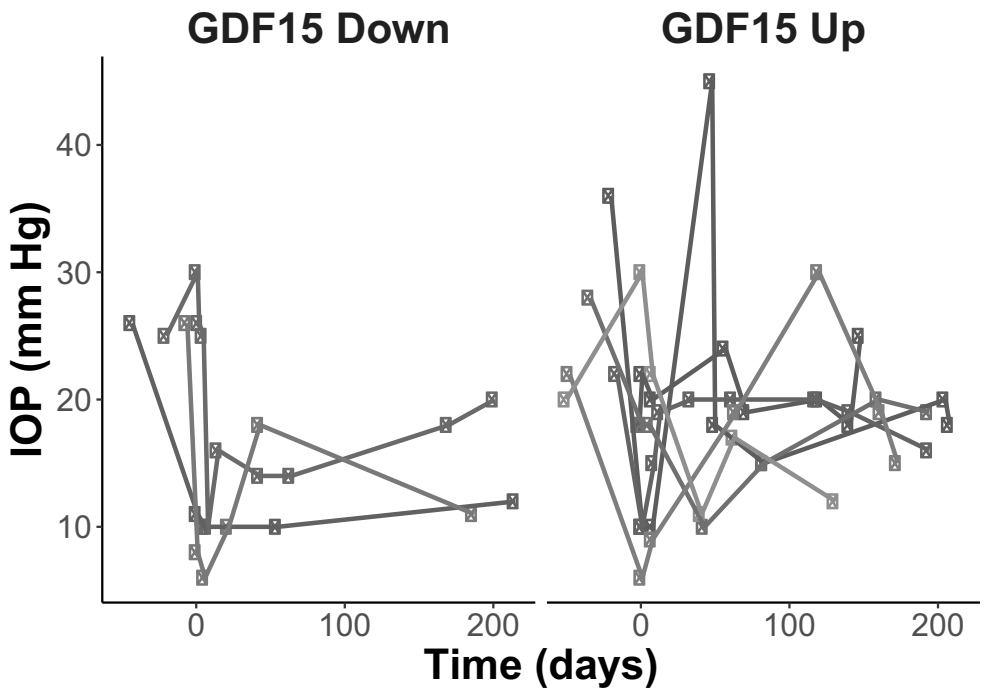

Figure 2. Serial intraocular pressure measurements by Goldmann Applanation Tonometry for participants whose aqueous humor (AH) Growth Differentiation Factor 15 (GDF15) increased ("GDF15 Up"; *N* = 6; shades of red) and those whose AH GDF15 decreased ("GDF15 Down"; *N* = 3; shades of blue). Day 0 was set as the day of glaucoma surgery when the initial AH sample was collected. Circles denote patients who received the Ahmed® glaucoma valve; squares denote patients who received the Molteno® glaucoma implant.

their correlation with IOP measurements obtained through other validated methods have yielded mixed results.[9]

Although glaucoma is one of the leading causes of blindness worldwide, identifying reliable molecular markers has been challenging.[10] This lack of molecular markers has led to reliance on surrogate markers of glaucomatous neurodegeneration for clinical decision-making, even though these surrogate markers are imprecise and sometimes unreliable. Additionally, there is a great need for novel molecular markers of RGC health that can be used as reliable surrogate endpoints for clinical trials.[11] Although further validation is necessary to demonstrate a direct link to glaucoma progression, we propose that AH GDF15 may be a molecular marker of long-term IOP fluctuation that may be used in future therapeutic trials.

One limitation of the present study is the relatively small sample size. Although we achieved the necessary sample size for adequate statistical power, our small sample size does not permit us to control for possible covariates, such as age and gender. Another limitation of the study is the heterogeneity of glaucoma subtype and the type of surgery that these patients underwent. We cannot rule out the possibility that differences in the underlying disease pathophysiology or underlying differences of the post-operative IOP profiles of the Ahmed® glaucoma valve versus the Molteno® glaucoma implant may have influenced our findings. Future longitudinal studies in larger populations are necessary to address these limitations and may also incorporate functional testing to directly measure glaucoma progression.

One strength of our study is that we have a well-characterized patient population for whom we have longitudinal GDF15 measurements. This within-subjects design allowed us to account for inter-individual variability since GDF15 has shown to be elevated in other contexts, such as neurodegenerative and cardiovascular disease.[12, 13]

Although many groups have explored AH biomarkers for numerous ocular diseases,[14] many of these studies have analyzed samples

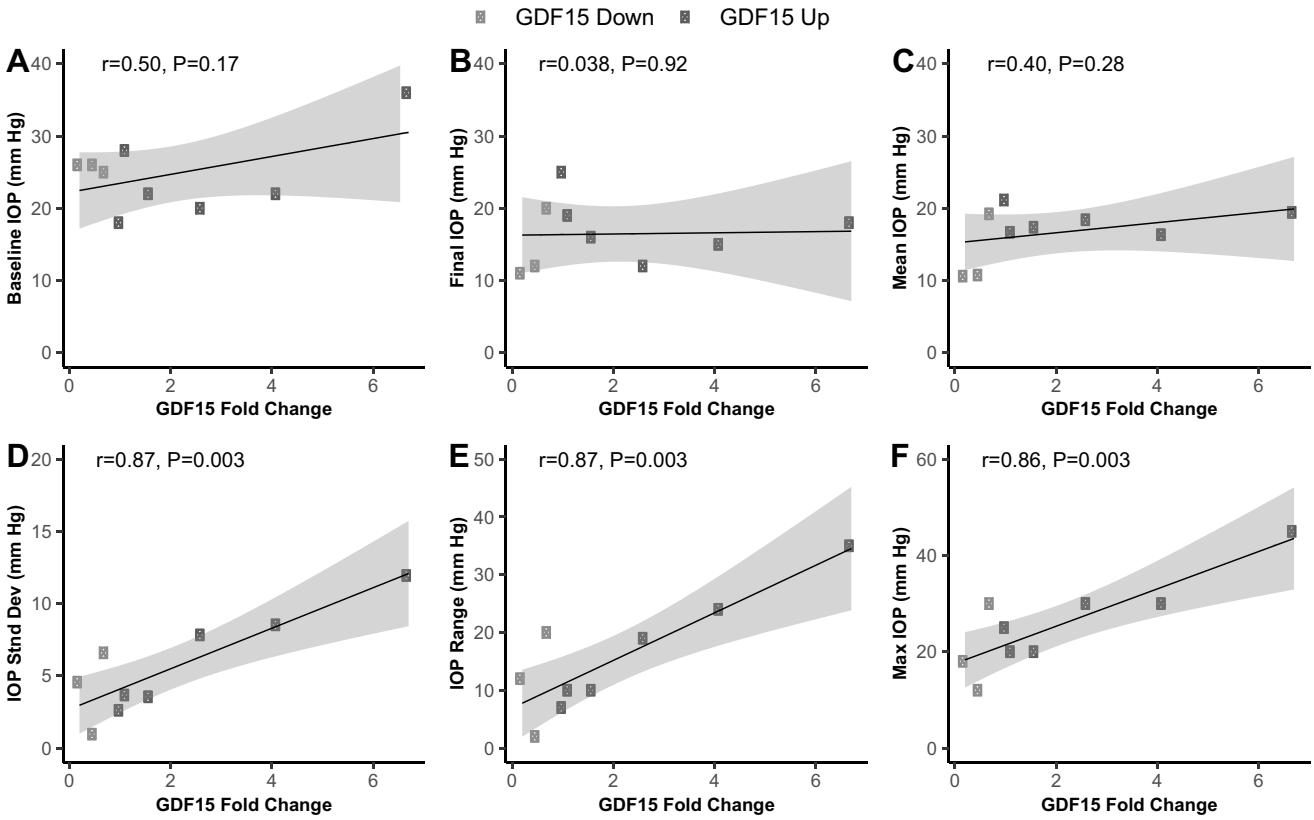

Figure 3. Aqueous humor Growth Differentiation Factor 15 (GDF15) fold change from baseline to six-month follow-up was not correlated with baseline intraocular pressure (IOP; A), final IOP (B), or mean IOP (C). In contrast, there was a strong correlation between GDF15 fold change and IOP standard deviation (stnd dev; D), IOP range (E), and maximum (max) IOP (F). *r* = Pearson correlation coefficients. Similar significance levels were found with non-parametric Kendall rank correlation coefficients. Shaded regions indicate 95% confidence interval bands. Circles denote patients who received the Ahmed® glaucoma valve; squares denote patients who received the Molteno® glaucoma implant.

obtained during cataract or glaucoma surgery. It is important to note that it is possible to collect AH in the outpatient setting. This procedure has minimal risks when performed by an experienced practitioner and was well tolerated by participants in this study. Although it is somewhat invasive, we propose that the ability to quantitatively assess RGC health may outweigh any risks associated with such as a procedure.

Resource Availability

The data analyzed in this study are available from the corresponding author on reasonable request.

Financial Support and Sponsorship

None.

Conflicts of Interest

There are no conflicts of interest.

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Original Article

Intraocular Injection of Stivant® (A Biosimilar to Bevacizumab): A Case Series

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Abstract

Purpose: To report the results of intravitreal injection of a bevacizumab biosimilar called Stivant®.
Methods: This prospective interventional case series was conducted on eyes with neovascular age-related macular degeneration (nAMD), retinal vein occlusion (RVO), and diabetic macular edema (DME). Stivant® was injected in three consecutive months and changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were measured at baseline and monthly up to one month after the third injection.
Results: Three hundred and eighty-five eyes with DME (234 eyes, 61%), nAMD (87 eyes, 22%), and macular edema secondary to RVO (64 eyes, 17%) were enrolled. The mean ± standard deviation age of the patients was 61.7 ± 7.20 years. The mean BCVA and CMT changed from 0.63 ± 0.3 to 0.51 ± 0.3 LogMAR (P = 0.12) and from 420.4 ± 47.3µm at baseline to 316.7 ± 50.6 µm (P < 0.001) in the DME group; from 0.79 ± 0.3 to 0.68 ± 0.3 LogMAR (P = 0.19) and from 376.1 ± 31.7 µm to 303 ± 31.3 µm (P = 0.019) in the nAMD group; and from 0.81 ± 0.4 to 0.63 ± 0.4 LogMAR (P = 0.05) and from 424.21 ± 18 µm to 303.4 ± 18.8 µm (P < 0.001) in the RVO group, respectively.
Conclusion: Our limited experience showed that the intravitreal injection of Stivant® was well tolerated. Although the results of this case series showed relative improvement in CMT one month after the last injection of Stivant®, BCVA improvement was statistically significant only in the RVO group. This would be essential to design a randomized clinical trial to evaluate the non-inferiority of Stivant® in comparison to bevacizumab.

Keywords: Stivant®; Bevacizumab; Anti-VEGFs; Anti-vascular Endothelial Growth Factors; Diabetic Macular Edema; Retinal Vein Occlusion; Neovascular Age-related Macular Degeneration

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INTRODUCTION

Introduction of anti-VEGFs has revolutionized the management of numerous retinal diseases over the past decade. They turned out to be

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the first-line treatment for diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion (RVO)-associated macular edema. Among various anti-VEGF drugs, the off-label intravitreal injection of bevacizumab [Avastin; Genentech/Roche /Basel, Switzerland] as a less expensive and effective alternative is the preferred choice in many countries[1].

Results of clinical trials such as CATT (Comparison of AMD Treatments Trials), MANTA (Multicentre Anti-VEGF Trial in Austria), IVAN (The Inhibition of VEGF in Age-related choroidal Neovascularization), LUCAS (Lucentis Compared to Avastin Study), and GEFAL (Groupe d'Etude Français Avastin versus Lucentis) showed the noninferiority of bevacizumab in comparison to ranibizumab with the same safety profile[2–6]. Besides, the 20 times lower cost of bevacizumab compared to ranibizumab and aflibercept makes this agent the most common anti-VEGFs used for intravitreal injection[7].

The World Health Organization (WHO) defines biosimilar drugs as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product. Biosimilars have the potential to reduce the healthcare costs relative to reference biologics, thereby increasing the treatment access [8–10]. Stivant® (CinnaGen Co., Iran) has been developed as a biosimilar to Avastin®. Both Stivant® and the reference product are humanized monoclonal antibodies of the IgG1 subclass. Safety of this product has already been shown during an animal study conducted by our team on New Zealand albino rabbits. Intravitreal injection of 2.5 mg Stivant® did not show any adverse effect on retinal function evaluated by electroretinography (ERG). Additionally, histologic examination of the enucleated globes did not reveal any visible histopathologic changes at the cellular level[8].

Herein, we aimed to share our experience with visual and anatomical outcomes of intravitreal injection of Stivant® in a case series.

METHODS

This prospective interventional case series was approved by the Institutional Review Board of Tehran University of Medical Sciences. Written informed consent was obtained from participants before enrollment. Patients with neovascular AMD (nAMD), DME, and macular edema due to RVO were recruited from September 2018 to February 2019 at Farabi Eye Hospital, Tehran, Iran. They were either treatment-naïve or had not receive the last intravitreal injection during the past six months.

The exclusion criteria of the study included previous vitrectomy, signs of any ocular infection, history of cerebrovascular accident or myocardial infarction, pregnancy, or breastfeeding. All patients were scheduled for three monthly injections of Stivant®.

Complete ocular examinations were performed by ophthalmologists and included measurement of best-corrected visual acuity (BCVA) with the Snellen chart being converted into LogMAR, applanation tonometry, slit-lamp biomicroscopy of the anterior and posterior segments, and indirect ophthalmoscopy at baseline and on days 1, 7, and 30 after each injection. Spectral-domain optical coherence tomography (SD-OCT) (RTVue-XR; Optovue, Inc., Fremont, CA, USA) imaging was obtained at baseline and 30 days after each injection for all patients.

Parameters for safety included severe inflammation or endophthalmitis and IOP > 21 mm Hg, retinal hemorrhages, retinal vasculitis, and retinal necrosis or detachment within three months post-injection. Systemic evaluations at baseline and on days 1, 7, and 30 included a detailed medical history during which patients were asked about current medications and any systemic adverse events (AEs), thromboembolic or neurological issues and measurement of arterial blood pressure. Primary outcome measures were changes in CMT and BCVA. Secondary outcome measures comprised any ocular or systemic AEs.

Intravitreal Injection

Stivant® is manufactured in a vial with a concentration of 25 mg/ml identical to the reference product (Avastin). Intravitreal injections were performed in the operating room under the sterile situation. Topical anesthetic drops were given first and then a lid speculum was inserted. After the application of povidone iodine 5% into the conjunctival sac for about 3 min, intravitreal injection of 1.25 mg/ 0.05 ml Stivant® was performed with a 29-gauge needle (1 ml tuberculin syringes; DispoVan) through the pars

plana 4 mm and 3.5 mm posterior to the limbus in phakic and pseudophakic eyes, respectively. The needle was carefully removed using a sterile cotton applicator to prevent reflux. Pre-injection topical antibiotics were not ordered, but all patients received topical chloramphenicol 0.5% four times a day for five days after the injection.

Statistical Analysis

Data were entered into a Microsoft Excel sheet and analyzed using the SPSS version 22 software (IBM). Categorical data were represented in the form of frequencies and proportions. Chi-square was used as the test of significance. Continuous variables were summarized by count, mean, standard deviation, median, and minimum and maximum. BCVA and CMT data were analyzed using two-tailed paired *t*-tests. $P \leq 0.05$ was considered statistically significant.

RESULTS

Three hundred and eighty-five eyes of 351 patients with DME (234 eyes, 61%), nAMD (87 eyes, 22%), and macular edema secondary to RVO (64 eyes, 17%) were enrolled. Intravitreal injection of Stivant® from separate glass vials was performed in both eyes of 34 patients with bilateral DME. The mean age of the patients was 61.7 ± 7.20 years. Out of the 385 injections, 212 (55.1%) were performed in male patients. Of the 385 eyes, 197 and 188 were phakic and pseudophakic, respectively.

BCVA Findings

The mean BCVA improved from 0.67 ± 0.41 LogMAR at baseline to 0.57 ± 0.37 LogMAR one month after the last injection (P = 0. 10). The mean BCVA improved from 0.63 ± 0.3 to 0.51 ± 0.3 LogMAR (P = 0.12) in the DME group; from 0.79 ± 0.3 to 0.68 ± 0.3 LogMAR (P = 0.19) in the nAMD group; and from 0.81 ± 0.4 to 0.63 ± 0.4 LogMAR (P = 0.05) in the RVO group [Figure 1].

Central Macular Thickness Findings

The mean CMT in all groups improved consistently from baseline through consequent injections. Although there was a trend in decreasing CMT after the first injection, the amount of change was not statistically significant until the third injection. The mean CMT of 425 ± 54.9 µm at baseline decreased to 312.20 ± 40.81 µm one month after the last intravitreal injection ($P < 0.001$) in all groups. In the DME group, the mean thickness decreased from 420.4 ± 47.3 µm at baseline to 316.7 ± 50.6 µm ($P < 0.001$) one month after the last intravitreal injection and from 376.1 ± 31.7 µm to 303 ± 31.3 µm (P = 0.019) in the nAMD group and from 424.21 ± 18 µm to 303.4 ± 18.8 µm ($P < 0.001$) in the RVO group [Figures 2 and 3].

Adverse Events (AEs)

There was no reported drug-related blurred vision and/or ocular pain at any of the follow-up visits. None of the eyes developed intraocular inflammation, endophthalmitis, corneal edema, cataract, vitritis, retinal detachment, or optic atrophy. Vitreous hemorrhage was reported in a diabetic patient one day after injection, which resolved three weeks later. None of the patients experienced moderate or severe vision loss (>0.3 LogMAR). The mean IOP at day 30 was 16.1 ± 3.0 mmHg. No systemic or serious AEs were reported.

DISCUSSION

In the current case series, we showed the relative safety of intravitreal injection of a bevacizumab biosimilar (Stivant®) in eyes with different indications for anti-VEGF therapy.

Although the short-term results in the present study showed statistically significant improvement in terms of CMT reduction following intravitreal Stivant® injection in all three groups, the mean BCVA improvement reached statistical significance only in the RVO group. To demonstrate the substitutability of Stivant® as a biosimilar of Avastin, there is a need to design a randomized clinical trial (RCT) with an appropriate sample size.

We previously disclosed the safety of Stivant® during an animal study. This biosimilar did not show histopathologic changes at the cellular level after being injected into the eyes of albino rabbits evaluated by clinical examinations, ERG, and histopathological assessment.[8]

Biosimilars which are produced by modified cellular processes are identical to their reference biologic agents in terms of structure and active substance, although some minor variations are

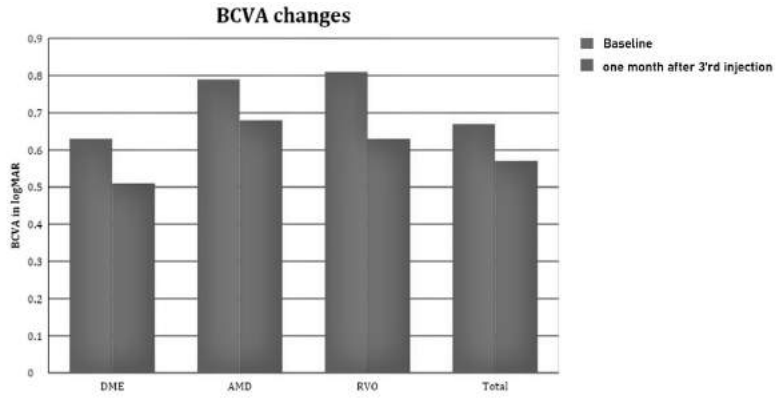

Figure 1. Mean BCVA (LogMAR) at baseline and one month after the third Stivant® injection. (*P*-value = 0.12, 0.19, 0.05, and 0.10 in the DME, wet-type AMD, RVO, and in all patients, respectively).

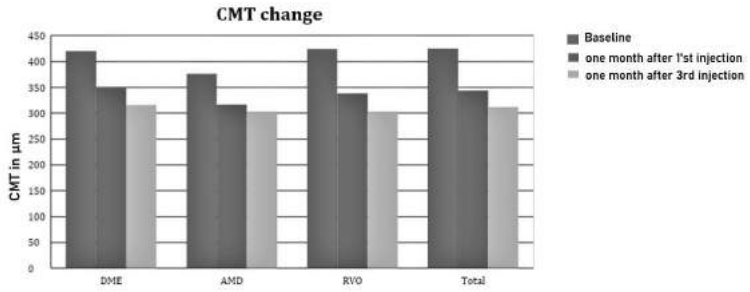

Figure 2. Central macular thickness (CMT) changes. Mean CMT ± SE (µm) at baseline and one month after the first and third Stivant® injection in the DME, AMD, RVO, and in all patients.

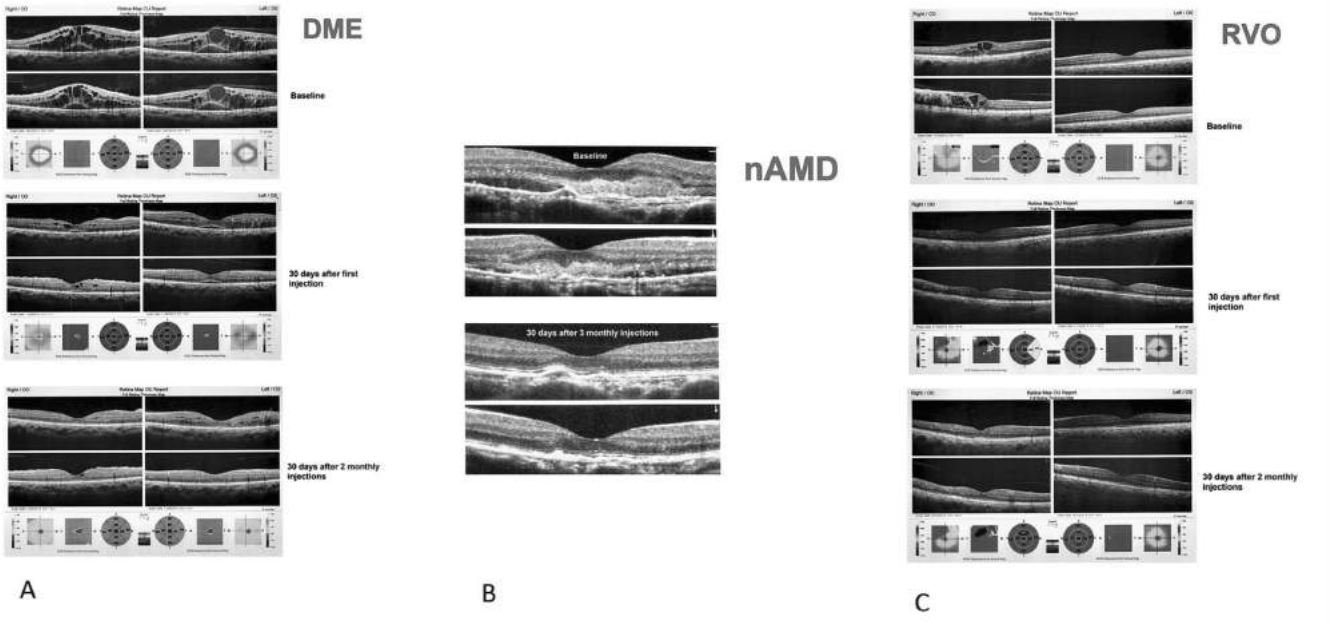

Figure 3. Response to Stivant® injections; samples from each subgroup (DME, nAMD, RVO) under study (A–C).

inevitable. Therefore, biosimilars are the end products similar to the original molecule with minor non-significant differences.[9–12]

In February 2015, Razumab® (Intas Pharmaceuticals, Ahmedabad, India), the first biosimilar to ranibizumab, was approved by the drug controller general of India for the treatment of nAMD, DME, RVO-associated macular edema, and myopic choroidal neovascularization. In a prospective study, the safety and efficacy of Razumab® was demonstrated in Indian patients with retinal vascular diseases including RVO.[13, 14] Afterward, Warudkar et al showed the safety and efficacy of intravitreal injection of Zybev (Cadila Healthcare, India) as a bevacizumab biosimilar for macular edema secondary to retinal vascular diseases.[15] As the patent of Avastin has recently expired, it is speculated that its biosimilars will soon grow in number.[10, 11]

Biosimilar production is >25% cheaper than that of the reference drug.[10, 11] As a result, more patients, especially in developing countries, can adhere to their treatment protocols and sustain their vision.

With the increasing production of biosimilar drugs in different countries and lower costs of these drugs compared to reference biologics, the widespread usage of these drugs requires special attention of healthcare systems to evaluate them from several aspects, including pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy in comparison to the reference drugs.[11]

While the main focus of the reference drug producer is to display safety and efficacy in large clinical trials, biosimilar expansion mainly relies on thorough studies to approve that the product is indistinguishable from reference drug in terms of construction, synthesis, and in vitro activity. As a minimum, one clinical investigation is required to compare the pharmacokinetics between a reference and biosimilar drug and at least one adequately large randomized controlled trial to exhibit the clinical equality.[9–11]

Safety and efficacy equivalency of the biosimilar drugs to the reference drug concerning pharmacokinetic, pharmacodynamic, and immunogenic properties must be confirmed through well-designed clinical trials. If the results of these trials are satisfactory and a biosimilar drug is approved for one indication, all other indications, for which the reference product is approved, are accepted, provided there is appropriate scientific justification. In general, patients are expected to be able to shift from a biosimilar to a reference product and vice versa without a drug efficacy lapse or increased risk.[9, 10]

Recently, the US Food and Drug Administration (FDA) gave directions to address the extra administrative requirements that biosimilars need to be endorsed as compatible drugs, and has recommended patrons to conduct at least one switching investigation to exhibit that the biosimilar and the reference drug can be securely substituted without loss of efficacy. Interestingly, in the European Union (EU), the European Medicines Agency (EMA) has not assigned biosimilars as interchangeable substitution of a reference medicine, leaving the choice to national authorities.[10]

As mentioned previously, this study is just a case series of patients and our findings cannot replace a well-designed, controlled RCT to show the equivalency of Stivant® with the reference drug. The other limitations of our study are the short-term follow-up of four months and the lack of data on metabolic profiles such as HbA1C and blood pressure of enrolled diabetic patients.

In conclusion, our limited experience showed that the intravitreal injection of Stivant® was well tolerated over four months. Although the results of this case series showed relative improvement in CMT one month after the last injection of Stivant®, the mean BCVA improvement was statistically significant only in the RVO group. To evaluate the non-inferiority, safety, and efficacy of Stivant® in comparison to the reference drug, it is essential to design a randomized clinical trial.

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Conflicts of Interest

None of the authors have any proprietary interests or conflicts of interest related to this study.

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Original Article

Effects of Oral Vitamin D Supplement Therapy on Clinical Outcomes of Intravitreal Bevacizumab in Diabetic Macular Edema

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Abstract

Purpose: To assess the effects of oral vitamin D supplement therapy on clinical outcomes of intravitreal bevacizumab (IVB) injections in patients with diabetic macular edema (DME).
Method: Seventy-one patients with center-involving DME received IVB injections three times monthly. Cases with serum 25-hydroxyvitamin D (25(OH)D) levels <30 ng/ml were divided into treatment and control groups. The treatment group received 50000 IU of oral vitamin D once a week for eight weeks. One month after the third IVB injection, changes in the best-corrected visual acuity (BCVA) and central macular thickness (CMT) were analyzed for each group.
Results: Thirty-seven patients had sufficient levels of 25 (OH) D, while 34 patients had insufficient levels. Nineteen cases with deficient levels of 25(OH)D were treated with oral vitamin D, while 15 patients were assigned to the control group. The mean of serum 25(OH)D in patients was 27.9 ng/ml [mean 20.3 ± 5.4 and 17.3 ± 5.4 ng/ml in control and treatment groups, respectively (P = 0.231)]. After three IVB injections, BCVA improved significantly in each group, but the difference between the study groups was not statistically significant. CMT decreased significantly in all the groups. The mean CMT reduction was more prominent in the vitamin D-treated group, but the difference between groups did not reach statistical significance (P = 0.29).
Conclusion: In DME patients with vitamin D deficiency, vitamin D supplement therapy had some beneficial effects on CMT reduction following three injections of IVB; nevertheless, these effects were not statistically significant. Definite conclusion needs further prospective studies with a larger sample size.

Keywords: 25-Hydroxyvitamin D; Insufficiency; Diabetic Macular Edema; Intravitreal Bevacizumab

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INTRODUCTION

Diabetic macular edema (DME) may develop in diabetic patients, independent of the severity

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of diabetic retinopathy (DR).[1] DME is the main cause of decreased vision in diabetic patients.[1] Elevated levels of various inflammatory and angiogenic factors lead to serious damage of retinal vascular endothelial cells, and the consequent impairment of blood–retinal barrier (BRB) causes fluid accumulation in the retinal tissue.[2]

Vitamin D is a well-known endocrine secosteroid which plays an essential role in many physiologic processes, including the control of cellular apoptosis and differentiation, as well as angiogenesis and metastasis potential of human cancer cells.[3–6] Various cardiovascular, infectious, and autoimmune diseases have been revealed to be linked with vitamin D deficiency.[7]

Both the vitamin D activator enzyme (1-α-hydroxylase) and its receptor have been found in the retina,[8, 9] suggesting that 25(OH)D abnormal levels may participate in the development and progression of various retinal disorders, including DR. Deficient serum 25(OH)D levels have been shown to be correlated with more advanced DR and its vision-threatening outcomes.[10, 11]

In this study, we measured the serum vitamin D levels in patients scheduled to receive intravitreal bevacizumab (IVB) for DME. We investigated the influence of oral vitamin D supplement therapy on the outcomes of IVB injections in these patients.

METHODS

The current prospective comparative case series study was carried out between March 2017 and August 2018. The protocol was approved by the Ethics Committee of the Ophthalmic Research Center at the Shahid Beheshti University of Medical Sciences and followed the Declaration of Helsinki. A written consent was obtained from all patients.

One eye from each patient was enrolled in the study. A diagnosis of center-involving DME was made if the central macular thickness (CMT) (within central 1-mm of macula) was >300 μm on optical coherence tomography (OCT) image (Spectralis OCT; Heidelberg Engineering, Vista, CA). Subjects were eligible for enrolment if BCVA was between 20⁄40 and 20/320 according to the Snellen chart in the eye enrolled in the study. The exclusion criteria were history of intravitreal anti-VEGF injections in the last three months of enrolment, history of intraocular surgery other than uncomplicated cataract surgery, patients with proliferative DR, retinal vascular occlusions, glaucoma, a creatinine (Cr) level > 3 mg/dl, thyroid and parathyroid diseases, liver disease or any other problem of vitamin D absorption, recent use of supplements containing vitamin D or 25(OH)D, use of medications with known effect on serum 25(OH)D levels such as anticonvulsants and corticosteroids, and serum 25(OH)D level ≤ 10 ng/ml.

All patients were scheduled to receive IVB (Avastin®, Genentech/Roche, CA, USA) three times monthly. All subjects underwent intravitreal injections at the Torfeh Eye Hospital. Ophthalmologists who performed the injections were masked to the groups. The study was performed during a single season to avoid variations in serum vitamin D levels due to seasonal exposures.

Before enrolment, all patients underwent complete ophthalmic examination. Parameters including age, sex, BCVA, and CMT were measured for each subject. On the day of first injection, venous blood specimen was analyzed for 25(OH)D, Cr, and HbA1c levels. Patients with >30 ng/ml of 25-hydroxyvitamin D (25(OH)D) were considered as vitamin D-sufficient group. Patients with <30 ng/ml were enrolled in the control group. The subjects were assigned to treatment groups on a random basis without considering the 25(OH)D levels. Thus, we had three study groups: group 1 (vitamin D-sufficient group with serum vitamin D ≥ 30 ng/ml), group 2 (vitamin D-deficiency group treated with oral vitamin D supplement), and group 3 (vitamin D-deficiency control group). The treatment group received a pearl of vitamin D3 (D-Vigel 50000 IU, Daana Pharmaceutical Company, Iran) once a week for eight consecutive weeks during the first two months of the IVB treatment period. Fundus examination and OCT imaging were repeated before any procedure.

Visual acuity measurements were obtained through Snellen chart examination by a trained optometrist who was masked as to which group the patients were assigned to, and were converted to LogMAR values. Severity of DR was determined by a single ophthalmologist using three field fundus photographs (optic disc centered, fovea centered, and centered on temporal edge of the macula), and was categorized according to the International DR Severity Scale.[12] Ophthalmic evaluations were repeated one month after the

third intravitreal injection. The mean changes in BCVA and CMT from baseline to one month after the third injection were measured as primary and secondary outcomes, respectively. After the completion of the study protocol, patients of the control group were also treated with oral vitamin D supplement.

To present data, mean and standard deviation were used. *T*-test was used for comparing serum vitamin D and HbA1c between the groups, and the correlation between HbA1c and vitamin D levels was evaluated by linear regression analysis. To evaluate the role of treatment on LogMAR and CMT changes, paired *t*-test analysis was used. The differences were considered as significant if *p*-value was < 0.05 (Figure 1). Finally, to determine the adequacy of the sample size and the power of the study, a post-hoc analysis was performed.

RESULTS

Eighty-three patients participated in the study. Four patients were excluded due to urgent need for supplement therapy (vitamin D level < 10 ng/ml). Eight patients (one patient from treatment group, five patients from control group, and two patients from sufficient group) did not complete the study. Out of the 71 subjects analyzed at the end of study, 37 patients had sufficient levels of 25(OH)D, 19 had insufficient 25(OH)D and were treated with oral vitamin D supplement (treatment group), and 15 cases with insufficient 25(OH)D levels were enrolled as the control group. Demographic characteristics and baseline parameters are summarized in Table 1. The study groups were matched in terms of age, sex, and severity of DR (Table 1).

The average HbA1c levels in the sufficient ($n = 37$) and the insufficient ($n = 34$) groups were 7.3% and 8.2%, respectively ($P < 0.05$, Figure 1a). The difference of HbA1c levels between the treatment and the control groups was not statistically significant ($P > 0.05$, 95% CI).

The mean serum 25(OH)D level was 27.9 ng/ml and it did not show any statistical correlation with patients' sex ($P = 0.653$). Regression analysis showed that serum 25(OH)D levels had negative correlation with the HbA1c levels (Pearson's correlation coefficient = –0.032) in all the patients. The *P*-value for the correlation was 0.007, showing a significant relationship (Figure 2).

The mean levels of serum 25(OH)D were 36.5 ± 6.7, 17.3 ± 5.4, and 20.3 ± 5.4 ng/ml in the sufficient group, the insufficient treatment group, and the insufficient control group, respectively (Figure 1b). The mean 25(OH)D level was significantly higher in the sufficient group, while the difference between the control and the treatment groups was not statistically significant ($P = 0.231$, 95% CI) (Table 1).

The mean BCVA values at the baseline were 0.51 ± 0.28, 0.48 ± 0.32, and 0.58 ± 0.25 LogMAR in the sufficient group, the insufficient treatment group, and the insufficient control group, respectively ($P > 0.05$, 95% CI). One month after the third IVB injection, BCVA improved significantly in all the study groups. The mean changes in BCVA were -0.13 ± 0.12, -0.15 ± 0.11, and -0.16 ± 0.17 LogMAR in the sufficient group, the insufficient treatment group, and the insufficient control group, respectively ($P = 0.66$). The mean changes in BCVA were not significantly different between the study groups (Table 2 and Figure 3a).

The mean CMT values were 517 ± 112 µm, 514 ± 105 µm, and 509 ± 74 µm in the sufficient group, the insufficient treatment group, and the insufficient control group, respectively ($P = 0.97$, 95% CI). One month after the third IVB injection, the mean CMT decreased significantly in all the study groups. The mean CMT changes were -100 ± 97, -131 ± 67, and -91 ± 53 µm in the sufficient group, the insufficient treatment group, and the insufficient control group, respectively ($P = 0.29$). Although the mean CMT decreased more in patients who received oral vitamin D supplement (–131 µm vs –100 µm and –91 µm), the difference was not statistically significant ($P = 0.29$, Table 2 and Figure 3b).

Post-hoc analysis showed that the sample size should be 41 in each group to find a significant difference (50 microns) in the changes of CMT to achieve the study power of 95%. However, the present study had a power of 60%. Endophthalmitis or significant ocular or systemic complications were not observed.

DISCUSSION

We observed that vitamin D supplement therapy in the subset of diabetic patients with DME and insufficient levels of vitamin D could not improve the outcome of IVB therapy. According to our knowledge, this study was the first to investigate the effect of oral vitamin D supplement therapy on clinical outcomes of IVB injection in DME.

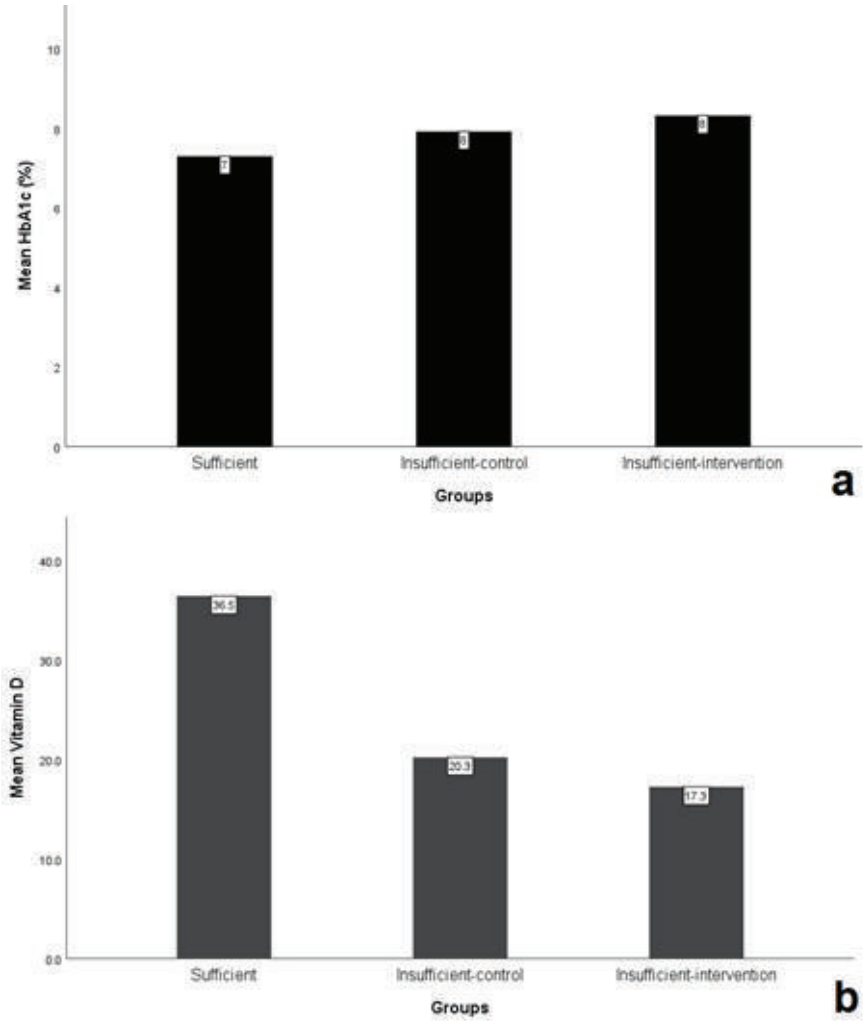

Figure 1. The mean HbA1c (a) and vitamin D levels (b) in different study groups.

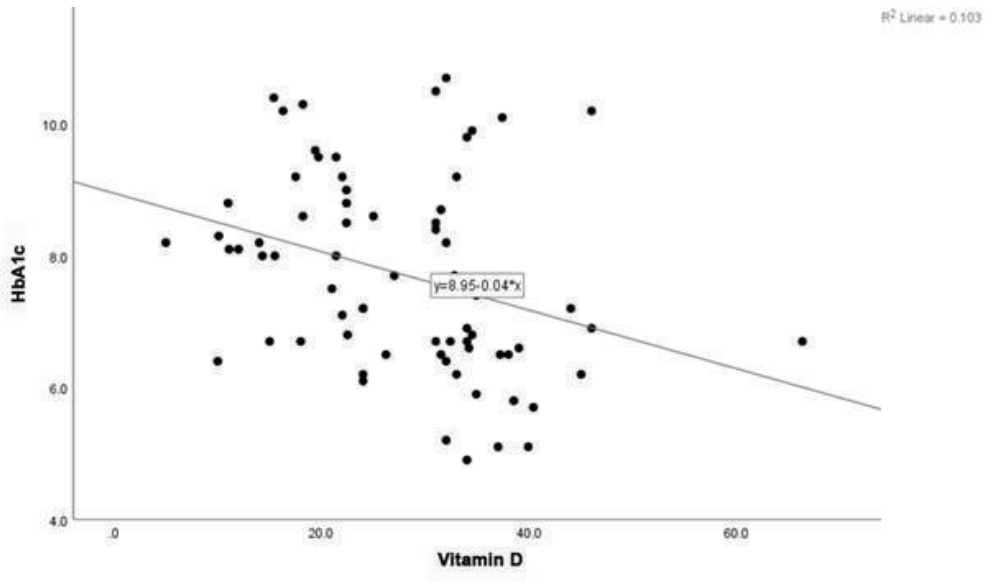

Figure 2. The correlation chart of vitamin D and HbA1c levels.

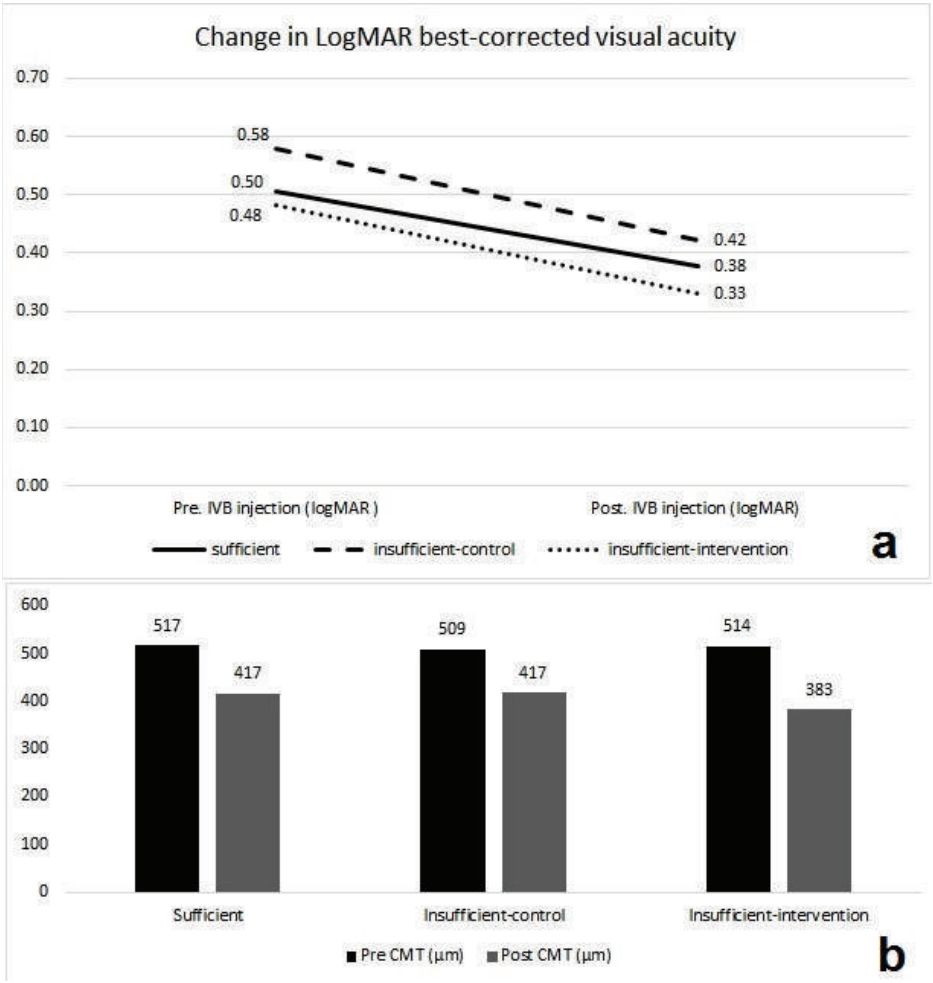

Figure 3. Changes in visual acuity (a) and central retinal thickness (b) following IVB therapy. CMT, central macular thickness; LogMAR, logarithm of minimal angel resolution; IVB, intravitreal bevacizumab

There is still a degree of uncertainty about the influence of serum vitamin D in occurrence, progression, and prognosis of DR. The controversy begins from the concept that serum vitamin D deficiency may not be correlated with a concurrent ocular deprivation. It is believed that the eye can produce vitamin D through exposure to ultraviolet light, and the BRB can limit the transmission of vitamin D from blood to the eyes.[13, 14] Accordingly, some authors have suggested that intraocular 25(OH)D levels may not depend on systemic 25(OH)D levels.[1]

It has also been reported that the 1,25-dihydroxycholecalciferol can upregulate the expression of the VEGFs; it has been shown that the regulation of VEGF promoter by vitamin D receptor increases the secretion of VEGFs in vascular smooth muscles.[15, 16] A similar effect has not been established in retinal cells, however, this finding can hypothesize a correlation between high ocular vitamin D levels and high concentration of ocular VEGFs.[1]

Previous studies have revealed paradoxical results about the relationship between the severity of DR and serum 25(OH)D levels. Some authors have reported an inverse relationship,[10, 11, 17–19] while others have not shown such a correlation.[20, 21] A meta-analysis on the topic reported that those patients with DM type 2 and vitamin D deficiency have a higher risk of DR development compared to subjects with adequate levels of the vitamin.[22] On the other hand, a recent study performed by Kim et al reported that patients with DME had a greater aqueous humor amounts of vitamin D than the patients without DME.[1] It should also be considered that studies on vitamin D levels encounter some challenges such as different cultural backgrounds as well as different

Table 1. Demographic and clinical features

Factors	Levels	Total	Groups				*P*-value
			Sufficient	Insufficient-control	Insufficient-treatment	Insufficient-control and Insufficient-treatment	
Age	Mean ± SD	63 ± 8	65 ± 6	59 ± 8	64 ± 9	62 ± 9	0.076
	Median (range)	64 (40,84)	64 (52,84)	59 (45,74)	64 (40,84)	63 (40,84)	
Sex	Male	37 (52.1%)	18 (48.6%)	7 (46.7%)	12 (63.2%)	19 (55.9%)	0.518
	Female	34 (47.9%)	19 (51.4%)	8 (53.3%)	7 (36.8%)	15 (44.1%)	
Eye	OD	37 (52.1%)	22 (59.5%)	5 (33.3%)	10 (52.6%)	15 (44.1%)	0.252
	OS	34 (47.9%)	15 (40.5%)	10 (66.7%)	9 (47.4%)	19 (55.9%)	
DR	NPDR	32 (45.1%)	19 (51.4%)	5 (33.3%)	8 (42.1%)	13 (38.2%)	0.511
	PDR	39 (54.9%)	18 (48.6%)	10 (66.7%)	11 (57.9%)	21 (61.8%)	
HbA1c	Mean ± SD	7.7 ± 1.5	7.3 ± 1.6	7.9 ± 1.3	8.3 ± 1.1	8.2 ± 1.2	0.043
	Median (range)	7.6 (4.9,10.7)	6.7 (4.9,10.7)	8.2 (6.1,9.6)	8.1 (6.7,10.4)	8.1 (6.1,10.4)	
Vitamin D (µg)	Mean ± SD	27.9 ± 10.8	36.5 ± 6.7	20.3 ± 5	17.3 ± 5.4	18.6 ± 5.4	<0.001
	Median (range)	31 (5,66.3)	34.2 (31,66.3)	22 (10,26.2)	18 (5,27)	19.5 (5,27)	

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; OD, right eye; OS, left eye; PDR, proliferative diabetic retinopathy; HbA1c, hemoglobin A1c; SD, standard deviation

Table 2. Best-corrected visual acuity changes after three intravitreal bevacizumab injections

BCVA (LogMAR)	Total	Groups			*P*-value
		Sufficient	Insufficient-control	Insufficient-treatment	
Baseline	0.51 ± 0.28	0.5 ± 0.28	0.58 ± 0.25	0.48 ± 0.32	0.587
Final F/U	0.37 ± 0.24	0.38 ± 0.24	0.42 ± 0.24	0.33 ± 0.23	0.554
Change	−0.14 ± 0.13	−0.13 ± 0.12	−0.16 ± 0.17	−0.15 ± 0.11	0.659
P-value		<0.001	0.002	<0.001	
CMT (µm)					
Baseline	514 ± 102	517 ± 112	509 ± 74	514 ± 105	0.97
Final F/U	408 ± 96	417 ± 111	417 ± 61	383 ± 87	0.42
Change	−106± 83	−100± 97	−91± 53	−131± 68	0.29
P-value		<0.001	<0.001	<0.001	

BCVA, best-corrected visual acuity; F/U, follow-up; CMT, central macular thickness

clothing and diet styles. Vitamin D in the body can be supplied both from dietary sources and from synthesis in the skin. Accordingly, it is difficult to control the dietary, environmental, seasonal, and cultural factors, in addition to predict serum vitamin D levels through single measurement, which can cause inconclusive results.

Since the prior studies have not resulted in an exact conclusion about vitamin D and its role in DR, we investigated the treatment of DME with an anti-VEGF agent, bevacizumab, in the presence of vitamin D deficiency. We also tested the role of concurrent vitamin D3 therapy in optimizing the IVB therapy for DME. We found that the concurrent vitamin D supplement therapy in this subset of patients did not significantly improve the outcomes of IVB in DME cases with vitamin D deficiency. Although improvement in

BCVA and decrease in CMT was more prominent in the treatment group, the difference between the control and the treatment groups was not statistically significant. Future studies on larger group of patients may reveal an association between vitamin D supplementation and improved outcomes of IVB injections in DME patients.

We found a negative correlation between HbA1c levels and serum 25(OH)D, implying that patients with 25(OH)D deficiency had a higher rate of uncontrolled hyperglycemia. This finding may be in accordance with prior reports regarding the correlation of vitamin D deficiency with poor glycemic control and DR severity.[22] It has been postulated that vitamin D may improve insulin secretion, stimulate insulin receptor, and improve glucose uptake in type 2 diabetes.[9, 23] According to these assumptions, vitamin D may improve insulin resistance. However, it should be proven in experimental studies.

A small sample size in addition to the lack of a control for those habits and restrictions which may affect vitamin D storage in the body are the main limitations of the present study. Although vitamin D deficiency was treated according to the standard protocol, effectiveness of vitamin D supplement therapy was not assessed at the end of the study. Short-term follow-up could also be considered as another limitation of the present study; however, longer follow-up was not possible due to the ethical issues.

In conclusion, we observed a negative correlation between HbA1c and 25(OH)D levels. Although vitamin D supplement therapy, added to IVB therapy, had some beneficial effects in terms of CMT reduction in DME patients with 25(OH)D deficiency, we could not find any statistically significant effect of the adjunctive therapy on the functional and anatomical outcomes of these patients. Further studies are required to investigate the effect of D3 supplement therapy on optimizing the treatment of patients with DR.

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None.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Original Article

Prognostic Factors Associated with Ocriplasmin Efficacy for the Treatment of Symptomatic Vitreomacular Adhesion and Full-thickness Macular Hole: Analysis from Four Studies

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Abstract

Purpose: To assess the effect of patient baseline characteristics on the efficacy of ocriplasmin treatment for symptomatic vitreomacular adhesion (VMA) with full-thickness macular hole (FTMH) from phase 3/4 studies.

Methods: Patients with symptomatic VMA and FTMH at baseline and receiving ocriplasmin treatment 125 μg were pooled from the MIVI-TRUST, OASIS, and ORBIT studies. Multivariable logistic regression analysis was used to evaluate whether patient baseline characteristics were predictors of having VMA resolution by Day 28 and FTMH closure by Month 6.

Results: Two hundred and seventy-four patients receiving ocriplasmin treatment were assessed. Overall, 22.6% (62/274) of the patients experienced both VMA resolution by Day 28 and non-surgical FTMH closure by Month 6. Patients with FTMH ≤250 µm at baseline had a significantly higher success rate compared to those with FTMH >400 µm (29.9% [41/137] vs 2.2% [1/48]; P = 0.009). In patients with VMA resolution by Day 28, both small FTMH size (P = 0.001) and FTMH width at RPE (P = 0.012) were significantly associated with a higher FTMH closure rate. Patients with VMA resolution had higher rates of FTMH closure. Previously identified baseline predictive factors, including age, lens status, or presence of epiretinal membrane (ERM) were not found to be predictive of both VMA release and FTMH closure.

Conclusion: The analysis revealed that FMTH ≤250 µm was the only factor predictive for achieving both pharmacological VMA resolution by Day 28 and nonsurgical FTMH closure by Month 6; neither lens status or presence of ERM, previously identified baseline characteristics favoring VMA resolution, showed statistically significant predictive power for both outcomes.

Keywords: Ocriplasmin; Full-thickness Macular Hole; Vitreomacular Adhesion; Symptomatic Vitreomacular Adhesion; Vitreomacular Traction; Vitreoretinal Interface

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INTRODUCTION

Aging of the eye often leads to separation between the posterior vitreous cortex and the internal limiting membrane, known as posterior vitreous detachment (PVD).[1, 2] This process may be affected by vitreomacular adhesion (VMA), or adherence of the vitreous cortex to the macula after partial detachment.[3–5] Symptomatic VMA (also referred to as vitreomacular traction) can occur if mechanical forces are large enough to cause anatomical changes to the macula.[6, 7] Effects resulting from symptomatic VMA may also lead to the development of a full-thickness macular hole (FTMH).[4] The occurrence of VMA and FTMH can lead to visual disturbances such as decreased visual acuity, photopsia, metamorphopsia, scotomas, and may result in irreversible vision loss if left untreated.[3, 4, 8–12]

Treatment options for symptomatic VMA include watchful waiting, vitrectomy, pneumatic vitreolysis, and pharmacological vitreolysis with ocriplasmin. Ocriplasmin was approved in the US in 2012 and the EU in 2013 based on the results of two pivotal phase 3 clinical trials (MIVI-TRUST) that established its efficacy and safety in patients with symptomatic VMA with or without an associated FTMH $\leq$400 μm.[13] An earlier post hoc analysis of the pivotal trials suggested that the efficacy of ocriplasmin may be increased by patient baseline characteristics, including younger age, phakic lens status, focal VMA, absence of epiretinal membrane (ERM), and presence of FTMH.[14] Subsequently, both prospective and retrospective studies ranging from 5 to 74 eyes were undertaken that assessed the effect of these baseline factors with respect to VMA release.[13, 15–32] VMA release rates in these studies ranged from 0% to 71%, with 14 of 18 studies showing higher efficacy than the pivotal phase 3 trial rate of 26.5% VMA release at Day 28.[13] A meta-analysis of these studies, which also included the phase 3 pivotal trials, confirmed that focal VMA, absence of ERM, phakic lens status, and younger age were all positive predictive factors for VMA release.[33]

The rate of FTMH closure for ocriplasmin-treated eyes was 40.6% in the pivotal clinical trials and 30.0% in the OASIS study.[13, 34] Although analysis of baseline predictive factors has resulted in real-world rates of VMA release higher than those in the pivotal phase 3 trials, multiple real-world studies have reported FTMH closure rates lower than those observed in these studies, suggesting that the predictive factors for FTMH closure may not be the same as those for VMA release and are not as well understood.[24, 28, 35] For instance, the absence of ERM did not have a clear association with FTMH closure in the MIVI-TRUST trials.[36] In addition, the predictive value of successful VMA release on FTMH closure remains unclear; there was no clear association between VMA release and FTMH closure in the MIVI-TRUST trials,[36] although a recent study showed a strong association between VMA release and FTMH closure.[37]

Although the baseline factors associated with VMA resolution and FTMH closure have been investigated individually, to our knowledge no study has assessed factors that may predict both VMA resolution and FTMH closure following ocriplasmin treatment. The current study aimed at assessing the baseline factors that may be predictive of both VMA release together with FTMH closure in patients treated with ocriplasmin in the completed phase 3/4 studies.

METHODS

Study Population

Patients diagnosed with both symptomatic VMA and FTMH at baseline and receiving treatment of ocriplasmin 125 μg were pooled from the MIVI-TRUST, OASIS, and ORBIT studies. MIVI-TRUST

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(NCT00781859 and NCT00798317) consisted of two phase 3, prospective, randomized, multicenter, double-blind, placebo-controlled clinical trials (TG-MV-006 and TG-MV-007) in which patients were randomized to receive a single intravitreal ocriplasmin (125 μg) or placebo injection.[13] OASIS (NCT01429441) was a phase 3b, randomized, multicenter, double-masked, sham-controlled clinical trial in which patients were randomized to receive a single intravitreal ocriplasmin 125 μg injection or sham treatment.[34] ORBIT (NCT02079883) was a phase 4, prospective, multicenter, observational study to assess a single intravitreal ocriplasmin injection of 125 μg.[38] Full details of individual study designs, treatment plans, and adherence to ethics practices have been published elsewhere.[13, 34, 38]

Baseline Demographics and Patient Characteristics

The following baseline demographic and ocular characteristics were evaluated in the study population based on availability across datasets: age (<65 years, ≥65 years), lens status (phakic, pseudophakic), ERM status (present, absent), ellipsoid zone (EZ) status (normal, abnormal), subretinal fluid (SRF) status (present, absent), BCVA (<65, 65–75, >75 ETDRS letters), diameter of VMA (≤1500 μm, >1500 μm), width of FTMH (≤250, >250–400, >400 μm), and width of FTMH at the retinal pigment epithelium (RPE) (≤600 μm, >600 μm) (Supporting Information Table S1).

For the MIVI-TRUST trials, the presence and size of VMA and FTMH status at baseline were assessed by a central reading center (CRC), using mandatory time-domain optical coherence tomography (TD-OCT) as required per protocol; additional spectral-domain (SD)-OCT readings if available were only used as supportive information for evaluation of individual cases.[13] FTMH was defined as a macular hole with bare/exposed RPE, with the largest of the minimum hole width measurements considered as the hole width based on macular thickness map (MTM) or fast macular thickness map (FMTM) scans. In the more recent OASIS study, the presence and size of VMA and FTMH status at baseline were assessed by a CRC using SD-OCT.[34] FTMH diameter was defined as the largest of the minimum hole width measurement. Although patients were enrolled in the OASIS trial based on favorable baseline characteristics,[14] determination of ocular characteristics differed between investigator and CRC assessment, resulting in inclusion of some patients despite their CRC assessment meeting exclusion criteria in retrospect (FTMH > 400 μm, presence or ERM).[34] In the ORBIT study, the presence of VMA and FTMH was determined by SD-OCT according to the treating physician before enrollment and reviewed independently by a CRC in retrospect. FTMH diameter was defined as the greatest width of the minimum distance between sides of the FTMH measured within the middle two thirds of the retina (not at surface and not at RPE) in any line of the 49-line volume scan. The review of the presence of VMA and FTMH by the CRC was performed post-treatment in all studies and was not used for treatment decisions.

EZ status was evaluated in the central macular region in all studies. SRF assessments were defined in each of the studies. In the MIVI-TRUST trials, SRF was a measure of the fluid beneath retina to other material perpendicular to Bruch's membrane at the foveal center from the retina to the RPE, not including fluid within the retinal layer (cysts) or fluid below the RPE. In the OASIS study, three foveal center point measurements were taken, including SRF, RPE elevation and/or subretinal hyper-reflective material (SHRM) such as choroidal neovascularization, and total retinal thickness. The total retinal thickness measurement included the RPE layer, RPE elevation, any SHRM, any SRF, and the retina at the foveal center. When a value was not reported for SRF or RPE elevation and/or SHRM, it was considered not present or ungradable. In the ORBIT study, SRF was considered present if it was identified in any line scan in the absence of FTMH.

Statistical Analysis

The integrated database included all patients who presented with symptomatic VMA and FTMH at baseline, were treated with ocriplasmin 125 μg, and had both a baseline assessment and at least one follow-up visit. Three different variables (i.e., treatment response) were considered: pharmacological resolution of VMA by Day 28 (VMAres), nonsurgical FTMH closure by Month 6 (MHclos), and combined success when experiencing both events (VMAres + MHclos). First,

Table 1. Patient demographics and ocular baseline characteristics in the four studies and the integrated dataset

Characteristic	MIVI-TRUST*(*N* = 106)	OASIS (*N* = *50)*	ORBIT(*N* = 118)	Integrated(*N* = 274)
Age (years)				
Mean (SD)	68.7 (7.4)	66.5 (6.3)	66.7 (7.3)	67.5 (7.2)
Median	69.0	65.5	66.0	67.0
Min, Max	48, 85	49, 79	45, 88	45, 88
Age group (years), *n* (%)				
<65 years	31 (29.2)	20 (40.0)	42 (35.6)	93 (33.9)
≥65 years	75 (70.8)	30 (60.0)	76 (64.4)	181 (66.1)
Sex, *n* (%)				
Male	22 (20.8)	10 (20.0)	28 (23.7)	60 (21.9)
Female	84 (79.2)	40 (80.0)	90 (76.3)	214 (78.1)
Race, *n* (%)				
White	99 (93.4)	46 (92.0)	105 (89.0)	250 (91.3)
Black or African American	3 (2.8)	4 (8.0)	9 (7.6)	16 (5.8)
Asian	2 (1.9)	0 (0)	3 (2.5)	5 (1.8)
Other	2 (1.9)	0 (0)	1 (0.9)	3 (1.1)
Lens status, *n* (%)				
Phakic	81 (76.4)	43 (86.0)	93 (78.8)	217 (79.2)
Pseudophakic	25 (23.6)	7 (14.0)	24 (20.3)	56 (20.4)
Aphakic	0 (0)	0 (0)	1 (0.9)	1 (0.4)
ERM status, *n* (%)				
Present	18 (17.0)	6 (12.0)	14 (11.9)	38 (13.9)
Absent	82 (77.3)	44 (88.0)	104 (88.1)	230 (83.9)
Missing	6 (5.7)	0 (0)	0 (0)	6 (2.2)
EZ status, *n* (%)				
Abnormal	0 (0)	49 (98.0)	116 (98.3)	165 (60.2)
Normal	0 (0)	1 (2.0)	2 (1.7)	3 (1.1)
Missing	106 (100)	0 (0)	0 (0)	106 (38.7)
SRF status, *n* (%)				
Present	77 (72.7)	49 (98.0)	0 (0)	126 (46.0)
Absent	26 (24.5)	1 (2.0)	118 (100)	145 (52.9)
Missing	3 (2.8)	0 (0)	0 (0)	3 (1.1)
BCVA (ETDRS letters), *n* (%)				
<65	89 (84.0)	37 (74.0)	96 (81.4)	222 (81.0)
65–75	16 (15.1)	12 (24.0)	19 (16.1)	47 (17.2)
>75	1 (0.9)	1 (2.0)	3 (2.5)	5 (1.8)
FTMH size, *n* (%)				
≤250 μm	48 (45.3)	23 (46.0)	66 (55.9)	137 (50.0)
>250–400 μm	38 (35.9)	17 (34.0)	33 (28.0)	88 (32.1)
>400 μm	19 (17.9)	10 (20.0)	19 (16.1)	48 (17.5)
Missing	1 (0.9)	0 (0)	0 (0)	1 (0.4)
VMA diameter, *n* (%)				
≤1500 μm	90 (84.9)	43 (86.0)	110 (93.2)	243 (88.7)
>1500 μm	3 (2.8)	2 (4.0)	1 (0.9)	6 (2.2)
Missing	13 (12.3)	5 (10.0)	7 (5.9)	25 (9.1)
FTMH width at RPE (μm)				
n	104	50	0	154
Mean (SD)	647.1 (283.8)	634.2 (320.8)	–	642.9 (295.4)
Median	611.0	596.0	–	611.0
Min, Max	113, 1572	164, 2120	–	113, 2120
FTMH width at RPE, *n* (%)				
≤600 μm	49 (46.2)	25 (50.0)	0 (0)	74 (27.0)
>600 μm	55 (51.9)	25 (50.0)	0 (0)	80 (29.2)
Missing	2 (1.9)	0 (0)	118 (100)	120 (43.8)

*MIVI-TRUST consisted of two phase 3 clinical trials (NCT00781859 and NCT00798317)
BCVA, best-corrected visual acuity; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; FTMH, full-thickness macular hole; RPE, retinal pigment epithelium; SD, standard deviation; SRF, subretinal fluid; VMA, vitreomacular traction

Table 2. Rates of VMA resolution and FTMH closure in the four studies and the integrated dataset

	MIVI-TRUST* *n* (%)	OASIS *n* (%)	ORBIT *n* (%)	Integrated *n* (%)
Number of patients	106	50	118	274
VMA resolution	53 (50.0)	27 (54.0)	74 (62.7)	154 (56.2)
FTMH closure	43 (40.6)	15 (30.0)	38 (32.2)	96 (35.0)
VMA resolution: Yes FTMH closure: Yes	24 (22.6)	8 (16.0)	30 (32.2)	62 (22.6)
VMA resolution: Yes FTMH closure: No	29 (27.4)	19 (38.0)	44 (37.3)	92 (33.6)
VMA resolution: No FTMH closure: Yes	19 (17.9)	7 (14.3)	8 (6.8)	34 (12.4)
VMA resolution: No FTMH closure: No	24 (22.6)	8 (16.0)	30 (25.4)	86 (31.4)

*MIVI-TRUST consisted of two phase 3 clinical trials (NCT00781859 and NCT00798317)
FTMH, full-thickness macular hole; VMA, vitreomacular adhesion

Table 3. Univariable logistic regression analysis for the effect of patient demographics and ocular baseline characteristics on VMA resolution by Day 28 and FTMH closure by Month 6 in the integrated dataset

		VMA resolution		FTMH closure		VMA resolution + FTMH closure	
Characteristic	**Status**	**Success (%)**	***P*-value**	**Success (%)**	***P*-value**	**Success (%)**	***P*-value**
Age	<65 years	65/93 (69.9)	0.0015	32/93 (34.4)	0.9783	22/93 (23.7)	0.735
	≥65 years	89/181 (49.2)		64/181 (35.4)		40/181 (22.1)	
Lens Status	Phakic	130/217 (59.9)	0.0129	71/217 (32.7)	0.1888	47/217 (21.7)	0.647
	Pseudophakic	23/56 (41.1)		24/56 (42.9)		14/56 (25.0)	
ERM status	Present	12/38 (31.6)	0.0028	13/38 (34.2)	0.7999	4/38 (10.5)	0.067
	Absent	137/230 (59.6)		81/230 (35.2)		56/230 (24.3)	
EZ status	Normal	1/3 (33.3)	0.3667	3/3 (100)	0.9852	1/3 (33.3)	0.645
	Abnormal	100/165 (60.6)		50/165 (30.3)		37/165 (22.4)	
SRF status	Present	67/126 (53.2)	0.2874	48/126 (38.1)	0.2327	28/126 (22.2)	0.124
	Absent	85/145 (58.6)		46/145 (31.7)		33/145 (22.8)	
BCVA (ETDRS letters)	<65	127/222 (57.2)	0.6215	71/222 (32.0)	0.0606	49/222 (22.1)	0.645
	65–75	25/47 (53.2)		22/47 (46.8)		13/47 (27.7)	
	>75	2/5 (40.0)		3/5 (60)		0/5 (0)	
VMA diameter	≤1500 µm	144/243 (59.3)	0.7324	87/243 (35.8)	0.8514	56/243 (23.0)	0.489
	>1500 µm	3/6 (50)		2/6 (33.3)		2/6 (33.3)	
FTMH size	≤250 µm	75/137 (54.7)	0.3412	67/137 (48.9)	<0.0001	41/137 (29.9)	0.009
	>250–400 µm	54/88 (61.4)		26/88 (29.6)		19/88 (21.6)	
	>400 µm	24/48 (50)		2/48 (4.2)		1/48 (2.2)	
FTMH width at RPE	≤600 µm	40/74 (54.1)	0.5185	38/74 (51.4)	0.0004	21/74 (28.4)	0.015
	>600 µm	39/80 (48.8)		19/80 (23.8)		10/80 (12.5)	

BCVA, best-corrected visual acuity; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; FTMH, full-thickness macular hole; RPE, retinal pigment epithelium; SRF, subretinal fluid; VMA, vitreomacular adhesion

Table 4. univariable logistic regression analysis for the effect of patient demographics and ocular baseline characteristics on FTMH closure by Month 6 for patients with VMA resolution by Day 28 in the integrated dataset

Patient Characteristic	Status	Success (%)	*P*-value
Age	<65 years	22/65 (33.8)	0.177
	≥65 years	49/89 (55.1)	
Lens Status	Phakic	47/130 (36.2)	0.027
	Pseudophakic	14/23 (60.9)	
ERM status	Present	4/12 (33.3)	0.619
	Absent	56/137 (40.9)	
EZ status	Normal	1/1 (100.0)	0.986
	Abnormal	37/100 (37.0)	
SRF status	Present	28/67 (41.8)	0.231
	Absent	33/85 (38.8)	
BCVA (ETDRS letters)	<65	49/127 (38.6)	0.434
	65–75	13/25 (52.0)	
	>75	2/2 (100.0)	
VMA diameter	≤1500 µm	56/144 (38.9)	0.311
	>1500 µm	2/3 (66.7)	
FTMH size	≤250 µm	41/75 (54.7)	0.001
	>250–400 µm	19/54 (35.2)	
	>400 µm	1/24 (4.2)	
FTMH Width at RPE	≤600 µm	21/40 (52.5)	0.012
	>600 µm	10/39 (25.6)	

BCVA, best-corrected visual acuity; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; FTMH, full-thickness macular hole; RPE, retinal pigment epithelium; SRF, subretinal fluid; VMA, vitreomacular adhesion

the effect of each patient baseline characteristic on success was evaluated separately in a univariable logistic regression model that also included study as a fixed-effects factor to accommodate for the clustering in the data due to combining data from different studies. Next, all patient baseline characteristics that were significant at the 5% significance level were included in a multivariable regression analysis to identify independent patient baseline characteristics that were significantly associated with treatment success. Additionally, the same analysis was performed for MHclos for those patients that experienced VMAres.

RESULTS

Demographics and Baseline Characteristics

A total of 274 patients were pooled from the MIVI-TRUST, OASIS, and ORBIT studies on the basis of having both symptomatic VMA and FTMH at baseline and having received a single intravitreal injection of ocriplasmin 125 μg. Demographics and ocular characteristics are shown in Table 1. Overall, the demographics and ocular characteristics were generally comparable in patients across the three datasets. The mean age of the patients was 67.5 years, with an age range of 45–88 years. Seventy-nine percent of the patients had phakic lens status. A majority (60.2%) of patients had EZ status categorized as abnormal, and 46.0% of patients had SRF present (Table 1).

VMA Resolution

An average of 56.2% (154/274) of eligible patients experienced VMA resolution by Day 28 (Table 2). The proportion of patients experiencing VMA resolution by Day 28 in this patient subpopulation

Supplemental Table 1. Availability of baseline characteristics and outcome measures in the ocriplasmin studies

	MIVI-TRUST	OASIS	ORBIT
Outcome measures			
Pharmacological VMA resolution at Day 28, post-resolution vitrectomy considered as a failure	Yes	Yes	No
Pharmacological VMA resolution at Day 28, post-resolution vitrectomy not considered as a failure	Yes	Yes	Yes
Non-surgical FTMH closure by end of study (post-closure vitrectomy not considered as a failure)	EOS (up to M6)	M6 EOS (up to M24)	M6 M12
Baseline characteristics			
Age (Years)	Available	Available	Available
Lens status	Phakic Pseudophakic	Phakic Pseudophakic	Phakic Pseudophakic Aphakic
ERM	Present Absent	Present Minimal Present Significant Absent	Present* Absent*
EZ	Not available	Definitely Fully Intact Likely site(s) of Incomplete EZ Definite site(s) of Incomplete EZ Unable to grade	Normal* Abnormal*
SRF	Present Absent	Present Absent	Present* Absent*
BCVA (ETDRS)	Available	Available	Available after transformation
FTMH size (μm)	Available	Available	Available
VMA diameter	Available	Available	Available
FTMH width at RPE	Available	Available	Not available

*Assessed by SD-OCT
BCVA, best-corrected visual acuity; ELM, external limiting membrane; EOS, end of study; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; FTMH, full-thickness macular hole; M, month; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid; VMA, vitreomacular adhesion

with FTMH at baseline was consistently higher than or equal to 50% for all studies (Table 2).

VMA resolution by Day 28 was achieved significantly more frequently in younger patients, in the absence of ERM at baseline and for eyes with phakic lens status at baseline (Table 3). In the multivariable model including these three variables, age (P = 0.006) and ERM status at baseline (P = 0.010) remained significant, but not lens status at baseline (P = 0.179).

FTMH Closure

The average rate of FTMH closure by Month 6 in the integrated dataset was 35.0% (96/274) (Table 2). Closure rates varied from 30.0% for the OASIS database and 32.2% for the ORBIT study

to 40.6% for the MIVI-TRUST trials (Table 2). FTMH closure by Month 6 occurred significantly more often with smaller FTMH size and smaller FTMH width at RPE (Table 3). We did not construct the multivariable model as these two variables are highly interrelated: the percentage of patients with FTMH width at RPE ≤600 μm decreases from 64.8% (46/71) to 45.5% (25/55) and 10.7% (3/28) for the ≤250 μm, >250–400 μm, and >400 μm FTMH size categories, respectively.

VMA resolution by Day 28 was a positive predictor for FTMH closure by Month 6. Patients with VMA resolution by Day 28 had a higher percentage of MH closure of 40.3% (62/154) compared to patients without VMA release equal to 28.3% (34/120) (P = 0.028). Within the group of patients who had VMA resolution by Day 28, MH closure by Month 6 occurred significantly more for eyes with pseudophakic lens status at baseline, with smaller FTMH size and smaller FTMH width at RPE (Table 4). In the multivariable models including lens status with one of the two FTMH measurements at a time, lens status was no longer significant (P = 0.244 with FTMH size and P = 0.173 with FTMH width at RPE), nor was the FTMH size (P = 0.057), but the FTMH width at RPE remained significant (P < 0.001).

VMA Resolution and FTMH Closure

Overall, 22.6% (62/274) of patients in this analysis experienced both VMA resolution by Day 28 and FTMH closure by Month 6 (Table 2). In contrast, 12.4% (34/274) experienced FTMH closure by Month 6 without VMA resolution by Day 28; 33.6% (92/274) experienced VMA resolution by Day 28 without FTMH closure by Month 6; and 31.4% (86/274) showed neither VMA resolution by Day 28 nor non-surgical FTMH closure by Month 6 (Table 2).

Univariable logistic regression analysis revealed a statistically significant effect for FTMH size at baseline on treatment success (P = 0.009; Table 3), with success increasing from 2.2% for patients with FTMH size at baseline >400 μm to 21.6% for patients with FTMH size at baseline between 250 and 400 μm, and further to 29.9% for patients with FTMH size at baseline <250 μm. Similarly, FTMH width at RPE at baseline had a significant effect on treatment success in the univariable logistic regression analysis (P = 0.015; Table 3), with treatment success increasing from 12.5% for patients with FTMH width at baseline >600 μm to 28.4% for patients with FTMH width at baseline <600 μm. None of the other patient characteristics previously shown to be predictive for VMA resolution, including younger age, phakic lens status, or absence of ERM,[14, 33] showed a statistically significant association with treatment success (Table 3). As the two significant patient baseline characteristics are necessarily highly correlated, and additionally FTMH width at RPE at baseline was unavailable for the OASIS dataset, they were not used jointly in a multivariable logistic regression analysis.

Case studies

Two patients are herein presented as case studies to exemplify real-world clinical findings with ocriplasmin use in patients with symptomatic VMA and FTMH.

Case 1

A 71-year-old white woman had initial presentation of blurred central vision for four–six weeks and ghosting of letters while reading in the left eye. Medical and ocular history were noncontributory. Visual acuity was 20/60 at initial visit. SD-OCT revealed VMA with tractional macular hole of 300 μm, with no presence of ERM (Figure 1A). The left eye had phakic lens status. The patient opted for ocriplasmin treatment and received the intravitreal injection 18 days after initial visit. Visual acuity was 20/60 pre-injection.

One week following the ocriplasmin injection, VMA resolved and the macular hole closed (Figure 1B). However, there was increased presence of SRF (Figure 1B). Visual acuity remained at 20/50. At seven weeks post-treatment, macular hole remained closed with no evidence of SRF (Figure 1C). Visual acuity improved to 20/40.

Case 2

A 63-year-old White woman initially presented with symptoms of blurred central vision for two–three months in the left eye. Medical history included essential hypertension. Visual acuity was 20/150 at initial visit. Patient had phakic lens status in the left eye. Upon examination, SD-OCT showed

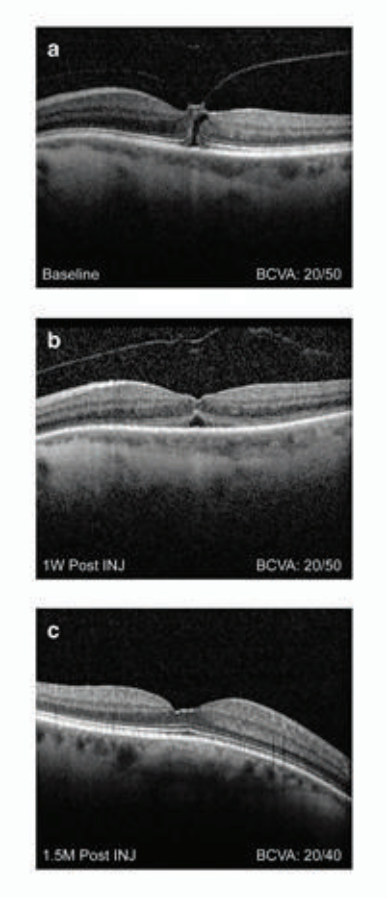

Figure 1. Case 1. Spectral domain optical coherence tomography of a 71-year-old female with VMA and a tractional macular hole in the left eye. (A) Baseline visit. No presence of ERM; BCVA 20/60. (B) One week post ocriplasmin injection. VMA resolved and macular hole closed, but increased presence of SRF; BCVA 20/50. (C). Seven weeks post treatment. Macular hole remains closed, no evidence of SRF; BCVA 20/40. BCVA, best-corrected visual acuity; ERM, epiretinal membrane; INJ, injection; M, month; SRF, subretinal fluid; W, week

FTMH with VMA, with no ERM or presence of SRF (Figure 2A). The size of the tractional macular hole size at baseline was 145 μm, minimum linear diameter (MLD). The patient opted for ocriplasmin treatment and received the intravitreal injection 14 days after the initial visit. Pre-injection visual acuity was 20/150.

One month following the treatment with ocriplasmin, the VMA released, but the macular hole remained open, enlarging to a size of 428 μm, MLD (Figure 2B). Visual acuity decreased to 20/200. The patient underwent standard macular hole repair via vitrectomy, internal limiting membrane peeling, and gas injection. The hole did not close and subsequent surgery including an internal limiting membrane patch and silicone oil was performed with macular hole closure. At the last examination, visual acuity was count fingers (CF) at 4 ft with a dense cataract and macular hole closure by OCT.

DISCUSSION

This study is the first to examine the baseline predictors of success for both VMA resolution and FTMH closure following ocriplasmin treatment. Our results show that FTMH $\leq$ 250 μm at baseline is significantly associated with VMA release by Day 28 and FTMH closure by Month 6 (P = 0.009), and may be the only positive baseline predictor for both pharmacological VMA release and nonsurgical FTMH closure, including previously identified predictors such as age, lens status, and absence of ERM.

Baseline factors associated with successful VMA release following ocriplasmin treatment have been

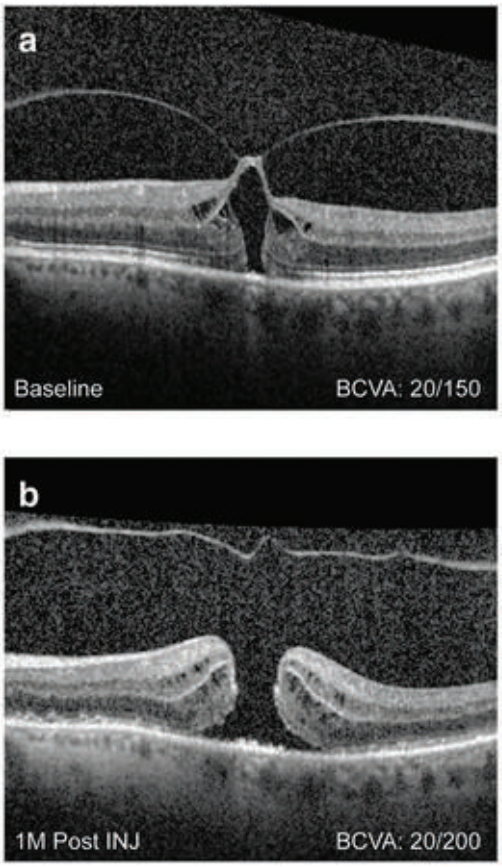

Figure 2. Case 2. Spectral domain optical coherence tomography of a 63-year-old female showing VMA with FTMH. (A) Baseline visit. No ERM or presence of SRF; BCVA 20/150. (B) One month post treatment. VMA released, but macular hole remained open, with the base enlarging to 1323 μm. BCVA decreased to 20/200. BCVA, best-corrected visual acuity; ERM, epiretinal membrane; INJ, injection; M, month; SRF, subretinal fluid

widely studied following approval in 2012.[14–32] A post hoc analysis of the phase 3 MIVI-TRUST trials revealed that baseline characteristics such as younger age, focal adhesions (VMA $\leq$ 1500 μm), phakic lens status, and absence of ERM promoted VMA resolution,[14] and these characteristics have since been confirmed in multiple studies.[15–32] These predictive characteristics were also shown to statistically favor VMA release (odds ratios 2.37–7.85) in a meta-analysis of 19 studies published in 2016.[33]

However, in our current analysis, most of these validated baseline factors were not shown to be predictive when analyzed for both VMA release and FTMH closure. The baseline factors of younger age, absence of ERM, and lens status did not reach statistical significance, with only FTMH size of $\leq$ 250 μm at baseline emerging as the only statistically significant factor favoring both VMA release and FTMH closure.

The fact that lens status was no longer significant in the multivariable model is due to the correlation between variables. The lens status of younger patients was more frequently phakic compared to older patients (93.6% vs 71.8%), and similarly, the lens status of patients without ERM at baseline was more frequently phakic compared to patients with ERM at baseline (83.0% vs 57.9%). For FTMH, the percentage of phakic lens status increases with increasing FTMH size, with 80.0% (60/75), 85.2% (46/54), and 100.0% (24/24) for the $\leq$250 µm, >250–400 µm, and >400 µm FTMH size categories, respectively, and with increasing FTMH width, with 85.0% (34/40) and 89.7% (35/39) for the $\leq$600 µm and >600 µm FTMH width at RPE categories, respectively.

Historically, whether FTMH at baseline serves as a predictive factor for successful VMA release has remained unclear. The presence of FTMH was initially identified as a predictive characteristic in the post hoc analysis of the MIVI-TRUST trials.[14] Subsequently, Chatziralli et al performed a meta-analysis and did not conclude that the presence of FTMH was a predictive factor for VMA release.[33] However, only 8 of the 19 analyzed studies assessed MH size as a predictive factor.[13, 15, 17, 23, 24, 28, 30, 32] Kuppermann (2015)[39] reported the results of 10 retrospective studies which assessed the presence of FTMH on VMA resolution, including 4 studies not included in Chatziralli et al.[40–43] Eight of these 10 studies[19, 23, 31, 32, 40–43] showed that the subgroup of patients with a FTMH had higher VMA resolution rates than those without.[39] These results were also consistent with the prospective OASIS trial.[34] However, other studies have not shown greater rates of VMA resolution in patients with FTMH at baseline.[28, 29] Therefore, the value of FTMH as a predictive factor for VMA resolution needs to be further elucidated.

In our current analysis, the majority of patients failing to achieve both VMA resolution and FTMH closure were due to lack of macular hole closure. Whereas VMA resolution rates were 50% or higher from all studies in this patient population (i.e., those with symptomatic VMA and FTMH at baseline treated with ocriplasmin with at least one follow-up visit), FTMH closure rates for OASIS and ORBIT studies were lower than that of the original phase 3 MIVI-TRUST trials, albeit higher than the closure rates experienced in the control groups (15.4% and 10.6%, respectively). These results suggest that the known baseline factors predictive of VMA resolution, which were used as key inclusion criteria for the OASIS study, may be necessary but not sufficient to predict FTMH closure. Nevertheless, consistent with our findings, previous studies investigating FTMH closure rates following ocriplasmin treatment have repeatedly shown FTMH size at baseline to be the most consistent predictive factor, with a greater proportion of patients experiencing hole closure with an FTMH $\leq$ 250 μm compared to those with an FTMH $>$ 250–400 μm.[14, 36, 37, 44] In contrast, the natural history of untreated FTMH has revealed that spontaneous closure rates are low, ranging from 3–11%.[45–49] Although smaller holes have a comparatively better chance of spontaneous closure compared to larger ones, previous studies have shown that the majority of stage 2 macular holes (<400 μm) progress to stage 3 and beyond if left untreated.[50–53]

Whether VMA resolution is correlated with FTMH closure has also remained unclear. Recently, Feng et al demonstrated that successful VMA resolution was a statistically significant positive predictor for FTMH closure following ocriplasmin treatment (P = 0.042).[37] This is consistent with our findings, which showed that patients with VMA resolution by Day 28 had a significantly higher rate of FTMH closure compared to those without VMA resolution. However, other analyses have not shown an association between VMA resolution and FTMH closure. In one study, 40% of patients required surgical closure for macular holes despite successful VMA resolution,[54] suggesting that additional factors may impact FTMH closure.

Although our finding that VMA resolution showed a positive correlation with FTMH closure is notable, beyond initial hole size, baseline characteristics predictive of macular hole closure prior to treatment have remained elusive. For instance, our findings are consistent with previous analyses showing that, unlike for VMA resolution, absence of ERM did not significantly impact FTMH closure rates.[35, 36] Additional studies have suggested that other factors, such as macular hole architecture, may affect closure.[55, 56] Recently, Steel et al found that macular hole "width factor," defined as the base diameter (BD) minus the MLD, was the most predictive factor of macular hole closure; holes having a BD close in size to the MLD were shown to have higher probability of closure compared to those with a wider base.[56] A similar outcome is shown in Case 2, where despite VMA resolution, the macular hole widens at the base with the edge elevated by a cuff of SRF. This is consistent with previous cases showing failure of FTMH closure due to base enlargement following ocriplasmin treatment and subsequent VMA resolution.[37, 57] SRF did not have a statistically significant predictive value in our analysis; however, the number of patients showing successful VMA resolution and FTMH closure with SRF were strikingly different between the MIVI-TRUST and OASIS vs ORBIT studies (SRF present: 87% [20/23], 100% [8/8], and 0% [0/30], respectively), perhaps owing in part to differences in SRF measurement protocols at study enrollment

and therefore limiting interpretation. In Case 1, presence of SRF did not impact VMA resolution or FTMH closure, although visual acuity improved following SRF resolution.

When selecting a treatment option for patients with VMA and FTMH, the risks and benefits of ocriplasmin versus vitrectomy should be carefully considered. For these patients, vitrectomy is considered the standard of care, with macular hole closure rates reported for 87.5% of patients in a meta-analysis.[33, 58, 59] However, persistence of a macular hole after vitrectomy remains one of the major complications of this type of surgery, with approximately one in eight macular holes failing to close.[58] A persistent macular hole typically increases in diameter, with an accompanying loss of visual acuity, and studies have shown lower treatment success for subsequent surgery.[55, 58] Additional complications of vitrectomy include cataract formation, retinal detachment, and hemorrhage.[33, 59–64] In addition, based on the OASIS trial, patients who underwent vitrectomy experienced retinal tear and retinal detachment more often than patients receiving ocriplasmin. Most adverse events in the ocriplasmin group were transient in nature, had a short onset time, and were mild to moderate in severity.[34]

Strengths of the current analysis include a robust and homogeneous patient sample pooled from multiple clinical trials, utilizing the same ocriplasmin treatment regimen. Limitations include the post hoc nature of the analysis, which was not prespecified in the clinical trials, as well as the lack of availability of certain baseline ocular characteristics in all trials.

Since the pivotal clinical trials, continued study and analysis has been undertaken to more fully understand the efficacy and safety of ocriplasmin, including the baseline characteristics predictive of VMA resolution and FTMH closure. These results suggest that patients presenting with symptomatic VMA and FTMH ≤ 250 μm may be ideal candidates for ocriplasmin treatment.

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Conflicts of Interest

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

BJ: Consultant for Oxurion; PW: Consultant for Oxurion; TR: Employee of Oxurion; LD: Consultant for Oxurion; JM: Consultant for Oxurion.

Research involving human participants and informed consent

This manuscript represents a retrospective analysis of four prospective phase 3/4 clinical trials.

Full details of adherence to ethics practices have been previously published [13, 34, 38].

Author Contribution

All authors contributed to the conception or design of the work, analysis and interpretation of the data, critical revision of the manuscript, and approval of the final version to be published.

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Original Article

An *In-Silico* Study on the Most Effective Growth Factors in Retinal Regeneration Utilizing Tissue Engineering Concepts

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Abstract

Purpose: Considering the significance of retinal disorders and the growing need to employ tissue engineering in this field, *in-silico* studies can be used to establish a cost-effective method. This *in-silico* study was performed to find the most effective growth factors contributing to retinal tissue engineering.
Methods: In this study, a regeneration gene database was used. All 21 protein-coding genes participating in retinal regeneration were considered as a protein–protein interaction (PPI) network via the "STRING App" in "Cytoscape 3.7.2" software. The resultant graph possessed 21 nodes as well as 37 edges. Gene ontology (GO) analysis, as well as the centrality analysis, revealed the most effective proteins in retinal regeneration.
Results: According to the biological processes and the role of each protein in different pathways, selecting the correct one is possible through the information that the network provides. Eye development, detection of the visible light, visual perception, photoreceptor cell differentiation, camera-type eye development, eye morphogenesis, and angiogenesis are the major biological processes in retinal regeneration. Based on the GO analysis, SHH, STAT3, FGFR1, OPN4, ITGAV, RAX, and RPE65 are effective in retinal regeneration via the biological processes. In addition, based on the centrality analysis, four proteins have the greatest influence on retinal regeneration: SHH, IGF1, STAT3, and ASCL1.
Conclusion: With the intention of applying the most impressive growth factors in retinal engineering, it seems logical to pay attention to SHH, STAT3, and RPE65. Utilizing these proteins can lead to fabricate high efficiency engineered retina via all aforementioned biological processes.

Keywords: Effective Growth Factors; *In-silico* Study; Regenerative Medicine; Retinal Tissue Engineering; Systems Biology

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INTRODUCTION

The aim of regenerative medicine as the primary process involved in cell growth and organ

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reconstruction is to return the main cell functions and recovery of the damaged tissue or organ via its replacing or regenerating.[1] In fact, there are three solutions for patients having organ impairment based on the severity of the destruction: graft implantation, substitution, and restoration. Graft implantation has an extensive waiting list candidates all around the world; for example, the organ transplantation waiting list is updated every 15 min in the United States of America.[2] The ultimate prospect of tissue engineering is creating and providing tissues that are preferably autologous in organ substitutions through cells and biomaterials utilization simultaneously.[3, 4] Besides, tissue engineering has been determined as an efficient method to assist in rescuing lives and improving the quality of life.

Considering the major components for tissue engineering, that is, scaffolds, cells, and growth factors and a variety of their available options would highlight the fact that selecting the most appropriate ones to fabricate an engineered tissue demands an optimization system. In fact, a wide range of biomaterials can be used as scaffolds; polymers and hydrogels are the most commonly used materials in this field.[5–7] Selecting the appropriate material is in close relation with the destination tissue. Poly-lactide-co-glycolide (PLGA), poly-caprolactone (PCL), poly-glycerol sebacate (PGS), and polymethyl methacrylate (PMMA) are some of the high consumption polymers in retinal tissue engineering.

In addition to scaffolds, growth factors play an essential role in tissue engineering.[8] Growth factors are generally the regulators of substances, namely proteins or hormones that can stimulate cell proliferation and differentiation. Growth factors play an important role in the healing and regeneration of the retina. Retinal disorders directly affect vision; therefore, retinal tissue engineering is fundamental.[3, 9–11] To understand the effective mechanisms in this process, it is better to compare growth factors' interaction with each other and then select the most appropriate one.

Looking at the literature, retinal regeneration and retinal tissue engineering have been studied by several researchers.[12–21] Liu *et al*[22] studied the application of hyaluronic acid (HA) hydrogels in retinal progenitor cell transplantation. Their reason for selecting HA was its role as a feeder layer in stem cell cultures. In addition, the relative ease with which various parameters could be controlled (e.g., hydrogel architecture, mechanics, and degradation) was effective in choosing the HA hydrogel. They concluded that HA hydrogels, with their developmentally relevant composition and malleable physical properties, provide a unique microenvironment for self-renewal and differentiation of the retinal progenitor cells (RPCs) for retinal repair. Furthermore, Fausett *et al*[23] showed that in the damaged zebrafish retina, the Muller glia re-enter the cell cycle, increase α1tubulin (α1T) promoter activity, and generate new neurons and glia for retinal repair. They suggested that the achaete-scute family bHLH transcription factor 1a (ASCL1a) is required to convert the quiescent Muller glia into the actively dividing retinal progenitors, and that ASCL1a is a key regulator in initiating the retinal regeneration.

Kador and Goldberg[24] studied the delivery of cell transplants for retinal degeneration. Focusing on the photoreceptor and progenitor-directed approaches, the authors reviewed how advances in tissue engineering and cell scaffold design were enhancing cell therapies for retinal degeneration. Furthermore, Yao *et al*[25] reviewed the current literature on synthetic polymer scaffolds used for stem cell transplantation, especially RPCs. The advantages and disadvantages of different polymer scaffolds, the role of different surface modifications on cell attachment and differentiation, and the controlled drug delivery were discussed in their paper. Tao and Klassen[18] have also presented a wide range of practical biomaterials in retinal tissue engineering. They studied the role of stem cells in retinal repair, and then focused on the material side, followed by considering cells and materials in combination. They also examined the current status of retinal tissue engineering and looked ahead to the challenges that investigators are involved within this field. In addition, Bainbridge *et al*[26] published their preliminary results of gene therapy for retinal degeneration. In their study, the patients were enrolled in trials of recombinant adeno-associated viral delivery of the retinoid isomerohydrolase (RPE65), which was administered as a subretinal injection during vitrectomy. The preliminary results from their investigations suggested that the procedure was safe in the short term, and their data were suggestive of efficacy.

Furthermore, Nelson *et al*[27] found out that signal transducer and activator of transcription 3 (STAT3) expression was observed in all Muller

glia, whereas ASCL1a expression was restricted to only the mitotic ones. They suggested that while ASCL1a and Lin-28 homolog A (LIN28a) are required for Muller glia proliferation, STAT3 is necessary for the maximal number of Muller glia to proliferate during regeneration of the damaged zebrafish retina. In another study, Spence *et al*[28] worked on the fibroblast growth factor (FGF)–hedgehog (SHH) interdependence during retinal regeneration. Their results support a model where the FGF and SHH pathways work together to stimulate retinal regeneration.

Recently, Singh *et al*[29] reviewed retinal tissue engineering from the pluripotent stem cells and summarized the progress in cell therapies of the retina, with a focus on the human pluripotent stem cell-derived retinal tissue, and critically evaluated the potential of retinal organoid approaches to solve a major unmet clinically needed retinal repair and vision restoration in conditions caused by retinal degeneration and traumatic ocular injuries.

Based on the published works, it can be concluded that there is no comprehensive study on the retinal growth factors that can draw up the existing relation among them. In addition, to the best of our knowledge, there is no *in-silico* study of retinal tissue engineering. In fact, in retinal regeneration, several proteins are used therapeutically. If the interaction between them would be clear, and the biological function of each one is determined, they can be used as growth factors in retinal tissue engineering.

In order to get the best results from the *in-vitro* and *in-vivo* tests, it is needed to select the best growth factors based on previous experiments and existing data. However, there are many reports about the effects of using each growth factor without any coherence and correlation among them. It seems that describing the interactions among growth factors is a critical fact that would lighten up the retinal tissue engineering path, that is, possible effects of increasing the amount of a growth factor on other growth factors' functions. One of the least expensive methods for detecting this kind of facts is evaluating them with an *in-silico* study.

In this work, retinal growth factors interactions have been studied via creating their interaction network. By creating this network, the influence of each growth factor on the biological processes can be determined. The higher degree in this network leads to higher interactions among them and causes much more effect. The main goal of this study is to find out which kind of retinal growth factor should be used to have the highest effect on the desired biological process.

METHODS

All *in-vivo* or *in-vitro* studies already performed on retinal tissue engineering were reviewed to know how cells were affected by their surrounding environmental factors. The final results of these studies were collected into databases to provide access to comprehensive and accurate information. In the current study, the regeneration gene database was used.[30] According to this database, 21 protein-coding genes participate in retinal regeneration. In order to reveal their interaction and realize how they affect each other, all of these proteins were gathered from this database. Then a study on systems biology was performed. The mathematical modelling of complicated biological systems is called systems biology. For this purpose, the "STRING App" in "Cytoscape 3.7.2 software" [1] was utilized. The STRING App is one of the Cytoscape software apps related to the STRING database.[31] This database is utilized for investigating the protein–protein interaction (PPI).

In this regard, the data source was adjusted on "STRING: protein query", and all 21 proteins were included in this query. Given that this study is on human proteins, the species section was set on *Homo sapiens*, and the analysis results were matched for humans. Selecting default options from multiple possible matches found for some proteins would lead to loading interactions from the STRING database. Then, a primitive model of PPI graph was drawn, meanwhile having the ability to alter into other layouts, that is, grid, circular, and hierarchical.

Creating a PPI network, there are 21 nodes and 37 edges. In other words, a 21 node-included graph was drawn using the STRING App. Then, gene ontology (GO) analysis was performed. GO analysis is a major bioinformatics initiative to unify the representation of gene and gene product attributes across all species.[32] The protein–coding genes which are involved in retinal regeneration are listed in Table 1.

In addition, a centrality analysis was performed based on the degree index. In network analysis,

Table 1. The list of protein-coding genes that are involved in retinal regeneration

No	Name	Gene ID	Degree
1	SHH	6469	10
2	IGF1	3479	8
3	STAT3	6774	8
4	ASCL1	429	7
5	CDH2	1000	7
6	WNT3A	89780	5
7	FGFR1	2260	5
8	VTN	7448	5
9	CALB2	794	3
10	CNTF	1270	3
11	MDK	4192	2
12	INSM1	3642	2
13	OPN4	94233	2
14	ITGAV	3685	2
15	C3	718	2
16	RAX	30062	1
17	RPE65	6121	1
18	APOBEC2	10930	0
19	TUBA1C	84790	0
20	HSPA1L	3305	0
21	VPS35	55737	0

based on graph theory, centrality indicators identify the most important nodes within a network. The results of this analysis lead to a degree based array of nodes in the network. In order to illustrate comprehensible figures, the circular layout was selected. Also, to recognize the most effective proteins, degree sorted layouts were selected.

RESULTS

Figure 1 shows the PPI network. In this figure, a PPI network and a GO analysis of retinal regeneration effective growth factors presented by STRING App database are shown. This figure presents the relationship among all proteins participating in retinal regeneration. These proteins are also listed in Table 1.

Based on Figure 1, there are four proteins that act individually: heat shock protein family A member 1 (HSPA1L), VPS35 retromer complex component (VPS35), apolipoprotein B mRNA editing enzyme catalytic subunit 2 (APOBEC2), and tubulin alpha 1c (TUBA1C). These proteins do not have any interactions with the other 17 effective proteins in the retina healing process. Mentioned proteins can show activity individually or via activating other proteins. For instance, the VPS35 impression is on the upregulation of the development process. As a matter of fact, there are 11 proteins involved in the upregulation of the development process, and VPS35 is one of them.

As mentioned previously, a centrality analysis based on the degree was performed. In order to get the best understanding, it is preferred to present the PPI network by the centrality analysis based on the degree. Figure 2 illustrates this analysis.

According to this centrality analysis, four proteins have the greatest influence on retinal regeneration: SHH, insulin-like growth factor 1 (IGF1), STAT3, and achaete-scute family bHLH transcription factor 1 (ASCL1). These proteins have the highest degree in the PPI network.

The most impressive biological processes considered in this study, that is, eye development,

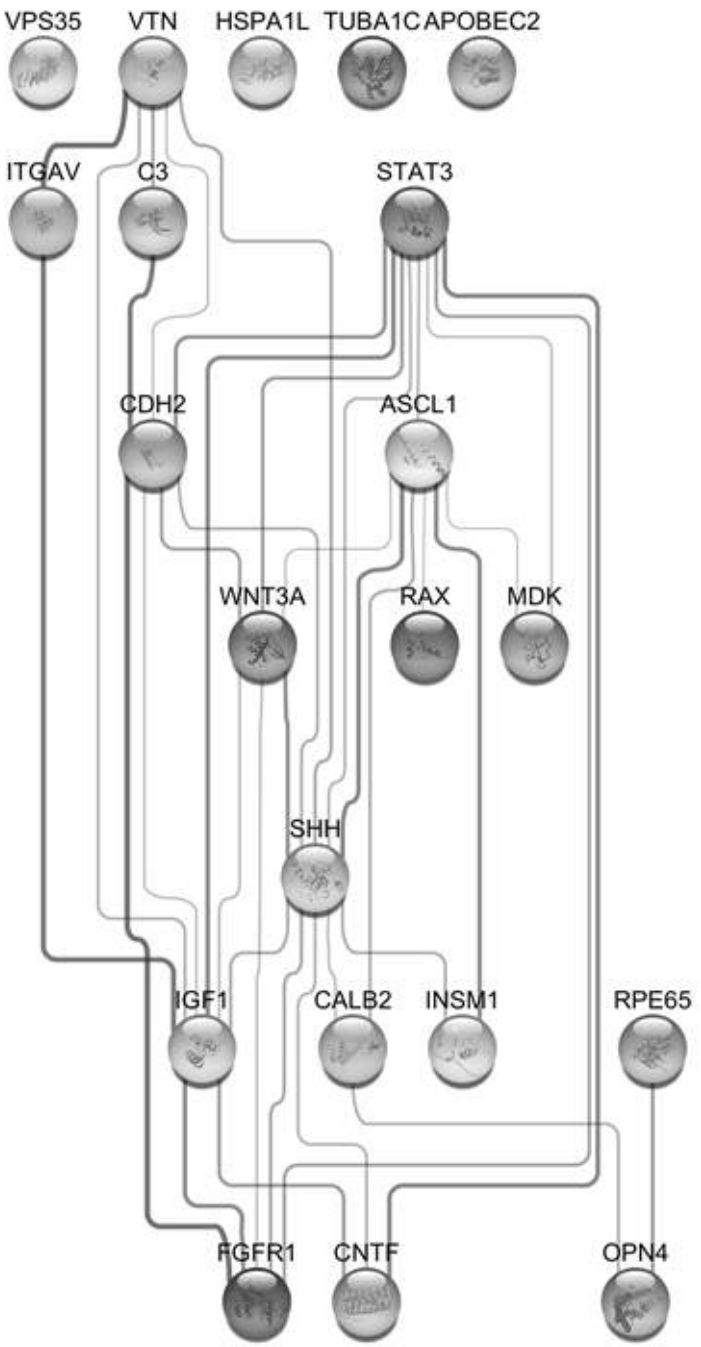

Figure 1. Hierarchical layout of the PPI network performed by STRING App in Cytoscape 3.7.2. This network presents GO analysis of retina regeneration effective growth. Each circle provides a schematic drawing of protein structure. The colors are set randomly, and the connection line's thickness illustrates the relation of power. Also, a thicker line presents much more evidence and documents to approve the connectivity.

detection of visible lights, visual perception, photoreceptor cell differentiation, camera-type eye development, eye morphogenesis, and angiogenesis, lead to retinal regeneration. Moreover, based on GO analysis, the most effective protein-coding genes that act in the mentioned biological procedures are SHH, STAT3, FGFR1, Opsin 4 (OPN4), integrin subunit alpha V

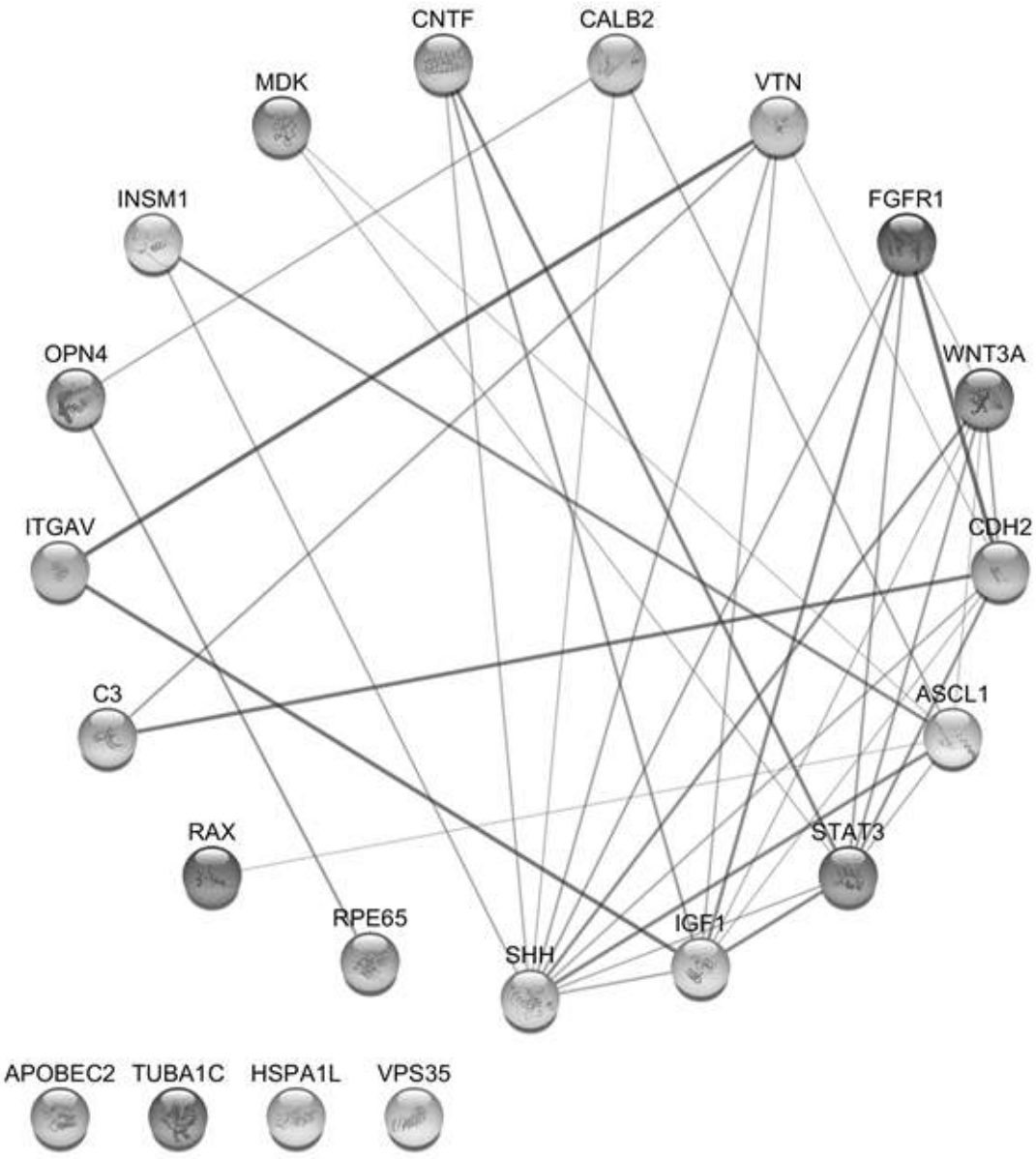

Figure 2. The degree-sorted circular layout of the PPI network performed by STRING App in Cytoscape 3.7.2. Each circle provides a schematic drawing of protein structure. The colors are set randomly, and the connection line's thickness illustrates the relation of power. Also, a thicker line presents much more evidence and documents to approve the connectivity.

(ITGAV), retina and anterior neural fold homeobox (RAX), and RPE65.

DISCUSSION

In this study, two analyses were performed: GO analysis and centrality analysis. Based on the GO analysis results, there were seven proteins participating in seven biological processes. In addition, the four most effective proteins in the retinal regeneration process were identified via degree index-based centrality analysis. To get the most appropriate growth factor for use in retinal tissue engineering, each protein's role needs to be identified.

Considering the four isolated proteins in Figure 1, it can be argued that these proteins are also involved in retinal regeneration; however, there should be some biological processes that these proteins could impress on. Positive regulation of transport is a biological process in which VPS35 and HSPA1L participate. Based on GO analysis

(GO: 0051094), a process that causes and expands the rate of development is an "upregulation of developmental process"; it points to a biological procedure, which results in the development of an organism from the primary situation till the last condition; for example, from a zygote to an adult. In addition, "Transport positive upregulation" is a process that grows the scope, rate, and frequency of substances movement such as ions, molecules in cells and between them by use of a factor, for example, a pore or a transporter (GO: 0051050).[33]

The four aforementioned proteins, which have the most influence on retinal regeneration based on centrality analysis, are SHH, IGF1, STAT3, and ASCL1. SHH is a protein functional in embryo formation. Interestingly, SHH and FGF can induce stem/progenitor cells in the regeneration process, and these two have simultaneous interdependence on each other. For example, if SHH is inhibited, FGF would also be inhibited and vice versa. Therefore, FGF and Hedgehog pathways work together to stimulate retinal regeneration. In fact, the complex relation between SHH and FGF regulates this process.[18] SHH has the highest degree in the network (Figure 2). It could be noted that the Hedgehog pathway plays an essential role as a modulator of retinal regeneration.[28]

IGF-1 has an impact on the activity of growth promotion. Nerve injury causes phospho-Akt inactivation; therefore, retinal ganglion cell (RGC) loss would occur. It is evident from the literature that supplementation of IGF-1-induced phospho-Akt expression upregulates and provides the cell survival of RGCs.[34] Consequently, during primary levels of nerve damage, IGF-1 would be a key molecule that possesses the apoptosis effect on RGCs.[34] IGF-1 is at the second rank according to its special role in glial cell survival.

Moreover, STAT3 is a transcription factor involved in retinal regeneration, supporting stem cell maintenance and tissue development. Furthermore, Muller glial cells are the kind of cells in the retina that support neurons like other glial cells. The role of STAT3 in the regeneration process is providing maximum proliferation of Muller glia cells in retinal damage.

In fact, STAT3 and ASCL1 have an important place in retinal regeneration. Considering and investing on them in tissue fabrication seems logical to get closer to the regeneration purpose. The study provides a mutual relation between the ASCL1 factor and STAT3 in the regeneration process. STAT3 is expressed in all Muller glial cells, while ASCL1 is only expressed in proliferating Muller glial cells. Although the expression of the ASCL1 is necessary for retinal regeneration, STAT3 in cell proliferation has priority to ASCL1.

Moreover, ASCL1 takes part in STAT3 expression. Both factors are efficient in the regeneration of cell cycles. ASCL1 is a critical regulatory factor in retinal regeneration. It helps and converts dormant Muller glia to retinal progenitors that are able to divide. ASCL1 is a protein expressed during retinal puncture and causes retinal regeneration by affecting the LIN-28 factor.[23, 27]

Hence, according to centrality analysis, ASCL1 is in relation with two important and high degree factors of the network, SHH and STAT3. As mentioned before, the relation of ASCL1 and STAT3 is direct and mutual, so it is important to consider the role of ASCL1 in glial cell proliferation and survival, which STAT3 is also involved in.

The role of these four proteins is critical in retinal regeneration. Furthermore, GO analysis demonstrated that these proteins have incredible effects on some biological processes. Seven most important biological processes were studied in this work. Table 2 shows the biological processes and the relation with the mentioned protein-coding genes.

Based on GO Analysis, "eye development" (GO: 0001654) is a process which its significant result is eye development over time along with the formation of the matured structures. In addition, "detection of visible lights" is a chain of incidents that a visible light stimulus is captured by a cell and turned into a molecular signal (GO: 0009584). "Eye morphogenesis" is a process in which the generation of anatomical structures of the eye happens and unifies (GO: 0048592).[33]

Furthermore, "visual perception" is a chain of incidents, which are essential for an organism to capture a visual stimulus, turn it out into a molecular signal, and describe and identify the signal. Signals are detected in the photon form and are converted to an image form (GO: 0007601). The definition of "photoreceptor cell differentiation" in the GO database is the specialization of formation of a photoreceptor, a cell that is responsive to electromagnetic ray, especially visible light (GO: 0001754). Drosophila

Table 2. Proteins involved in Retina Biological Processes

Biological process/ Protein names	SHH	STAT3	FGFR1	OPN4	ITGAV	RAX	RPE65
Eye development	*	*				*	*
Detection of visible lights				*			*
Visual perception				*		*	*
Photoreceptor cell differentiation		*					*
Camera-type eye development	*					*	*
Eye morphogenesis		*					*
Angiogenesis	*		*		*		

melanogaster is an example of this procedure.[33] "Camera-type eye development" (GO: 0043010) is a biological process, which its specific outcome is the progression of the camera-type eye over time, from its formation to a mature structure. The camera-type eye is an organ of sight that receives light through an aperture and focuses it through a lens, projecting it on a photoreceptor field.[33]

Angiogenesis is another crucial process that can lead to prosperous tissue fabrication. In fact, blood vessel formation is called angiogenesis when new vessels emerge from the proliferation of the pre-existing blood vessels. Based on evaluations, three proteins are involved in this process: SHH, FGFR1, and ITGAV. Figure 3 shows these proteins involved in the PPI network.

Regarding the most impressive protein-coding genes, which participate in those seven biological procedures based on GO analysis, that is, SHH, STAT3, FGFR1, OPN4, ITGAV, RAX, and RPE65, there are some interesting findings. SHH is able to induce angiogenesis, characterized by distinct large-diameter vessels and also augmented blood-flow recovery. *In-vitro*, SHH does not affect endothelial cell migration or proliferation; instead, it induces expression of two families of angiogenic cytokines, including all three vascular endothelial growth factor-1 (VEGF1) isoforms and angiopoietins-1 and -2 from the interstitial mesenchymal cells.[35]

Lack of FGF signaling in retinal pigment epithelium (RPE) during eye development strongly affects choroidal angiogenesis, including the absence of astrocytes, which are responsible for VEGF production. FGF-induced angiogenesis also requires activation of the VEGF system, while FGFs promote a strong angiogenic response.[36] The product of this gene belongs to the integrin alpha chain family. Integrins are heterodimeric integral membrane proteins composed of an alpha subunit as well as a beta subunit that function in cell surface adhesion and signaling.[37] However, the protein encoded by RPE65 is a component of the vitamin A visual cycle of the retina, which supplies the 11-cis retinal chromophore of the photoreceptors' opsin visual pigments. It performs the essential enzymatic isomerization step in the synthesis of the 11-cis retina. Mutations in this gene are associated with early-onset severe blinding disorders, such as Leber congenital amaurosis.[38]

Opsins are members of the guanine nucleotide-binding protein (G protein)-coupled receptor superfamily.[39] OPN4 encodes a photoreceptive opsin protein that is expressed within the ganglion and amacrine cell layers of the retina. The protein functions as a sensory photopigment and may also have photoisomerase activity. Furthermore, RAX encodes a homeobox-containing transcription factor that functions in eye development.[40] RAX is expressed early in the eye primordia and is required for retinal cell fate determination and regulates stem cell proliferation. Mutations in this gene have been reported in patients with defects in ocular development, including microphthalmia, anophthalmia, and coloboma.

Therefore, based on the extracted data from Table 2, SHH is accounted for eye

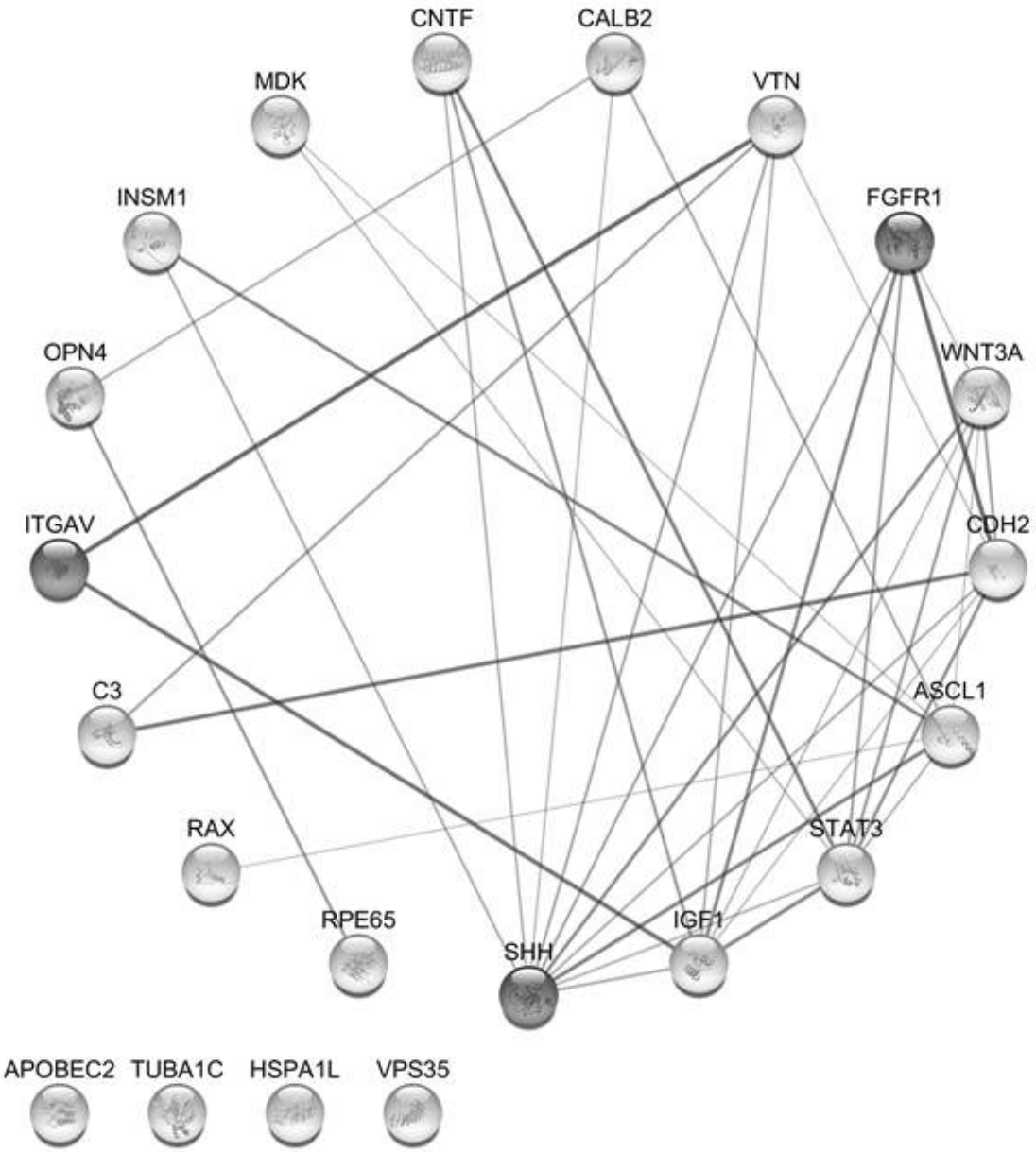

Figure 3. Angiogenesis involved proteins in retina regeneration, presented in a degree-sorted circular layout of the PPI network performed by STRING App in Cytoscape 3.7.2. Each circle provides a schematic drawing of protein structure. The colors are set randomly, and the connection line's thickness illustrates the relation of power. Also, a thicker line presents much more evidence and documents to approve the connectivity.

development, camera-type eye development, and angiogenesis, whereas STAT3 is dedicated to eye development, photoreceptor cell differentiation, and eye morphogenesis. FGFR1 and ITGAV are also only involved in angiogenesis. OPN4 plays a great role in detecting visible lights and visual perception, while RAX is active in eye development, visual perception, and camera-type eye development. Finally, RPE65 is an impressive protein in all mentioned biological processes except angiogenesis.

Overall, explained biological processes and participated protein-coding genes must be considered in retina tissue fabrication. To fabricate artificial tissues or tissue regeneration, it is needed

to understand the effective mechanisms to utilize them in an appropriate trend. Applying these proteins as growth factors may help in retinal tissue engineering. The results of this study positively correlate with earlier published reports. In fact, a variety of proteins have been shown to play a role in the retina development and regeneration process. The salient examples of these proteins are small peptide growth factors, SHH, taurine, epidermal growth factor (EGF), and FGF.[41–43] RPE65, meanwhile, is considered as a strong marker for differentiation of bone marrow-derived stem cells (BMSC) into RPE.[44–46] Furthermore, in the last decade, STAT3 was introduced as a recently recognized regulator of RPE survival. In addition, proliferation and visual cycle maintenance are functional roles of STAT3.[47]

In summary, due to the importance of retinal disorders and the growing need for tissue engineering in this field, *in-silico* studies are very useful to predict the general condition. This would lighten up the path and lead us to the right answer in an inexpensive way. In order to find out the most effective growth factors in retinal tissue engineering, an *in-silico* study was performed. This study demonstrates the importance and preview of the 21 proteins that play different roles in retinal regeneration.

According to each protein's biological function and role in different paths, selecting the correct ones is possible through the information that the network provides. Eye development, detection of visible lights, visual perception, photoreceptor cell differentiation, camera-type eye development, eye morphogenesis, and angiogenesis are the major biological processes in retinal regeneration. Based on GO analysis, each biological process has the most effective proteins in retinal regeneration, that is, SHH, STAT3, FGFR1, OPN4, ITGAV, RAX, and RPE65. In addition, based on degree index centrality analysis, the effectiveness of each protein on regeneration process was identified. In this regard, SHH, IGF1, STAT3, and ASCL1 are the proteins, which have the greatest influence on retinal regeneration. Based on these perspectives and nodes with the highest degree in the network, as well as GO analysis results, it is logical to focus on SHH, STAT3, and RPE65 in retinal tissue engineering.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Original Article

Autologous Neurosensory Retinal Transplantation: A Report of Three Cases

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Abstract

Purpose: To present the anatomical and functional outcomes of autologous surgical transplantation of a free neurosensory retinal graft in three cases of recurrent and chronic full thickness macular hole (MH).

Method: A retrospective case series, reporting the profile, preoperative presentation, surgical technique, and postoperative outcome of three consecutive eyes of three patients who had autologous retina transplantation (ART) surgery for recurrent and chronic MHs, and had a minimum of six months follow-up. The technique involved excision of a free neurosensory graft after laser demarcation of the harvest site. The graft was slid under perfluorocarbon liquid (PFCL) into the MH. A five-day tamponade with PFCL was used to secure the graft within the MH and then exchanged with air.

Results: The patients were one female and two males aged 60, 44, and 67 years, respectively. All eyes had successful surgery. Postoperative vision improved from 6/36 to 6/18 in patient 1 and remained same as preoperative vision in the other two eyes. No eye lost vision postoperatively. The main complication of surgery was occurrence of retinal and vitreous hemorrhage in one eye (this did not appear to jeopardize the outcome) and retraction of graft tissue in two eyes.

Conclusion: ART appears to be a safe and effective treatment for difficult MHs. Our results are comparable to previous studies. Short-term use of PFCL can be useful to secure the graft within the MH. Methods of improving visual function should be the focus of further research in this promising area.

Keywords: Autologous Transplant; Macular Hole; Neurosensory Retina; Vitrectomy

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INTRODUCTION

There are few reports on the techniques for autologous retinal transplantation (ART). ART

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has shown to be promising for the treatment of recurrent, chronic, and myopic macular hole (MH).[1, 2] It involves the harvest of a free patch of neurosensory retina from an extra macular site and placing this graft within the MH. It is hoped that the piece of neurosensory retinal tissue will remain within the hole and eventually get integrated into the surrounding retina and that the surviving graft tissue will provide vision. Initial cases reported dislocation of the neurosensory retinal patch from within the MH intra- and postoperatively.[3]

We report our experience of three consecutive eyes that had ART with short-term perfluorocarbon liquid (PFCL) tamponade and a minimum of six months follow-up.

METHODS

Surgical Steps For ART

Our technique was a standard 23G unimanual vitrectomy, for all three cases. The Constellation vitrectomy unit (Constellation®, Alcon, Fort Worth, TX, USA) was used. PFCL injection was followed by a laser demarcation of the chosen site for the free graft harvest. Neurosensory retinal tissue was excised within the laser-demarcated area, using a 23G intraocular vertical scissors. The free graft was then slid under the PFCL into the MH with the use of intraocular forceps. The harvested piece of retinal tissue was teased open and spread over the MH (but not tucked into it) to cover the MH using the soft edge of a silicone-tipped cannula. PFCL was left in the eye for five days to secure graft stability and prevent graft dislocation from the MH. On the fifth day, air-fluid exchange was performed.

There was no positioning of the patient within this five-day period. The patient was allowed to assume any face or head position they chose during this five-day period.

The fluid-air exchange was performed in the operating theatre and took approximately 15 min to do. The procedure involved the use of a 23G system. Air was infused into the eye, while silicon-tipped cannula was utilized to aspirate the PFCL. After all the PFCL bubble was removed, a fluid rinse of the vitreous cavity using balanced salt solution (BSS) was done to ensure that all possibly trapped bubbles of the PFCL in the vitreous base and elsewhere were rinsed out into the vitreous-filled BSS, and this was removed with a repeat fluid-air exchange. This fluid rinse was repeated several times to ensure the vitreous cavity was free of PFCL droplets. An irrigation of the anterior chamber (AC) with saline was also performed to ensure that there were no PFCL bubbles in the AC.

All the eyes were commenced on frequent topical steroids (Pred Forte eye drops) and antibiotics as a standard protocol. All three patients gave a written informed consent before the procedure.

RESULTS

There was one female and two males aged 60, 44, and 67 years, respectively. Patient 3 was diabetic, but achieved a good control of blood sugar. The other two patients had no systemic comorbidities. All three eyes had successful surgery with retention of the free neurosensory retinal graft within the MH. Integration of the graft with surrounding retinal tissue was evident on OCT after three months in patient 1, as shown in Figure 3. In patients 2 and 3, the free neurosensory graft plugged the MH as seen in Figures 5 and 8, which show the appearance of tissue plugging the MH. Postoperative visual acuity improved from 6/36 to 6/18 in one eye and remained same as preoperative vision in two eyes. No eye suffered a loss of vision. All three eyes were pseudophakic and maintained normal intraocular pressures postoperatively. There was no complication or excessive inflammation noticed from the five-day use of PFCL as tamponade. Full details of the cases are described below.

Complications

The only intraoperative complication of note, which occurred in patient 3, was intraoperative retinal hemorrhage that happened during the time of neurosensory retina harvest and continued as a postoperative vitreous hemorrhage. He had been on anticoagulants prior to the surgery. This hemorrhage was limited by the PFCL and an adjacent fresh site of harvest was then chosen, and the procedure was completed as planned. Two eyes had retraction of graft tissue, which was evident on postoperative OCT.

Case 1

The first case is of a 60-year-old female, who had a reopened right eye MH after an initial

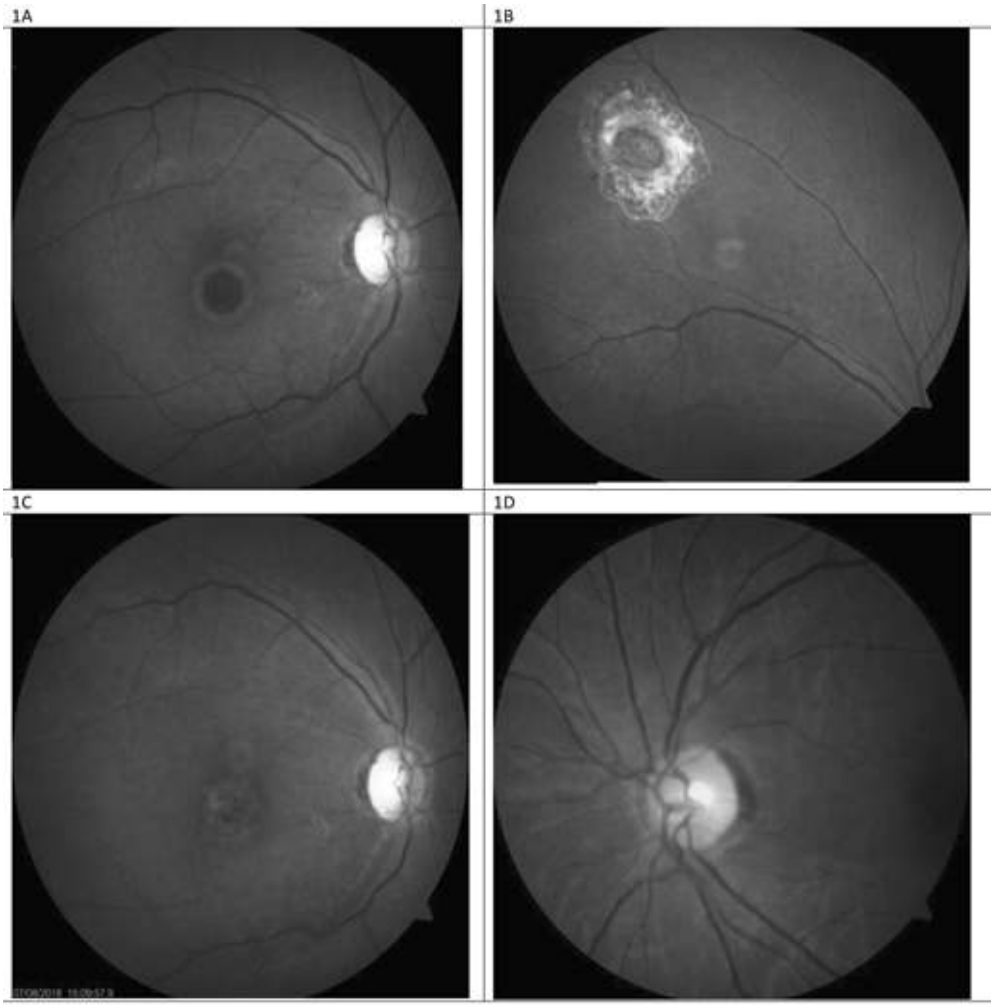

Figure 1. (A) Right eye preoperative fundus photograph showing the appearance of a recurrent macular hole occurring in patient 1; Pre-ART surgery. (B) Laser scar surrounding the site of neurosensory retinal harvest, anterior to the superotemporal arcade. (C) Post-ART surgery fundus photograph showing appearance of the free neurosensory retinal graft over the macular hole. (D) Normal-appearing left eye of the same patient.

internal limiting membrane (ILM) peel procedure in November 2014. Visual acuity was 6/36, and she complained of a persistent central scotoma due to the recurrent MH (Figure 1A). The pre-ART MH base diameter was 1200 microns (Figure 2). ART surgery was performed in July 2018. Site of neurosensory retinal harvest was anterior to the superotemporal arcade (Figure 1B). Post ART surgery, visual acuity improved to 6/18 at two months postoperative visit and had remained so till her last clinic visit in December 2019. The MH was closed, and the retinal graft remained within the MH (Figure 1C). Her left eye macula was normal (Figure 1D). There was preservation of some of the ellipsoid zone (EZ) in the free retinal patch, and this appeared to be continuous with the EZ of the adjacent host retina as seen on OCT (Figure 3).

Case 2

The second case is of a 44-year-old male, who presented with a chronic total retinal detachment and proliferative vitreoretinopathy of greater than six months duration, with multiple peripheral retinal breaks and a MH. Right eye was blind from rubeotic glaucoma.

He had a vitrectomy with silicone-oil tamponade in January 2017 followed by removal of the silicone oil in August 2017 with successful retinal reattachment. He regained a postoperative vision of 6/36, however, the MH persisted as shown in the OCT image (Figure 4).

The pre-ART MH base diameter was 1060 microns. ART surgery was performed in January

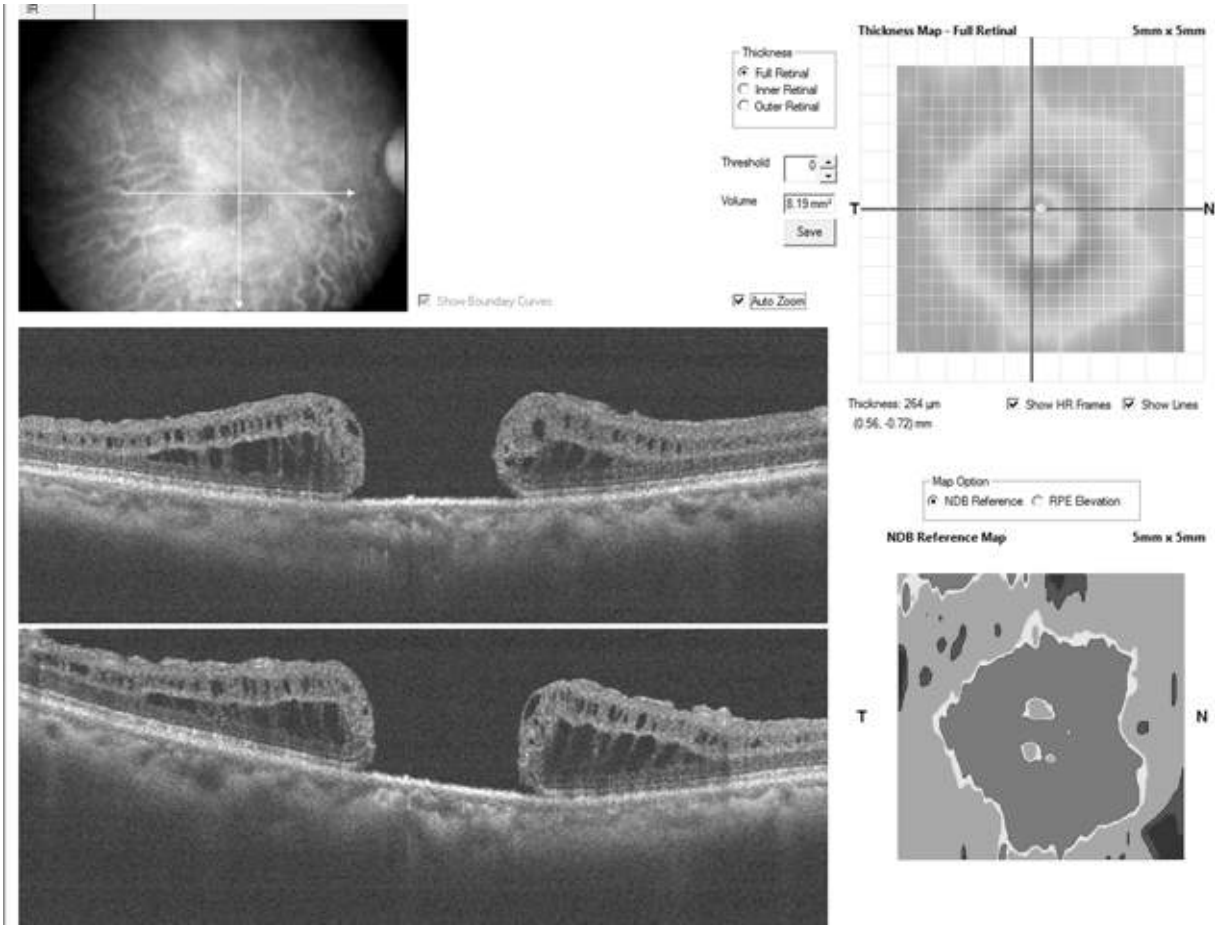

Figure 2. Patient 1; preoperative OCT cross-line horizontal and vertical scans of the macular hole.

2019. Site of neurosensory retinal harvest was anterior to the inferotemporal arcade.

Post ART surgery, visual acuity remained 6/36, however, he gave a subjective impression of visual benefit since he claimed to now see facial details better than preoperatively (including facial marks which he could not see prior to ART surgery).

There was anatomical MH closure, with retention of the retinal graft within the MH in the early postoperative period as seen on OCT (Figure 5). However, there were persistent intraretinal cystic spaces. At the third postoperative month, the graft tissue was noticed to have retracted as there was now a gap between the edge of the tissue graft and the edge of MH as seen on OCT (Figure 6). Despite this, the outer retina was noted to be present in the graft tissue on OCT (Figures 5 and 6).

Case 3

The third case is of a 67-year-old male who presented with a chronic MH and emulsified silicone oil in the right eye (Figure 7). He had a history of having had combined vitreoretinal and cataract surgery in November 2014 during which silicone oil tamponade was used. Visual acuity was 6/36. The MH base diameter was 790 microns and there was emulsified silicone oil within the MH as seen on OCT.

Silicone oil removal combined with ART was performed in January 2019. The site of neurosensory retinal harvest was anterior to the inferotemporal arcade. Intraoperatively, at the time of graft tissue harvest there was a significant retinal hemorrhage. This hemorrhage occurred because the patient was on anticoagulant therapy prior to surgery. The hemorrhage was however limited by the PFCL. This hemorrhage necessitated the abandoning of the harvest site and moving to an adjacent site. Postoperative vision remained 6/36. Postoperative OCT revealed that the retinal graft remained within the MH as shown in Figure 8. However, retraction of the graft as happened in patient 2 was evident, and outer

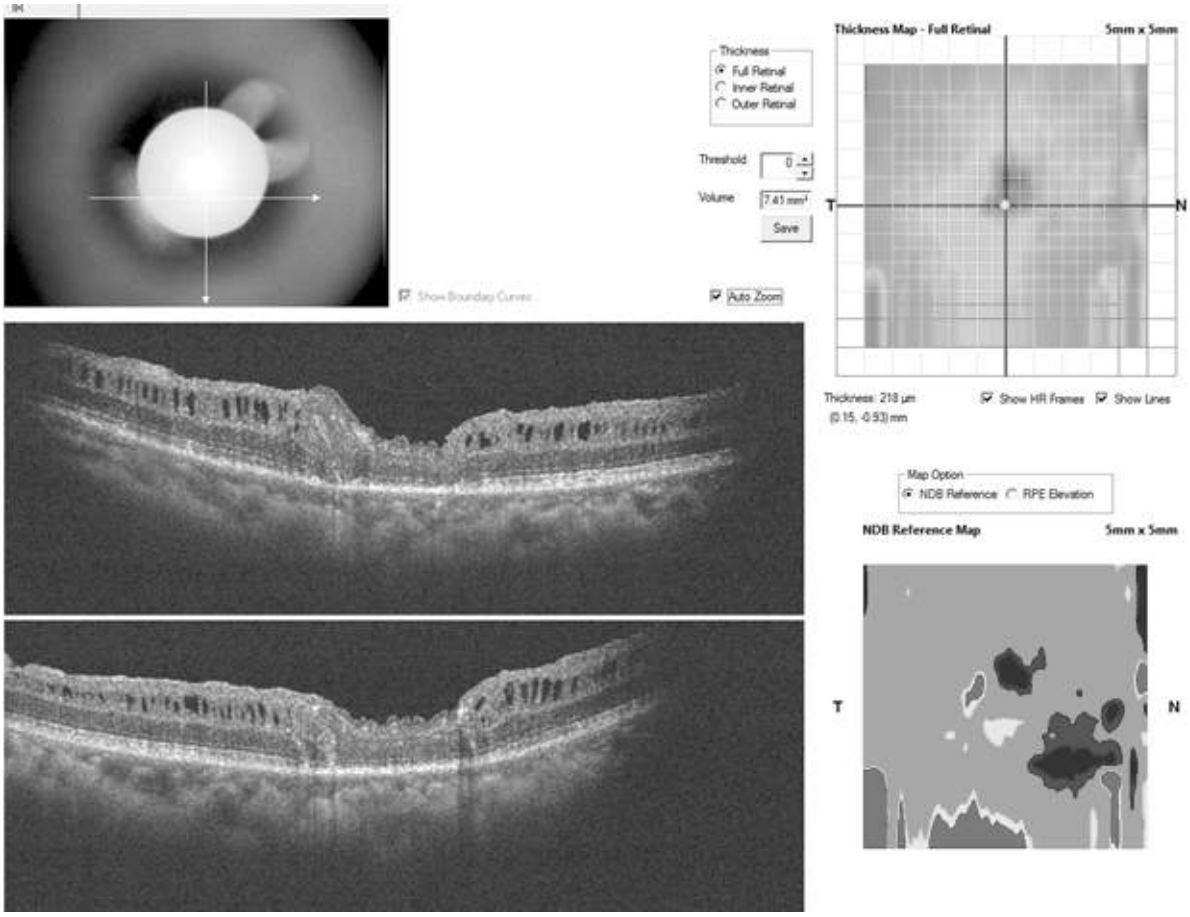

Figure 3. Patient 1; postoperative OCT cross-line horizontal and vertical scans showing integration of the ellipsoid zone of the retina graft tissue with the adjoining host retinal tissue.

retinal layers or intraretinal structures were not preserved.

DISCUSSION

Grewal and Mahmoud first reported the successful transplantation of extramacular retinal tissue into a refractory MH, with good anatomical and functional outcome.[1] Prior to this, several authors have published works on transplantation of retinal pigment epithelium for the treatment of neovascular age-related macular degeneration (AMD).[4–6] Since this first report, there have been few case reports on the use of ART for treatment of difficult to treat MHs, such as those associated with retinal detachment.[7, 8] Recently, an international collaboration published the largest series on the use of ART for the repair of refractory, large MHs.[9] The findings by this group could provide a yardstick against which future outcomes can be measured. Our consecutive series adds to the growing number of cases and seems to agree with current reports. We found that ART can be performed with relative safety and that it was effective for achieving anatomical MH closure. However, improvements in visual acuity are possibly not yet optimized and may revolve around graft size and harvest site.

Graft size may be an important factor as it was for patients 2 and 3; there was a postoperative retraction of the graft tissue with a reduction in graft size. This suggests that the size of the free retinal graft should be larger than the MH to ensure MH closure even after the anticipated graft retraction, as was suggested in the original report.[1]

Improving visual acuity remains a challenge. In our study, one eye had a Snellen acuity improvement in vision, but vision remained the same in the other two eyes. In the collaborative study, vision remained unchanged in 41.5% of eyes and worsened in 21.9% of eyes. None

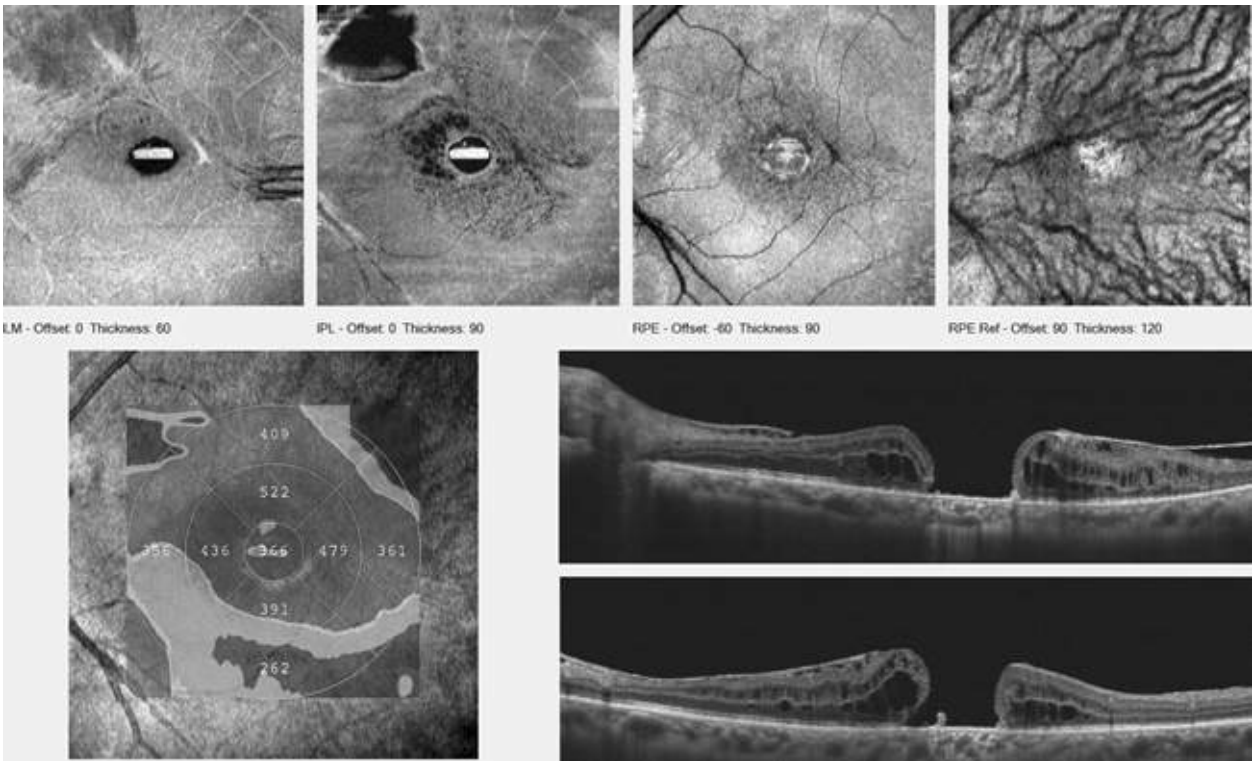

Figure 4. Patient 2; preoperative OCT cross-line horizontal and vertical scans of the macular hole; plus enface images of the macular hole.

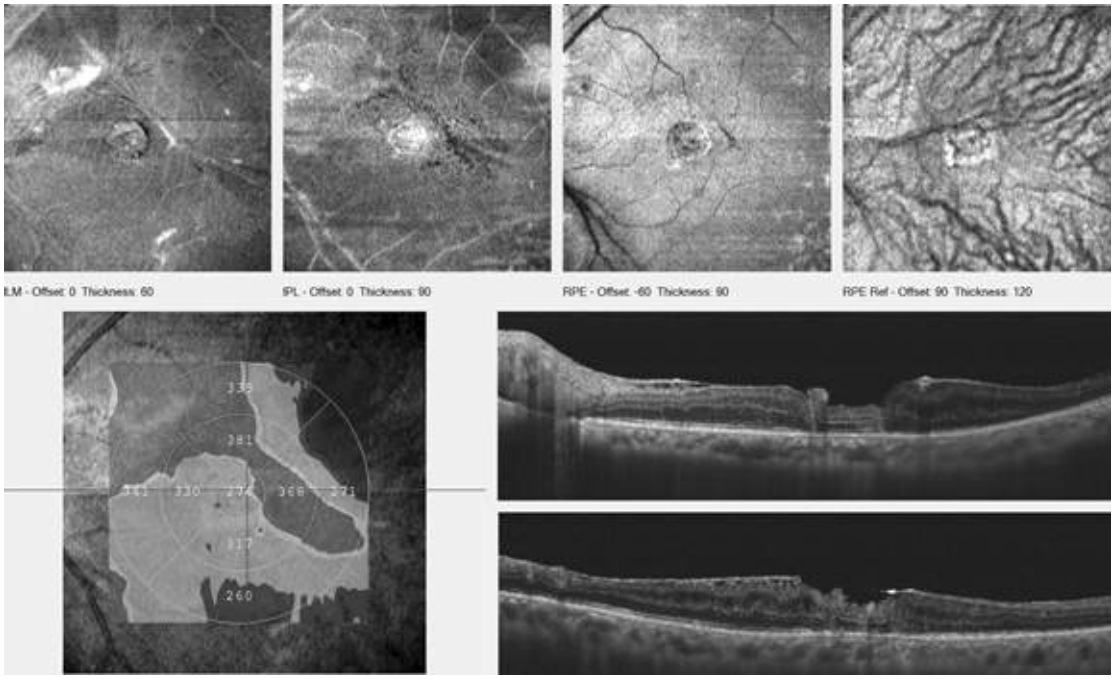

Figure 5. Patient 2; early postoperative OCT cross-line horizontal and vertical scans with graft tissue plugging the macular hole. The intraretinal architecture is preserved.

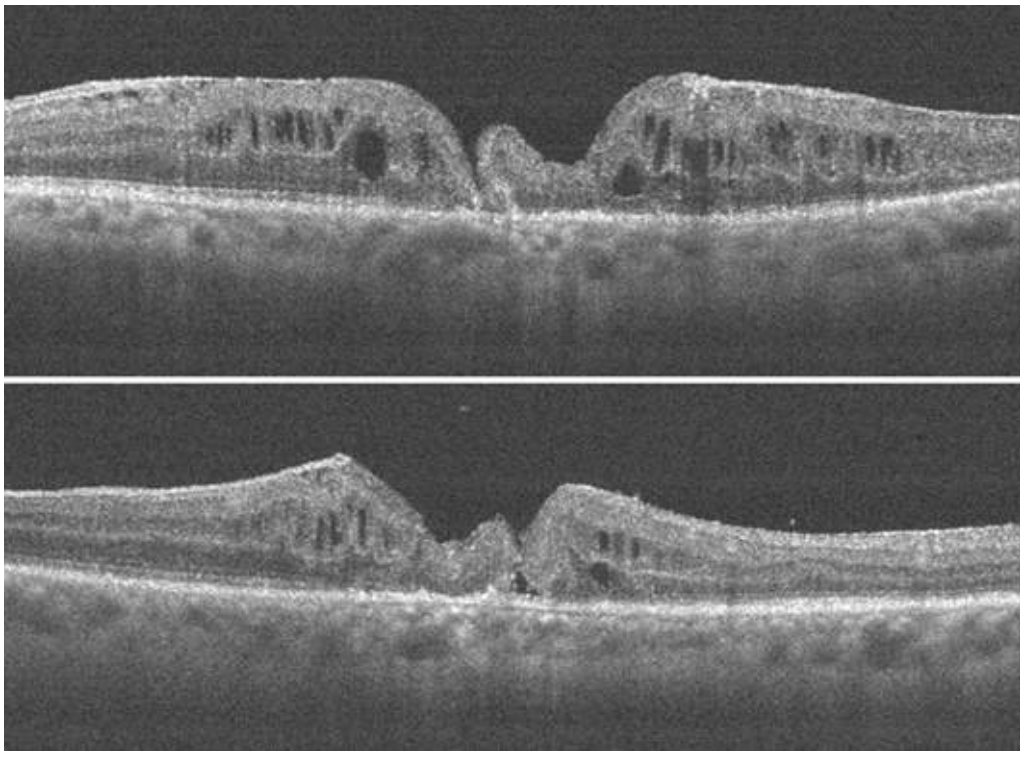

Figure 6. Patient 2; later postoperative OCT cross-line horizontal and vertical scans with retraction of the retinal graft. There is a gap between the edge of the graft and the macular hole.

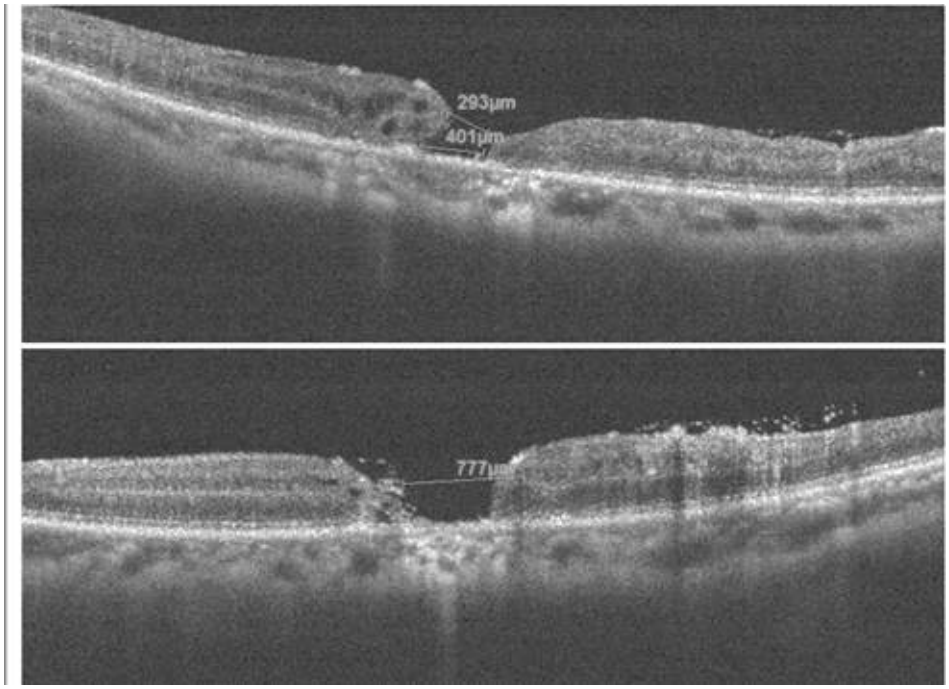

Figure 7. Patient 3; preoperative OCT cross-line horizontal and vertical scans of the macular hole. Emulsified silicon oil is present on the retinal surface and within the macular hole.

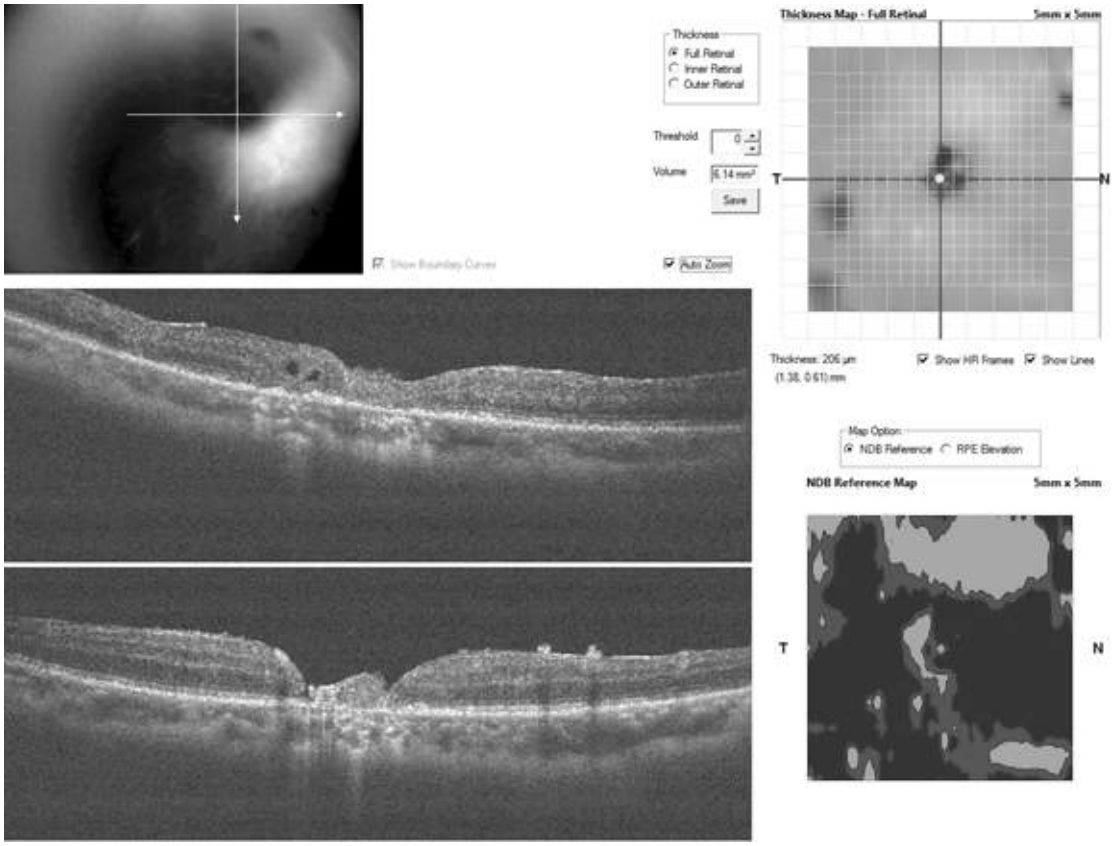

Figure 8. Patient 3; postoperative OCT cross-line horizontal and vertical scans showing retraction of the retinal graft and no preservation of the intraretinal architecture.

of our patients had a worse postoperative vision, including patient 3 who suffered intraoperative hemorrhage. However, our sample size is much smaller than the reference study. Understanding the functionality of the graft is important to be able to determine visual outcomes in future. Microperimetry can be a useful tool in assessing functionality of the graft tissue, when testing response to light. Other studies reported retinal graft tissue response to microperimetric light testing, but we were not able to perform this in our study.[2, 9]

In terms of complications, the major postoperative complication encountered was in patient 3 who suffered a retinal and vitreous hemorrhage. The collaborative study also reported one case of the vitreous hemorrhage. Our patient had been on anticoagulants. We therefore recommend considering discontinuation of anticoagulant use before performing this procedure. In our patient, this hemorrhage was limited by the PFCL. Stopping and limiting intra- and postoperative hemorrhage is another useful function of PFCL, as was demonstrated, in this case.[10] In all three cases, PFCL was used as tamponade for only five days and was then replaced with air. No complications of PFCL tamponade were noticed. In particular, no exaggerated intraocular inflammation due to the use of PFCL was seen within the period of follow-up. Short-term use of PFCL tamponade has been reported previously without significant complications and was also used in the collaborative study.[2, 9, 11] PFCL served as a good tool to ensure the free graft covered the MH. Furthermore, it is possible that the PFCL may provide oxygen for graft survival in the early stages of transplantation.[13]

To conclude, this study appears to concur with previous reports, suggesting that ART is a relatively safe technique in the management of refractory, chronic MHs. The visual outcome, which may be unpredictable, requires further research to determine optimum graft to host (MH) size and functionality at the macula.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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Original Article

The Adequate Number of Histopathology Cross-sections of Temporal Artery Biopsy in Establishing the Diagnosis of Giant Cell Arteritis

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Abstract

Purpose: To determine the appropriate number of histopathological cross-sections that are required for a conclusive diagnosis of giant cell arteritis (GCA).

Methods: In this cross-sectional study, the number of sections per slide for paraffin-embedded blocks for 100 randomly selected cases where GCA was suspected and those for negative temporal artery biopsies (TABs) were compared with the number of cross-sections per specimen for eight positive-TABs. All aforementioned examinations were conducted at our center from 2012 to 2016. Then, negative-TABs were retrieved and re-evaluated using light microscopy considering the histopathological findings of GCA.

Results: Ninety-five paraffin blocks were retrieved. The original mean biopsy length was 15.39 ± 7.56 mm. Comparison of the mean number of cross-sections per specimen for both the positive- and negative-TABs (9.25 ± 3.37 and 9.53 ± 2.46) showed that 9.87 ± 2.77 [95% confidence intervals (CI)] cross-sections per specimen were sufficient for a precise GCA diagnosis. There was no statistically significant difference in the mean biopsy length (P = 0.142) among the eight positive-TABs. Similarly, no significant difference was observed in the number of cross-sections per specimen (P = 0.990) for positive-TABs compared to those for the negative-TABs. After the retrieval of negative-TABs, the mean number of total pre- and post-retrieval cross-sections per specimen was 17.66 ± 4.43. Among all retrieved specimens, only one case (0.01%) showed the histopathological features of healed arteritis.

Conclusion: Positive-TABs did not reveal more histological cross-sections than the negative ones and increasing the number of cross-sections did not enhance the accuracy of TAB.

Keywords: Giant Cell Arteritis; Histopathology Cross-sections; Temporal Artery Biopsy

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INTRODUCTION

Giant cell arteritis (GCA) is characterized by granulomatous vasculitis of large and medium-sized vessels, and its worldwide annual

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incidence rate ranges from 1.28 to 29.1 per 100,000 among individuals aged over 50 years.[1–3] Approximately 15–20% of GCA patients may develop permanent loss of vision.[4] As per the guidelines of the American College of Rheumatologists (ACR), diagnosis of GCA is primarily based on the presence of characteristic clinical features and laboratory findings of elevated levels of acute-phase reactants.[5–7] Temporal artery biopsy (TAB) is considered as the gold standard diagnostic test for GCA.[8, 9] A positive-TAB test is mainly defined as vasculitis with infiltration of mononuclear cells with or without the presence of multinucleated giant cells, disruption of the internal elastic lamina, and intimal hyperplasia.[10–12] However, sometimes TAB may indicate intermediate findings that make it difficult to distinguish GCA from other pathologies such as healed arteritis or even arteriosclerosis that occurs in elderly patients.[13, 14] Thus, TAB has low sensitivity and it may show negative results in 15–40% of patients.[15–19] Additionally, the number of biopsies, length of the artery sampled, sectioning techniques, and histopathological criteria for diagnosing arteritis, presence of skip lesions, and previous treatment with corticosteroids may contribute to false-negative results.[20, 21]

This study was performed at a tertiary referral center to determine the appropriate number of cross-sections for a TAB examination that are required for a conclusive GCA diagnosis.

METHODS

In our center, TAB cross-sections are routinely cut into 2–3 mm-long slices and each of them is embedded transversely in a paraffin block. Next, hematoxylin and eosin-stained serial sections of 5-μm thickness are prepared at three-step levels with 25-μm intervals. TAB specimens are considered positive if a narrow lumen, irregular intimal thickening, and fragmentation of the internal elastic lamina with inflammation of the vessel wall (composed of lymphocytes and epithelioid histiocytes with or without multinucleated giant cells) are observed. In borderline cases including those wherein inflammation is limited to the adventitia, additional levels are requested. In this cross-sectional study, the histopathology reports of 205 archived temporal artery biopsies (TABs; performed between 2012 and 2016) were re-evaluated. The length of the biopsy and total number of cross-sections per specimen for eight positive-TAB cases were compared with those for a 100 computer-assisted randomly selected negative-TABs, which were performed during the same period. Then, paraffin-embedded blocks of these original negative-TABs were retrieved and >90% of each paraffin block was sectioned. A single ophthalmic pathologist (RAAN) re-evaluated all the newly retrieved sections, considering the previously mentioned histopathological findings that characterize GCA. The methods and main outcomes of the study have been summarized in Figure 1. In addition, the revised ACR-2016 (rACR) scores from the available medical records of patients with positive- and negative-TABs conducted in 2016 were evaluated.

SPSS software version 22.0 (IBM Corp., Armonk, NY) was used for statistical analyses. Results are reported as mean ± standard deviation. The Mann–Whitney U test was used to analyze quantitative variables. *P*-value < 0.05 was considered statistically significant.

RESULTS

Of the total 205 TABs conducted during 2012–2016, eight reports were positive for GCA. From the remaining 197 negative biopsies, initially a 100 paraffin-embedded blocks were randomly selected for retrieval. Since five paraffin blocks were not suitable for retrieval, finally the results of 95 specimens were evaluated.

The mean age of the patients was 62.75 ± 12.83 years and 54% were female. Two patients had non-simultaneous bilateral biopsies. The mean biopsy length was 15.39 ± 7.56 mm.

The number of slides per specimen, cross-sections per slide, and the number of slides per mm of biopsy length before and after retrieval have been summarized in Table 1.

In the eight positive-TAB specimens, the mean artery length was 16.70 ± 8.48 mm and the mean number of cross-sections per specimen was 9.25 ± 3.37. No statistically significant differences were found in the biopsy length (P = 0.142) and the number of cross-sections per specimen (P = 0.990) among the eight positive-TABs and when the positive TABs were compared to the pre-retrieval negative-TABs (Table 1). Comparison of the number of cross-sections per specimen for pre-retrieval

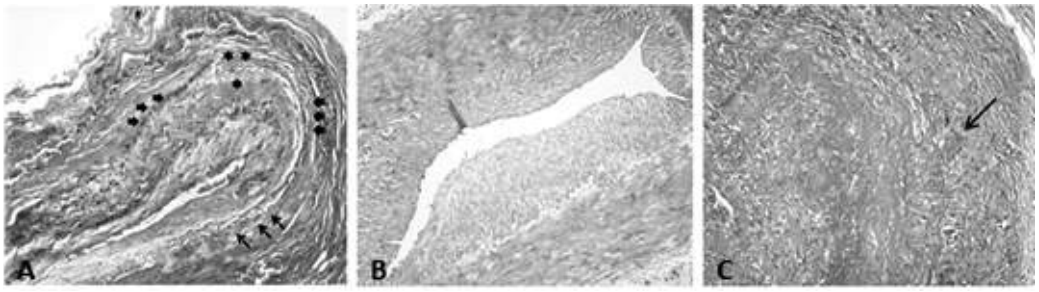

Figure 1. (A) Healed arteritis: note the narrow lumen and minimal intramural lymphocytic infiltration, scarring, and fibrosis (asterisks) in areas with destroyed elastic lamina (short arrows) compared to the areas of intact elastic lamina (long arrows), (H&E staining ×40). (B) Normal artery, negative for GCA (H&E staining ×40). (C) Active GCA: note the obstruction of the lumen, arterial wall thickening, elastic lamina fragmentation, and intramural inflammation with multinucleated giant cells (arrow), (H&E staining ×100). GCA, giant cell arteritis; H&E, Hematoxylin and Eosin

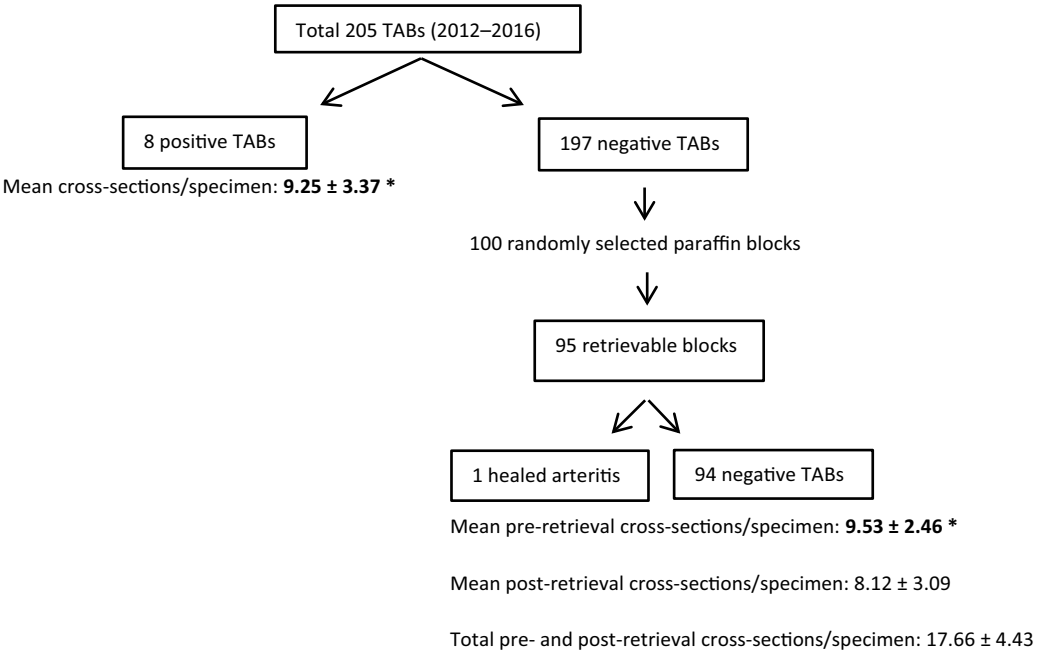

Figure 2. Summary of the methods and main outcomes of the study.
*There was no significant difference in the mean number of cross-sections per specimen between the positive- and original negative-TABs (P = 0.990). Based on the comparison of these two items, 9.87 ± 2.77 (95% confidence intervals) cross-sections per specimen were considered sufficient for precise results.
In addition, retrieval of the original negative-TABs at multiple levels did not enhance the accuracy of TAB for diagnosing GCA.
GCA, giant cell arteritis; TAB, temporal artery biopsy

negative-TABs (9.53 ± 2.46) and those for the eight positive-TABs (9.25 ± 3.37) showed that 9.87 ± 2.77 [95% confidence intervals (CI): 9.16–10.59] cross-sections per specimen were sufficient for precise diagnostic results.

In the clinical evaluation of 95 negative-TABs, we only found 50 cases with complete medical records that met the 2016 rACR criteria,[7] and the mean overall rACR score for these patients was 3.86 ± 1.12. In contrast, the mean overall rACR score for the eight patients with positive TABs in our study was 5.87.

Histopathological evaluation of retrieved biopsies revealed only one case (0.01%) of healed arteritis with mild intramural lymphocytic infiltration, narrowing of the lumen, fragmentation, and destruction of the internal elastic lamina with scarring of the artery wall (Figure 1). This patient had an rACR score of 3, and had undergone bilateral TAB, with original pathology reports showing negative results for GCA.

Table 1. Comparison of positive- and negative-TABs (pre- and post-retrieval)

Parameter	Negative-TAB (*N* = 95)		Positive-TAB (*N* = 8) (original)	*P*-value (between positive-TABs and pre-retrieval negative-TABs)
	Pre-retrieval (original)	Post-retrieval		
Mean biopsy length (mm)	15.39 ± 7.56	N/A	16.70 ± 8.48	*P* = 0.142
Mean number of slides/specimen	3.24 ± 0.74	2.83 ± 0.96	3.25 ± 0.82	N/A
Mean number of cross-sections/slide	2.93 ± 0.26	2.84 ± 0.39	2.87 ± 0.36	N/A
Mean number of cross-sections/specimen	9.53 ± 2.46	8.12 ± 3.09	9.25 ± 3.37	*P* = 0.990*
Mean number of cross-sections/mm biopsy length	0.72 ± 0.29	N/A	0.55 ± 0.46	N/A
Mean number of total pre- and post-retrieval cross-sections/specimen	17.66 ± 4.43		N/A	N/A

*Comparisons of positive-TABs and pre-retrieval negative-TABs
N/A, not applicable; TAB, temporal artery biopsy

DISCUSSION

Currently, no specific guidelines have been formulated regarding the adequate number of cross-sections needed for accurate biopsy results of TAB specimens.

Although TAB is considered as the gold standard test for diagnosing GCA, ambiguous findings may lead to inconclusive diagnosis or inaccurate results.[8, 9] The extent of sectioning, length of the artery, and presence of skip lesions as well as unilateral or bilateral biopsies are among the factors that may affect TAB results.

Characteristic histopathological findings of active GCA include pan-arteritis that is most pronounced in media, with or without multinucleated giant cells and fragmented internal elastic lamina. In contrast, healed arteritis is characterized by diffuse intimal thickening, intimal and medial fibrosis with variable degree of lymphocytic infiltration, loss of internal elastic lamina, and adventitial scarring which correlates with prior history of GCA symptoms and a higher-than-normal erythrocyte sedimentation rate (ESR). Increased ESR is part of the reparative process and not considered a marker for active arteritis.[22] However, occasionally, it may be difficult to distinguish the aforementioned pathology from changes resulting from aging and atherosclerosis.[23–25]

According to the literature, routine evaluation of TABs at multiple levels does not enhance the diagnostic yield and is not cost-effective.[20, 26–29] In a study conducted by Taylor *et al*[29] for determining the threshold specimen length for pathological examination and interpretation, there was no statistically significant difference between the number of total cross-sections per specimen used for positive-TABs (22.3) and those for the negative ones (21.6). In our study, there was no statistically significant difference in the mean biopsy length and mean number of cross-sections per specimen for the eight positive-TABs compared to those of the negative-TABs before retrieval. These results indicate that diagnosis in positive-TAB cases did not require a greater number of cross-sections than those required in negative ones.

Methods for the technical processing of a temporal artery differ across centers. Some centers examine the artery in one longitudinal section and two transverse ones, which may be obtained from either end of the artery if the arterial length is sufficient.[20, 29, 30] TAB processing at our center is performed using transverse sections

according to a recommended protocol,[31] with some modifications that have been described in the Methods section.

In this study, we determined that 9.87 ± 2.77 cross-sections per specimen were sufficient to achieve precise results at our center. Further, additional retrieval of the negative-TAB specimens did not increase the chances of obtaining positive GCA results. However, additional studies are required to determine the appropriate number of cross-sections for a TAB evaluation.

"Skip lesions," which are foci of discontinuous vasculitis, are found in 8–28% of GCA-positive biopsies.[23, 26, 32] Skip lesions are not common in temporal arteritis, and skipped areas are approximately 330 μm to 1 mm in length.[27] Although the idea is controversial, it has been suggested that a length of 5–7 mm could be the threshold for diagnostic sensitivity of TAB.[27, 33] This implies that even short TAB specimens might be sufficient to visualize the histological features of arteritis.[27] Our results indicate that there was only one case of healed arteritis among 95 negative-TAB cases. These results are compatible with those of Chakrabarty *et al*,[20] wherein only 1 out of 132 cases showed positive GCA features after performing sections at multiple levels. However, the length of the artery in our positive case was 13 mm. The extent of the agreement between the first and second slide readings using the Kappa coefficient before and after the retrieval of the negative-TAB specimens could not be calculated due to high similarity between the results. However, regardless of statistical significance, there was approximately a 98% agreement between the two readings since 94 out of 95 negative-TAB specimens were also negative in the second histopathological evaluation.

In general, it is standard to perform a unilateral TAB when GCA is clinically suspected; the contralateral artery biopsy is done if the clinical suspicion is high and the first biopsy is negative.[34] Otherwise, the chance of a positive second biopsy ranges from 5% to 9%,[35] and if the clinical suspicion is low, a unilateral biopsy is sufficient to rule out the diagnosis. The single biopsy after retrieval that was positive for healed arteritis was that of a left temporal artery from a 67-year-old female, which was taken seven days after a negative-GCA result from the first biopsy of the right artery. She had been treated with intravenous methylprednisolone for three days followed by oral prednisolone at a dose of 1 mg/kg before performing TAB.

In general, for cases where GCA is suspected, immediate treatment with high-dose steroids even before a biopsy is recommended. Since the resolution of inflammatory infiltration is usually slow, the chance of detecting active inflammation is not affected by steroid therapy if the biopsy is performed within two weeks.[36] In our case of healed arteritis after retrieval, the specimen was taken seven days after starting steroid therapy. Therefore, the findings could be due to a previous episode of GCA rather than aging-related arterial changes.

The diagnosis of GCA does not always require a positive-TAB, and approximately 15–40% of patients with GCA are TAB-negative.[15–19] This phenomenon where a high percentage of people who have negative biopsies are diagnosed with GCA has resulted in disagreement among neuro-ophthalmologists and rheumatologists regarding the criteria for GCA. It has been recommended that TAB should be performed only for patients with rACR scores of 3 and 4, since there is higher variability in TAB results for other patients.[7] Among the 95 suspected GCA cases with negative TABs, we reviewed the medical records of 50 patients whose mean overall rACR score was 3.86 ± 1.12. These results were similar to those of Abri Aghdam *et al*[37] (mean score of 3.88 ± 1.19 for negative biopsies). In addition, the mean overall rACR score of the eight patients with positive-TABs in our study was 5.87. After retrieval of negative-TABs, we identified only one case of healed arteritis with an rACR score of 3.

Positron emission tomography[38] and 3 tesla-magnetic resonance imaging[39] are new technologies that are now being regularly used in the diagnosis and monitoring of GCA disease progression. Although, the use of non-invasive color duplex ultrasonography reduces the chances of false-negative TABs due to skip lesions,[40] it is an operator-dependent technique.

It is important to consider that the final diagnosis in TAB-negative patients may indicate a spectrum of conditions mainly including other rheumatologic diseases, presence of non-temporal arteries with GCA, infectious diseases, neoplastic diseases, and neuro-ophthalmic conditions.[7, 41]

In conclusion, positive-TABs in our study did not require more cross-sections than the negative

ones. Further, TAB examination at multiple levels did not increase the diagnostic yield of the test. In this study, 9.87 ± 2.77 cross-sections per specimen were sufficient for a precise diagnosis of GCA.

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Conflicts of Interest

There are no conflicts of interest.

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Review Article

Medication-induced Uveitis: An Update

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Abstract

Drug-induced uveitis is an uncommon but important cause of ocular inflammation. Uveitis can be seen in association with various systemic, topical, and intraocular medications. In this article, we review common medications associated with uveitis. Most cases of drug-induced uveitis resolve with termination of the suspected medication with or without administration of topical or systemic steroids. It is important for clinicians to readily identify medications that may cause uveitis in order to provide rapid treatment, avoid consequences of longstanding inflammation, and prevent costly and excessive laboratory testing.

Keywords: Uveitis; Medication; Medication-induced Uveitis

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INTRODUCTION

Uveitis is generally defined as inflammation in the uveal tract, which is composed of the iris, ciliary body, and choroid. Uveitis most commonly affects young, working-age adults, and it has been reported to be responsible for 5–20% of all cases of blindness in the United States and worldwide.[1, 2] According to the International Uveitis Study Group, uveitis is classified based on anatomic location of involvement, and can manifest as anterior, intermediate, posterior, and panuveitis.[3–5] It can also be classified based on etiology, including infectious, non-infectious, and masquerade syndromes.[3]

Medications are a rare cause of uveitis, comprising <0.5% of cases.[1, 6] Drug-induced uveitis, although uncommon, can sometimes cause severe inflammation and is easily misdiagnosed. Hence, a high degree of suspicion is required to establish the diagnosis. Several criteria have been proposed to describe the causality of adverse events from medications, including a reaction that is frequently described and documented, recovery upon drug withdrawal, more severe reaction with higher doses, and recurrence with drug rechallenge; rarely does a drug meet all of these criteria.[7] The pathogenesis of drug-induced uveitis is not fully understood, but various mechanisms have been proposed

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including a direct effect from topical application or intracameral injection, metabolite effects from drug detoxification, type III hypersensitivity reaction with immune complex deposition of antidrug antibodies, and antigens liberated from drug-induced death of microorganisms.[8] Medications may also be broken down into free radicals that bind melanin in the uveal tract, which can cause toxicity and reduce melanin's ability to scavenge other free radicals, causing uveitis.[8, 9]

In the current article, we review common systemic, topical, intracameral, and intravitreal medications associated with uveitis. New medications linked to uveitis that have been reported in the literature will also be highlighted.

TOPICAL MEDICATIONS

Brimonidine

Brimonidine is an alpha-2 adrenergic agonist that is administered topically to reduce intraocular pressure. Acute granulomatous or non-granulomatous anterior uveitis with an elevated intraocular pressure has been reported with brimonidine use.[10, 11] The mechanism by which this inflammatory response occurs is largely unknown, but there is a higher risk in patients with history of allergic conjunctivitis from brimonidine use and in patients using drops for >12 months.[12] Stopping the medicine usually resolves the inflammation and rechallenge results in recurrence of uveitis.[11]

Prostaglandin analogues

Topical prostaglandin analogs increase uveoscleral outflow of aqueous humor, and are used in the treatment of glaucoma.[13] Latanoprost is associated with a 5% risk of anterior uveitis within the first several months of treatment.[14, 15] A significant increase in anterior chamber cell and flare has been reported at three and six months after the initiation of latanoprost, travoprost, and bimatoprost.[16] This may be due to breakdown of the blood–aqueous barrier and subsequent elevation of cytokines in the anterior chamber.[16, 17] Use of these drops has also been associated with the development of cystoid macular edema.[15]

INTRAOCULAR INJECTIONS

Vancomycin

Intracameral vancomycin is used for prevention of endophthalmitis following cataract surgery.[18] However, vancomycin use has been associated with hemorrhagic occlusive retinal vasculitis (HORV), often presenting with anterior chamber and vitreous inflammation as well as painless vision loss.[18] All reported cases of HORV presented within 1–21 days (mean ~8 days) after vancomycin use. These patients received vancomycin via intracameral injection, intravitreal injection, or through the irrigation bottle. Retinal vasculitis in most of these patients resulted in poor visual outcomes.[18] The proposed mechanism by which this reaction occurs is via a delayed immune response to the drug itself.[18]

Anti-vascular endothelial growth factor (anti-VEGF) agents

Anti-vascular endothelial growth factors (anti-VEGFs) such as bevacizumab (Avastin®), ranibizumab (Lucentis®), and aflibercept (Eylea®) are commonly used in the treatment of neovascular age-related macular degeneration, macular edema secondary to diabetic retinopathy and vascular occlusion, and proliferative retinopathies. After two years of anti-VEGF therapy, there is a two-fold increase in the prevalence of uveitis compared to disease-matched controls.[19]

Intraocular inflammation has been the dose-limiting variable for intravitreal use of ranibizumab.[20] During the FOCUS trial, a 12% rate of uveitis was found following ranibizumab injection; however, the majority of these cases occurred prior to switching from the lyophilized formulation (no longer in use) to the liquid formulation, as well as prolonging the interval between injection and verteporfin photodynamic therapy.[21] These changes were made to the protocol due to concerns that these factors increased the risk of uveitis.[21] ANCHOR and MARINA clinical trials estimated that approximately 2% of patients receiving intravitreal injections of ranibizumab developed significant inflammation (classified as 3+ or more cell in the anterior chamber) within three weeks of injection.[21, 22] The HORIZON extension study evaluated the long-term safety of ranibizumab in patients

who had completed the ANCHOR, MARINA, or FOCUS trials, and found that significant intraocular inflammation presented in 1.7–2.6% of the eyes receiving ranibizumab for one to three years.[23] Another study reported that both bevacizumab and aflibercept were associated with a <1% risk of significant intraocular inflammation.[24]

The newest drug in the anti-VEGF family is Brolucizumab (Beovu®), which comprises a humanized single-chain antibody fragment with a molecular weight of 26kDa, and recently received FDA approval for use in patients with wet age-related macular degeneration.[25] The efficacy and safety of brolucizumab was evaluated and compared with aflibercept in the HAWK and HARRIER phase-three multicenter randomized trials, which found that uveitis was present in 2.2% and 0% of patients taking brolucizumab and aflibercept, respectively.[25] About 90% of these cases were mild to moderate, and were treated successfully with topical corticosteroids.[25] In the post-hoc analysis of the HAWK and HARRIER data, Mones et al[26] reported that the incidence of intraocular inflammation was 4.6% in eyes treated with brolucizumab; 3.3% of patients developed retinal vasculitis with occlusive vasculitis in 2.1% of the eyes.[26] In addition, 0.7% of the cases experienced at least moderate vision loss (≥15 ETDRS letters), and most of these events occurred in the first six months of drug use. In the same study, the incidence of intraocular inflammation in aflibercept-treated eyes was 1.1%, with at least moderate vision loss in 0.14%.[26] The mechanism for intraocular inflammation secondary to anti-VEGF injections is not fully understood, but some experts suggest that it is due to the formation of anti-drug antibodies and subsequent hypersensitivity reactions to the medicine.[27]

Triamcinolone acetonide

Intravitreal injection of triamcinolone acetonide, used in the treatment of non-infectious uveitis and macular edema, has been associated with sterile inflammation and non-infectious endophthalmitis. The reported incidence is between 0.5% and 9.7% of injections, and significantly increases with the use of preservatives.[14]

SYSTEMIC MEDICATIONS

Cidofovir

Cidofovir is a nucleotide analog that inhibits viral DNA polymerase and is used for the treatment of infection with herpesviruses such as cytomegalovirus (CMV).[28] Uveitis has been reported in 25–50% of patients after a median of 11 weekly doses of intravenous cidofovir.[29–32] Uveitis is more common after intravitreal use of cidofovir.[31] HIV patients who receive cidofovir for CMV retinitis are at higher risk of uveitis. In these patients, treatment with highly active anti-retroviral therapy (HAART) is an independent risk factor, likely secondary to higher circulating levels of cidofovir in setting of HAART.[33] Moreover, it has been suggested that an elevated level of CD4+ T-cells in HIV+ patients is a risk factor for cidofovir uveitis, which makes it difficult to differentiate from immune recovery uveitis.[33, 34] Concurrent use of probenecid, on the other hand, can significantly decrease the rate of ocular side effects as it minimizes intraocular secretion of cidofovir.[35] Cidofovir-induced hypotony is seen in 10–20% of HIV+ patients treated for CMV retinitis.[31, 32] The inflammation and hypotony usually respond to treatment with topical steroids and cycloplegic agents, but hypotony can persist for a long period of time.[30, 35, 36]

Rifabutin

Rifabutin, used for prevention and treatment of Mycobacterium avium complex (MAC) in immunocompromised patients, can cause unilateral or bilateral anterior uveitis (usually associated with hypopyon), intermediate uveitis, posterior uveitis, or retinal vasculitis.[14, 37] Uveitis is usually dose-dependent and commonly occurs between two weeks and seven months following the initiation of therapy.[38] Serum concentration and hence risk of inflammation increases with concurrent use of antifungal azoles, azithromycin, ethambutol, and some protease inhibitors through inhibition of hepatic cytochrome P450 enzymes.[28, 37] Notably, rifabutin-induced uveitis has also been reported in children and immunocompetent patients.[28] Inflammation usually resolves with topical steroids.[28]

Fluoroquinolones

Fluoroquinolones, which disrupt bacterial DNA synthesis by inhibiting DNA gyrase and DNA topoisomerase IV, have a broad spectrum of antibacterial activity indicated for the treatment of community-acquired pneumonia, sinusitis, chronic bronchitis, intra-abdominal abscesses, and skin infections.[39, 40] In Hinkle et al's retrospective analysis of 40 case reports of fluoroquinolone-induced uveitis, moxifloxacin was associated with 25 cases, but ofloxacin, ciprofloxacin, levofloxacin, norfloxacin, and gatifloxacin have also been reported to cause uveitis.[1, 28, 40, 41] The mean onset of uveitis is 13 days after the initiation of the drug (range: 0–20 days) and is usually bilateral; three characteristic findings in these patients include pigment dispersion with pigmented keratic precipitates and high intraocular pressure, diffuse iris transilluminating defects, and atonic pupils.[40–42] Fluoroquinolone-induced uveitis is more common in women and has been associated with HLA-B27 and HLA-B51 haplotypes, suggesting a possible autoimmune predisposition.[40] Uveitis is treated by discontinuing the drug and administration of topical corticosteroids.[41]

Bisphosphonates

Bisphosphonates, pyrophosphate analogs that inhibit osteoclast activity, are commonly used to inhibit bone resorption in osteoporosis and metastasis to bone.[28] They are strongly associated with anterior uveitis, scleritis, and episcleritis, with onset as early as 6 hr after intravenous administration.[1, 43, 44] In a large retrospective pharmacovigilance study, zoledronate caused 51% of bisphosphonate-induced uveitis, with alendronate and pamidronate causing 23% and 13%, respectively.[1] The bisphosphonates promote the release of inflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor (TNF)-α, which can target the uveal tract.[45] Resolution typically requires topical steroids and discontinuation of the medicine.[28]

TNF-α Inhibitors

TNF-α inhibitors are a group of anti-inflammatory biologics that are used for the treatment of rheumatologic diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease, as well as scleritis and uveitis.[41] Five anti-TNF- α drugs are currently approved for the use in autoimmune diseases, including four monoclonal antibodies (infliximab, adalimumab, golimumab, and certolizumab) and a soluble receptor blocker (etanercept).[46] All of these medications have been paradoxically associated with the development of anterior uveitis and chorioretinitis. Inflammation is more common with etanercept but has also been reported with infliximab and adalimumab.[47] The onset of uveitis is usually three weeks to six years after starting the therapy.[41, 47, 48] Sarcoidosis has also been reported in patients using etanercept.[46] The etiology of anti-TNF-α-induced uveitis is not fully understood, but it is hypothesized that decreased TNF-α levels leads to higher interferon levels and cytokine imbalances, resulting in auto-antibody formation and increased inflammation.[49] Treatment involves discontinuation of the drug, with severe cases requiring systemic steroids[41] [Figure 1].

Immune Checkpoint Inhibitors

Immune Checkpoint Inhibitors (ICIs) are emerging cancer immunotherapies used in metastatic melanoma and solid tumors.[1] They upregulate the immune system by blocking immune checkpoints that are regulators of immune system, thus leading to activation of T-cells and an immune response to tumor cells.[50, 51] The different types of ICIs approved for use in cancer patients include a CTLA-4 inhibitor (ipilimumab), programmed cell death protein 1 (PD-1) inhibitors (pembrolizumab, nivolumab, and cemiplimab), and PD-1 ligand inhibitors (atezolizumab, avelumab, and durvalumab).[14, 52] These medications have recently been linked to ocular inflammation. Uveitis is seen in 1% of patients and is usually bilateral with onset between one and six months after the initiation of treatment.[14, 51, 53, 54] There are also reports of Vogt-Koyanagi-Harada (VKH) syndrome in patients receiving ICIs.[1] Ocular inflammation in these patients is managed with topical or periocular steroids, but severe cases require systemic steroids and discontinuation of ICIs[51] [Figure 2].

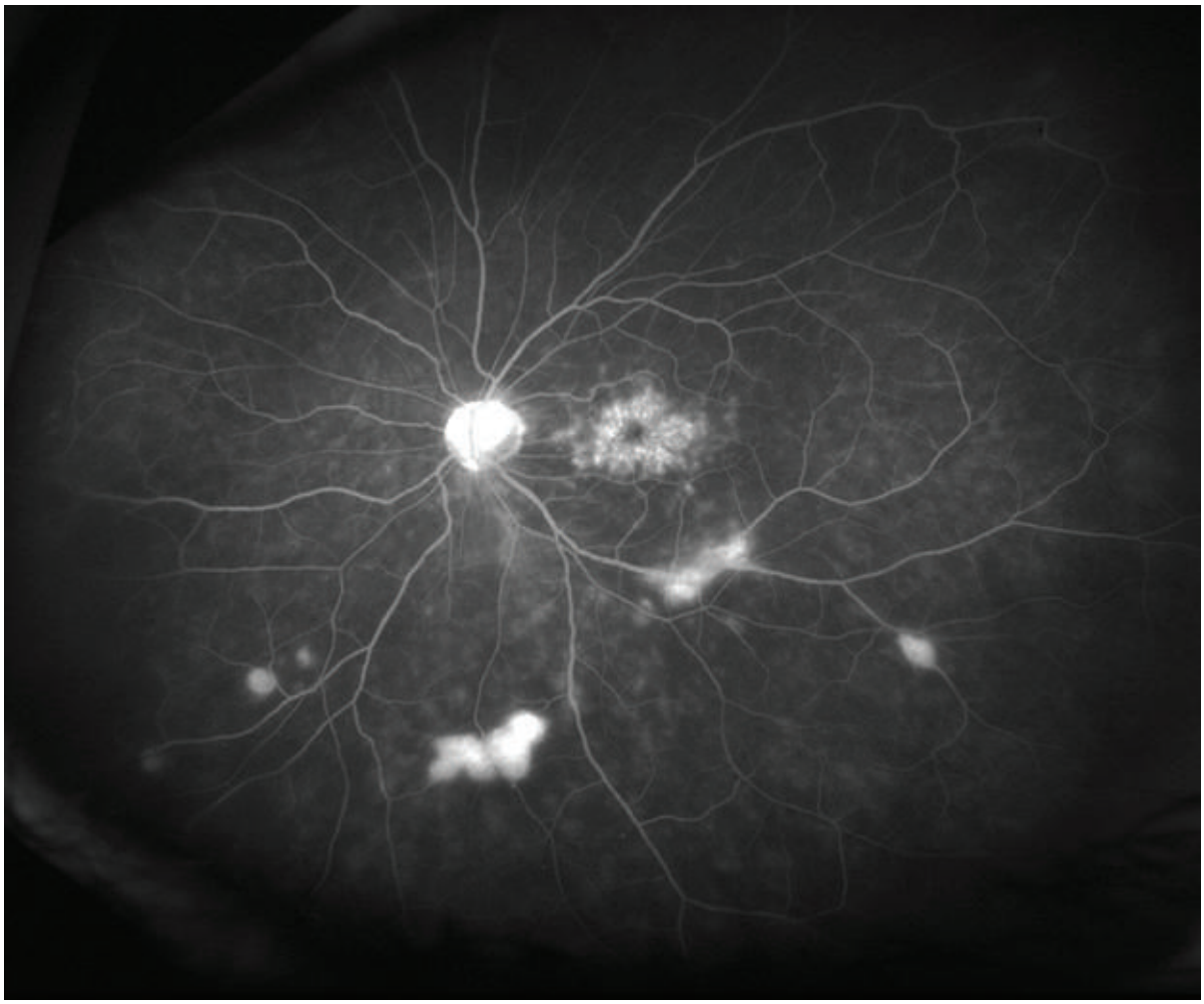

Figure 1. Fluorescein angiography of a 67-year-old female with history of rheumatoid arthritis treated with etanercept who developed uveitis and retinal vasculitis three months after the initiation of etanercept. Etanercept was discontinued and infliximab was started which resulted in resolution of ocular inflammation.

Protein Kinase Inhibitors

Dysregulations in mitogen-activated protein kinase (MAPK) signaling pathways and BRAF gene mutations, seen in 50% of skin melanoma patients, can cause cell proliferation and cancer formation.[14] BRAF inhibitors, such as vemurafenib and dabrafenib, and mitogen-activated protein kinases (MEK) inhibitors, such as trametinib, are new drugs of interest in the treatment of metastatic cutaneous melanomas. These medications have recently been linked to ocular inflammation.[1] Uveitis usually occurs between six weeks and eight months after the initiation of treatment, and can present as anterior, intermediate, posterior, or panuveitis; resolution typically involves topical steroids.[14] There are also reports of drug-induced VKH syndrome linked to the combination treatment with dabrafenib–trametinib.[1]

MISCELLANEOUS

Vaccines

There are reports of uveitis in association with BCG, influenza, hepatitis B, varicella, and human papilloma virus vaccines.[14] Most of these cases respond to topical steroid treatment or observation and permanent vision loss is rare.[14]

Other medications

Sulfonamides, including antibiotics (most commonly trimethoprim-sulfamethoxazole), diuretics, and sulfonylureas, have been associated

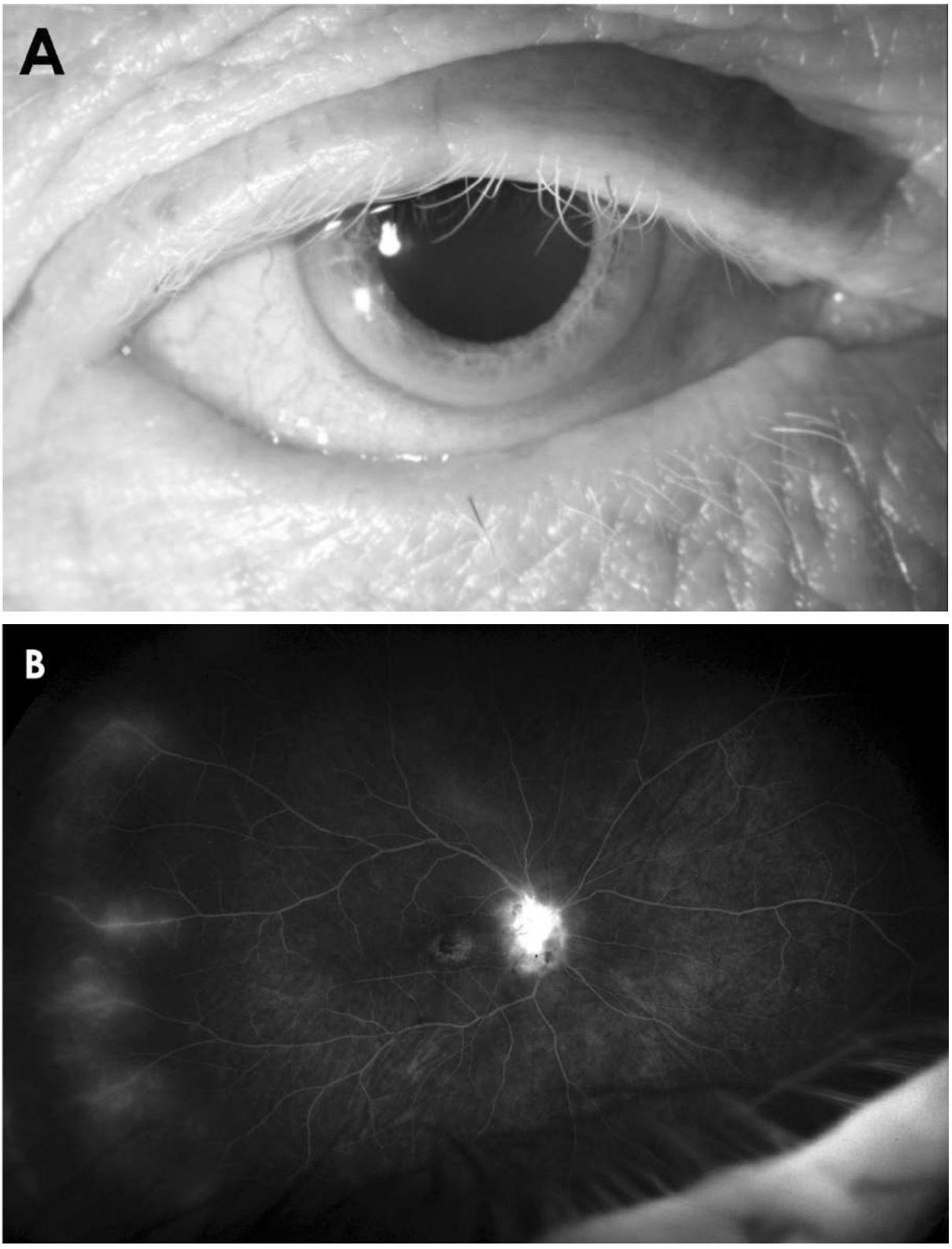

Figure 2. (A) 77-year-old man with history of malignant skin melanoma treated with nivolumab presented with blurry vision in both eyes. External exam showed poliosis of the eyelashes. Ultrawide field fluorescein angiography showed optic nerve and vascular leakage (B) which improved after intravitreal injection of triamcinolone acetonide.

Figure 3. Inflamed, indurated skin tattoos in a young patient with tattoo uveitis.

with bilateral anterior uveitis usually within a week of drug initiation.[28, 41, 55] Topical metipranolol, a nonselective β-blocker used to treat glaucoma, has been linked to granulomatous anterior uveitis most commonly when used at a higher concentration of 0.6%.[28, 56] Onset ranged from 2 to 31 months, and strong dechallenge and rechallenge data have also been reported.[41, 56] Other medications that can rarely cause uveitis include podophyllum, capsaicin, betaxolol, oral contraceptives, diethylcarbamazine, corticosteroids, quinidine, topiramate, and tuberculin skin tests.[6, 8, 14, 28] Almost all of these cases resolved with cessation of the medication and initiation of topical steroids.[6, 14, 28]

Tattoo ink

There are multiple reports of patients with simultaneous bilateral uveitis and elevated inflamed skin tattoos. Skin biopsies from the indurated tattoos in these patients revealed granulomatous inflammation surrounding tattoo pigments, and some patients developed non-caseating granulomas in the draining lymph nodes corresponding to the location of the tattoos.[57] An association between systemic sarcoidosis and tattoo uveitis has been reported by some authors, but uveitis can be found with or without a sarcoidosis diagnosis.[57, 58] Inflammation is more commonly seen in association with black ink, and there are reports of resolution of uveitis after removal of the skin tattoos.[58] The etiology has not been clearly defined, but a type IV delayed hypersensitivity reaction has been proposed[58] [Figure 3].

CONCLUSION

Drug-induced uveitis is seen in association with a growing list of various topical, intraocular, and systemic medications. Although uncommon, medication-induced uveitis can cause severe, vision-threatening inflammation, and will increase in frequency with the development of new medications. The diagnosis is often made by a thorough history and evaluation of medication list, and after ruling out other potential infectious or non-infectious etiologies of ocular inflammation. Early identification of uveitis and rapid treatment can lead to decreased morbidity and complications of longstanding uveal inflammation, thus improving visual outcomes. Most of these cases respond to cessation of the insulting agent in conjunction with topical and/or systemic corticosteroids.[14]

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Conflicts of Interest

There are no conflicts of interest.

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Review Article

Pattern of Uveitis in Iran: A Systematic Review

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Abstract

Purpose: Uveitis is the third leading cause of blindness worldwide. This study aimed to summarize the pattern of uveitis in Iran through a systematic review.
Methods: This review was conducted according to the guidelines for systematic reviews in the following four steps: literature search, study selection and assessment, inclusion and exclusion criteria, and statistical analysis.
Results: One hundred and fifteen articles were identified by an encyclopedic literature search, and three independent investigators examined them according to the defined inclusion and exclusion criteria. Eventually, 109 manuscripts were retrieved and six cross-sectional studies covering 3,567 patients were included and reviewed. According to the results, the mean age of patients was 40 years, and sex was not a statistically significant predisposing factor. The most common anatomical pattern of involvement was anterior uveitis, and the prevalence of the other three types of uveitis, including middle, posterior, and pan-uveitis, were almost equal. Overall, the most common etiologies of uveitis in the Iranian population were idiopathic uveitis, toxoplasmosis, Behcet's syndrome, and Fuchs heterochromic iridocyclitis.
Conclusion: This study depicted the pattern of uveitis in the Iranian society; this can help physicians in the diagnostic approach, management, and treatment of patients.

Keywords: Epidemiology; Iran; Systematic Review; Uveitis

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INTRODUCTION

Uveitis is an umbrella term that includes a wide spectrum of intraocular inflammatory conditions in which the various parts of the eye may be attacked by the immune system.[1]

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Uveitis refers to inflammation of the uveal tract (iris, ciliary body, and choroid); however, retina, vitreous body, optic nerve, and sclera may also be involved.[2] The etiology of the disease is categorized into traumatic, infectious, and noninfectious-immunologic causes and masquerade syndromes.[3, 4]

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Noninfectious-immunologic uveitis comprises vision-threatening diseases that can be associated with systemic or ocular autoimmune disease, with specific or unknown etiology.[5]

More than two million patients worldwide have uveitis,[1] and it has an estimated incidence of 17–52/100,000 person-years. Approximately 35% of these individuals experience severe visual loss and legal blindness[2] and it is the third leading cause of blindness (approximately 5–10% worldwide).[1, 6, 7] Intermediate, posterior, and pan-uveitis are responsible for visual disabilities in most of these patients. The most common sight-threatening complications are macular edema, retinal detachment, retinal vasculitis, and optic neuropathy. Other causes include phthisis bulbi, hypotony,[8] band keratopathy, and glaucoma.[1]

The prevalence, phenotypic features, and distribution of different types of uveitis depend on genetic and epidemiologic factors such as age, sex, race, geographic and environmental influence, and social habits.[6, 9] Uveitis may occur in any age group, from infancy to adulthood, but individuals aged 20–60 years old are more susceptible (the incidence in adults is approximately fivefold of that in children).[2] Global studies have found anterior uveitis to be the most common type of involvement seen in both adults and children, but the underlying etiologies differ; for example, juvenile idiopathic arthritis (JIA)-associated uveitis is more common in children and HLA-B27-associated uveitis predominantly affects young adults.[9]

In most studies, male and female patients were equally affected.[3, 10] However, some causes are more prevalent in a particular gender; for example, HLA-B27-associated anterior uveitis is more common among male patients,[2] and JIA-associated uveitis and multiple sclerosis (MS)-associated intermediate uveitis are more common in young girls.[11–13]

The epidemiology of non-infectious uveitis is more dependent on racial rather than regional features.[14] The prevalence of infectious uveitis (estimated at 30–50% of all uveitis cases) and some non-infectious posterior uveitis, such as Behcet's and Vogt-Koyanagi-Harada (VKH) syndrome, is higher in developing countries.[4, 15, 16] Common infectious causes include toxoplasmosis,[15, 17] tuberculosis (TB), onchocerciasis, cysticercosis, leprosy, and leptospirosis.[2] The prevalence of some causes of non-infectious uveitis depends on the regional area: for instance, sarcoidosis in Japan.[18] Behcet's disease in countries along the ancient Silk Road (Iran, Turkey, China, Japan, Saudi Arabia, and Greece),[9, 19] and VKH syndrome in Asian or Eurasian countries.[18] Generally, the prevalence of infectious uveitis is lower in developed countries; common causes are herpes virus and toxoplasmosis, while other infections, such as TB and syphilis, are rare.[4]

Ocular inflammation embraces a broad range of pathologies, both with respect to its etiology and the anatomical location within the eye. For proper listing of the differential diagnosis, practitioners should survey all important information, such as the anatomical location of involvement, pathology (granulomatous vs non-granulomatous), laterality (unilateral vs bilateral), and chronicity (acute, recurrent, or chronic) of the inflammation.[4] The classification of uveitis helps physicians in the diagnostic approach, management, and treatment of patients.

To date, several classification systems have been proposed that vary according to the anatomical location of involvement (primary site of the inflammation), clinical course, etiology, and histopathology.[20, 21] Based on the Standardization of Uveitis Nomenclature Working Group,[21] the anatomical location of involvement is classified into four types as follows: anterior, intermediate, posterior, and pan-uveitis (Table 1). This classification is widely accepted today and is now the standard required for the publication of uveitis studies in peer-reviewed literature.

The etiologic distribution of uveitis varies from region to region and parallels that of many studies that have investigated the pattern of uveitis in different parts of the world. Most of the data in this field are from the US and Europe, and reports from developing countries are limited.[4, 14, 22] Today, an acceptable number of reports that focus on the epidemiology of uveitis in Iran are available; however, all these studies have been conducted in university-based ophthalmology centers. In this study, we review all the available articles on the epidemiology of uveitis in Iran to discuss novel and interesting data regarding the pattern of the disease.

Table 1. Anatomical location of involvement in uveitis based on the Standardization of Uveitis Nomenclature (SUN) Working Group

Type	Primary site of inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

METHODS

This review was conducted according to the guidelines for systematic reviews in healthcare[23] in four steps as described below (methodology described in Figure 1):

Literature Search

An encyclopedic literature search for articles published up to July 2019 was conducted on MEDLINE, EMBASE, and the Cochrane library. No language limitations were applied.

All studies that reported the epidemiology of uveitis in Iranian patients were detected based on the medical subject heading (MeSH) terms for the following search strategy:

"{[("Uveitis" or "Panuveitis" or "Ophthalmia, Sympathetic" or "Uveitis, Anterior" or "Uveitis, Posterior" or "Uveitis, Intermediate" or "Pars Planitis" or "Uveitis, Suppurative" or "Panophthalmitis").af.] AND (ocular inflammation) AND (iran.mp. [mp=ti, ot, ab, tx, ct, sh, kw, ps, sj, do, dv, po, go, rs, nm, hw, an, ui])}."

In addition, a broad literature search was conducted using Persian databases such as IranMedex (www.iranmedex.com), Scientific Information Database (www.sid.ir), and MagIran (www.magiran.com). A manual search was performed in the following journals: *Journal of Ophthalmic and Vision Research* (http://www.jovr.org), *Journal of Current Ophthalmology* (https://www.journals.elsevier.com/journal-of-current-ophthalmology), and *Bina Journal of Ophthalmology* (binajournal.org).

Finally, the cited references in the obtained studies were manually reviewed for relevant articles. A total of 15 articles were found in this step.

Study Selection & Assessment

Articles that were most relevant to our topic were selected, and among them, the reported prevalence, incidence, or epidemiologic pattern of uveitis were thoroughly studied.

Inclusion & Exclusion Criteria

Two researchers, M.B. (MD, ophthalmologist, vitreoretinal surgeon) and A.J. (MD, general ophthalmologist), independently assessed the titles and abstracts identified in the previous step for potential eligibility, and the full-text articles were retrieved for studies on the epidemiological pattern of uveitis in the Iranian population. Fifty-nine studies were found and all their full-text versions were obtained. To avoid potential bias or errors, three independent individuals, M.B., A.J., and H.S.H. (MD, statisticians) examined the quality of the papers separately according to the checklist

Table 2. The characteristics of the included studies for meta-analysis and summarized uveitis pattern in the studies carried out at tertiary ophthalmology referral centers in Iran

Study	First author	City (university)	Publication date (duration of study)	Sample size	Mean age (range)	Male / female	Unilateral / bilateral	Ant. uveitis n (%)	Int. uveitis n (%)	Post. uveitis n (%)	Pan-uveitis n (%)	Infectious/ non-infectious	Granulomatous/ non-granulomatous
Patterns of Uveitis at a Tertiary Referral Center in Northeastern Iran [25]	Hosseini SM	Eye Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.	2018 (Feb 2013 to Mar 2014)	235	35.75 ± 16.34 (3–82)	94/141	85/150	87 (37)	28 (11.9)	10 (4.25)	110 (46.8)	46/189	32/179 (24 undefined)
Clinical Course of Uveitis in Children in a Tertiary Ophthalmology Center in Northwest Iran[26]	Alizadeh Ghavidel L	Department of Ophthalmology, Nikookari Eye Center, Tabriz University of Medical Sciences, Tabriz, Iran.	2017 (2003 to 2015)	243	12.3 ± 4.53 (1–18)	113/130	105/138	73 (30)	146 (60.1)	12 (4.9)	12 (4.9)	28/215	40/203
Demographic and Clinical Features of Pediatric Uveitis at a Tertiary Referral Center in Iran[27]	Rahimi M	Department of Ophthalmology, Poustchi Eye Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.	2016 (Jan 2007 to Dec 2013)	54	12.5 ± 5 (2–18)	24/30	31/23	22 (40.7)	18 (33.3)	10 (18.5)	4 (7.5)	10/44	—
Clinical Patterns of Uveitis in an Iranian Tertiary Eye-care Center[28]	Kianersi F	Isfahan Eye Research Center, Feiz Eye Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.	2015 (1999 to 2012)	2016	33.76 ± 10.56 (2.5–98)	915/1101	1232/784	865 (42.9)	390 (19.3)	432 (21.42)	329 (16.3)	474/1542	176/1840
Patterns of Uveitis at a Tertiary Referral Center in Southern Iran[29]	Rahimi M	Poustchi Eye Research Center and Ophthalmology Department, Shiraz University of Medical Sciences, Shiraz, Iran.	2014 (Jun 2005 to July 2011)	475	30.5 ± 15.4 (5–56)	216/259	292/183	190 (40)	53 (11.1)	133 (28)	99 (20.8)	110/365	52/423
Patterns of uveitis in a tertiary eye care center in Iran[30]	Soheilian M	Ocular Inflammatory and Uveitis Service, Ophthalmology Department and Ophthalmic Research Center, Labbafinejad Medical Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran. Negah Eye Center, Tehran, Iran.	2004 (1997 to 2000)	544	32.3 ± 15.2 (—)	238/306	275/269	209 (38.41)	96 (17.6)	101 (18.6)	138 (25.4)	90/454	79/465

Ant. uveitis: anterior uveitis; Int. uveitis: intermediate uveitis; Post. uveitis: posterior uveitis

Table 3. Common etiologies of uveitis in different types in studies carried out at tertiary ophthalmology referral centers in Iran

Study (First author)	Ant. uveitis (%)	Int. uveitis	Post. uveitis	Pan-uveitis (%)	Total (%)
Hosseini SM, et al (2018)[25]	Idiopathic (27.5) > FHI (17.24) > Herpetic Uveitis (13.7) = Seronegative Spondyloarthropathy (13.7) > JIA (4.6)	Idiopathic (60.7) > Behcet's syndrome (10.7) = Seronegative Spondyloarthropathy (10.7) > Sarcoidosis (7.1)	Toxoplasmosis (30) > Serpiginous Choroidopathy (20) > Idiopathic (10) = Herpetic Uveitis (10) = Sarcoidosis (10) = Presumed tuberculosis (10)	Idiopathic (22.72) = Behcet's Syndrome(22.72) = VKH(22.72) = Herpetic Uveitis (6.3) = Presumed tuberculosis (6.3)	Idiopathic (28.5) > Behcet's Syndrome (16.6 > VKH (10.6) > Herpetic Uveitis (21) > Seronegative Spondyloarthropathy (6.8) > FU (6.4)
Rahimi M, et al (2016)[27]	Idiopathic (59) > JIA (22.7) > Posner-Schlossman (9) > Herpetic Uveitis (4.5) = ALL-L2 (4.5)	Idiopathic (94.4) > Sarcoidosis (5.6)	Toxoplasmosis (40) = Toxocariasis (40) > Idiopathic (20)	Idiopathic (50) > VKH (25) > Sympathetic Ophthalmia (25)	Idiopathic (62.9) > JIA (9.2) > Toxoplasmosis (7.4) = Toxocariasis (7.4) > Herpetic Uveitis (1.8)
Kianersi F, et al (2016)[28]	Idiopathic (50.5) > FHI (32.8) > Herpetic Uveitis (7.6) > Behcet's Syndrome (2.6) > JIA (1.3)	Idiopathic (81.6) > Behcet's Syndrome (6.1) >Multiple Sclerosis (4.1)	Toxoplasmosis (90.7) > Idiopathic (4.7) > Behcet's Syndrome (1.4)	Behcet's Syndrome (48) > Idiopathic (32) > VKH (2.7) > ARN (2.4) = Sarcoidosis (2.4)	Idiopathic (43.9) > Toxoplasmosis (19.3) > FHI (14.1) > Behcet's Syndrome (10.5) > Herpetic Uveitis (3.2)
Rahimi M, et al (2014)[29]	Idiopathic (44.2) > FHI (17.8) > Seronegative Spondyloarthropathy (10) > Herpetic Uveitis (7.8) = JIA (7.8)	Idiopathic (92.4)	Toxoplasmosis (42.1) > Behcet's Syndrome (15.7) > ARN (8.2) > VKH (6) > Toxocariasis (4.7)	Behcet's Syndrome (34.3) > VKH (17.1) > Endogenous Endophthalmitis (11.4) > Sympathetic Ophthalmia (3)	Idiopathic (37.9) > Behcet's Syndrome (12.4) > Toxoplasmosis (11.8) > FHI (7.1) > VKH (5.2)
Soheilian M, et al (2004)[30]	Idiopathic (52.1) > FHI (17.2) > Seronegative Spondyloarthropathy (10) > JIA (4.8) > Herpetic Uveitis (3.8)	Idiopathic (86.5) > Sarcoidosis (7.3) > Multiple Sclerosis (4.2)	Toxoplasmosis (54.5) > Eales Disease (11.9) > Toxocariasis (10.9) > ARN (8.9) > Serpiginous Choroidopathy (4) = APMPPE (4)	Behcet's Syndrome (34.1) > Idiopathic (22.5) > VKH (15.2) > Multifocal Choroiditis and Panuveitis (10.1) > Sarcoidosis (5.1) = Sympathetic Ophthalmia (5.1)	Idiopathic (45.5) > Toxoplasmosis (10.1) > Behcet's Syndrome (8.6) > FHI (6.6) > VKH (3.9)

Ant. uveitis: anterior uveitis; Int. uveitis: intermediate uveitis; Post. uveitis: posterior uveitis

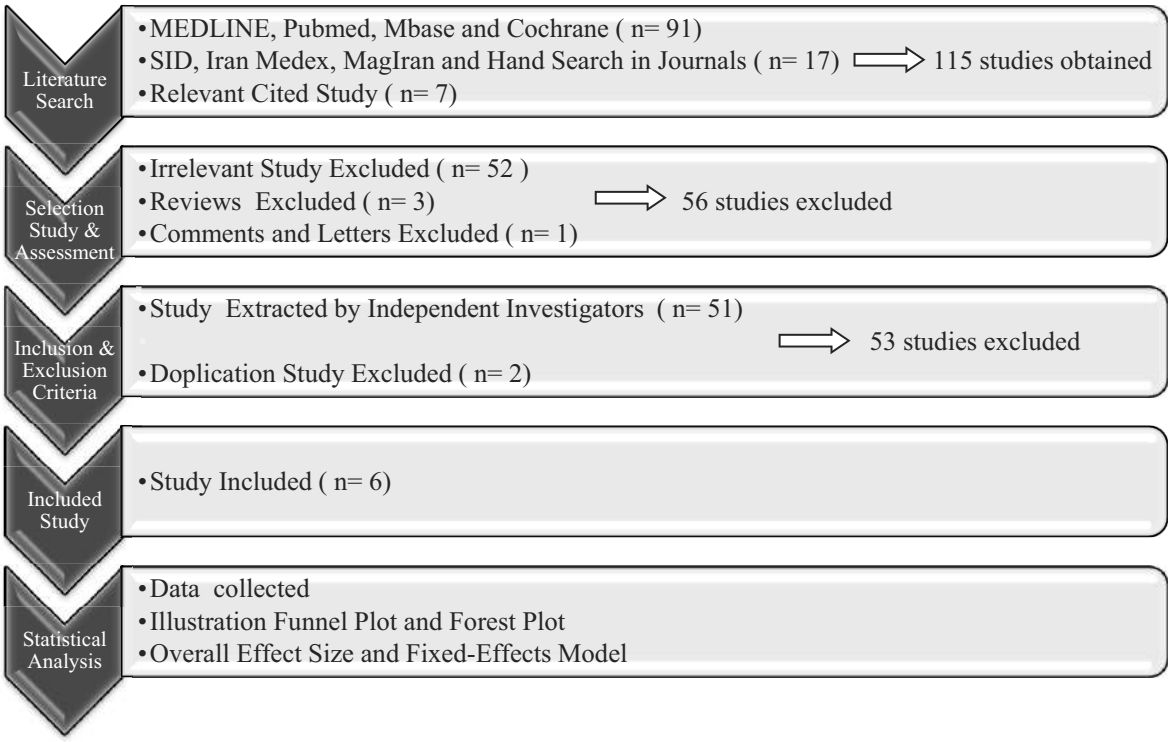

Figure 1. The methodology of the study step by step. During an encyclopedic literature search and survey of relevant cited studies, 115 studies were found, where 56 were excluded in the second step (irrelevant studies, reviews, comments and letters). After reviewing the inclusion and exclusion criteria, 53 more studies were excluded, and finally, 6 studies were included for statistical analysis.

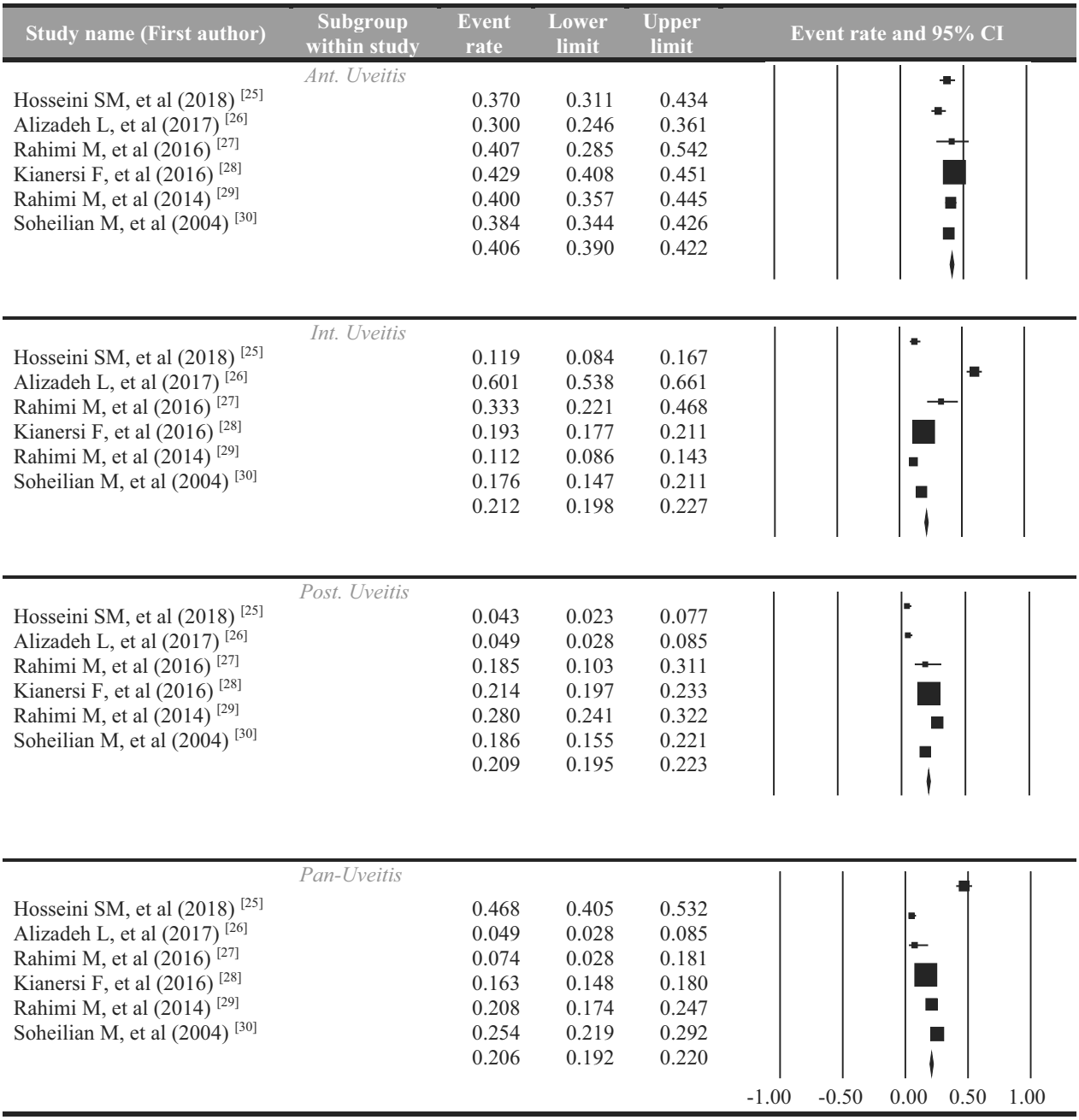

Figure 2. Pattern of uveitis based on anatomical location of involvement explained in this figure according to the studies separately. Ant. uveitis: anterior uveitis; Int. uveitis: intermediate uveitis; Post. uveitis: posterior uveitis

for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS).[24] Then, the data were extracted. Discrepancies were resolved by a consensus or discussion with the fourth reviewer, M.H.A. (MD, ophthalmologist, vitreoretinal surgeon), if necessary. Eventually, six cross-sectional studies covering 3,567 patients and data extracted by the investigators were included, and the final data were matched.

Statistical Analysis

The following data were collected from each study: the name of the first author, publication date, city or academic center, duration of the study, number of patients, demographic characteristics, anatomical pattern of involvement, etc. (Table 2).

Data were analyzed using the Comprehensive Meta-Analysis.2 (CMA.2) software. The heterogeneity index was assessed using the

I^2 test. A random-effects model was employed if the test revealed substantial heterogeneity ($I^2 >$ 50%). If non-significant ($I^2 \leq 50\%$), a fixed-effects model was used.[31] The level of significance for both heterogeneity and the pooled effect was adjusted at $P < 0.05$.

RESULTS

Of the nine studies that examined the epidemiology of uveitis in the Iranian society, three were excluded because two were duplicates[32, 33] and one was conducted only in patients with posterior uveitis.[34] Finally, data from six studies were analyzed; two involved cases of pediatric uveitis and four involved adults. Except for two studies that examined pediatric uveitis (patients enrolled in the age range <18 years),[26, 27] the mean age of the patients included in the studies was 40 years.[25, 28–30]. In all reports, the disease was more common in women than in men, except in the study by Hosseini *et al*, where this ratio was statistically significant (female to male ratio was 1.5).[25]

Statistical analysis showed that the most common anatomical pattern of involvement in the tertiary referral ophthalmology centers was anterior uveitis (event rate: 40.6% among all uveitis patients), but the prevalence of the other three types including middle, posterior, and pan-uveitis was almost equal (because of the non-significant I^2, the fixed-effects model was used to estimate the overall effect size; data not shown). In the majority of studies, the most common anatomical site of involvement was anterior uveitis[27–30] except in the reports by Hosseini *et al*[25] (pan-uveitis was prevalent in 110 out of 235 involved; 46.8%) and Alizadeh-Ghavidel *et al*[26] (intermediate uveitis was prevalent with 146 out of 243 involved; 60.1%). The rarest anatomical site of involvement in three studies was pan-uveitis;[26–28] however, this was not the case in the reports by Hosseini *et al*[25] (posterior uveitis was the rarest with 10 out of 235 cases involved; 4.25%), Rahimi *et al*,[29] and Soheilian *et al*[30] (intermediate uveitis was the rarest with 53 out of 475 cases [11.1%] and 96 out of 544 cases [17.6%], respectively). The study-wise pattern of uveitis based on the anatomical location of involvement has been shown in Figure 2.

In most studies, binocular involvement was more common, but in the studies by Hosseini *et al* and Alizadeh-Ghavidel *et al*, monocular involvement was more prevalent.[25, 26] In all studies conducted in ophthalmology referral centers, the most common type of pathological involvement in patients was non-granulomatosis uveitis (compared to the granulomatous type). The prevalence of non-infectious uveitis in all studies was higher than that of infectious uveitis, although in the pattern of posterior uveitis, the infectious type was more common than the non-infectious type due to toxoplasma retinochoroiditis. Table 2 summarizes the uveitis pattern in the studies carried out at tertiary ophthalmology referral centers in Iran.

In the study by Hosseini *et al*, which was conducted at an ophthalmology referral center in north eastern Iran, idiopathic uveitis was more common overall (67 cases of 235; 28.5%) and in different uveitis types, except posterior uveitis in which toxoplasma retinochoroiditis was prevalent (3 cases, 10; 10%). After idiopathic uveitis, Behcet's syndrome (39 patients; 16.6%), VKH (25 patients, 10.6%), herpetic uveitis (21 patients, 8.9%), and seronegative spondyloarthropathy (16 patients, 6.8%)[25] were the other common etiologies in different uveitis types.

In the study by Alizadeh-Ghavidel *et al*, which was conducted at an ophthalmology referral center in the northwest of Iran, idiopathic uveitis was more common overall (117 cases of 243; 48.1%), followed by toxoplasma retinochoroiditis (5.3%).[26]

In the study by Kianersi *et al*, conducted at an ophthalmology referral center in Iran, idiopathic uveitis was more common overall (882 cases of 2016; 43.9%), followed by toxoplasma retinochoroiditis (19.3%), Fuchs heterochromic iridocyclitis (FHI) (14.1%), Behcet's syndrome (10.5%), and herpetic uveitis (3.2%).[28]

In the study by Rahimi *et al*, which was conducted at an ophthalmology referral center in southern Iran, idiopathic uveitis was more common overall (180 cases of 475; 37.9%). The most common etiologies of idiopathic uveitis were Behcet's syndrome (12.4%), toxoplasma retinochoroiditis (11.8%), FHI (7.1%), and VKH (5.2%).[29]

The first study on the epidemiology of uveitis in the Iranian population was reported by Soheilian *et al* in 2004 at a tertiary referral center in Tehran. Similar to other studies, idiopathic uveitis was the most common type of involvement (231 patients out of 544; 45.5%). Other prevalent etiologies

in different uveitis types were toxoplasma retinochoroiditis (10.1%), Behcet's syndrome (8.6%), FHI (6.6%), and VKH (3.9%).[30] Table 3 shows the common etiologies of uveitis in different types of studies carried out at tertiary ophthalmology referral centers in Iran.

DISCUSSION

Uveitis as a potentially sight-threatening ocular disease poses diagnostic and therapeutic challenges for general ophthalmologists as well as uveitis specialists. Epidemiological studies of the pattern and etiologies of uveitis can help clinicians diagnose, manage, and treat the disease. However, epidemiological studies on the disease at a national level can aid in assessing the burden of the disease on the country's health community, making it possible to plan for the future. In contrast, studies on the incidence and prevalence of uveitis in our society are limited, especially in the general population. Based on the extensive literature review, to the best of our knowledge, no study has reported the epidemiological pattern of uveitis in the general Iranian population, and no study has been conducted in the field of general ophthalmology (all reports were from referral tertiary ophthalmology centers).

The clinical pattern of uveitis may change over time for several reasons such as emerging diseases, new surgical procedures that can lead to uveitis as a complication, and new laboratory equipment that may help to better understand or further diagnose the disease. Certainly, the limitations of laboratory equipment can make it difficult to detect some etiologies and cause some specific diagnosis to fall into the category of idiopathic uveitis. Thus, the pattern of uveitis in one community may be different from that in other societies and may also change over time. This justifies the need for national and regional studies and repeated epidemiological studies over time. Comparison of these studies could help identify the predisposing factors in different regions, provide new insights into the pathogenesis of the disease, and clarify the path for future studies.

In the present study, the mean age of the patients included in the articles reviewed was 40 years, and gender was not a statistically significant predisposing factor. The most common anatomical pattern of involvement was anterior uveitis. However, the prevalence of the other three types including middle, posterior, and pan-uveitis was almost equal. The most common clinical features of the disease were binocular uveitis (compared to the monocular), non-granulomatosis uveitis (compared to the type of granulomatosis), and non-infectious (compared to the infectious) involvement. Overall, the prevalent etiologies were idiopathic uveitis, toxoplasmosis, Behcet's syndrome, and FHI. In the subgroup analysis, the most common etiologies for anterior uveitis were idiopathic uveitis, FHI, and herpetic uveitis; for intermediate uveitis, Behcet's syndrome and MS were common; and for posterior uveitis toxoplasmosis, idiopathic uveitis and Behcet's syndrome were common. In pan-uveitis, Behcet's syndrome, idiopathic uveitis, and VKH syndrome were most prevalent.

All published studies have examined the epidemiology of uveitis in university referral ophthalmology centers. Therefore, the results of this study cannot be generalized to the public because there are significant differences between the pattern of disease in these studies compared to general ophthalmology practice or the community.

Similar to the present study, most worldwide reports have shown that anterior uveitis is the most common type of involvement, followed by pan-uveitis, posterior, and intermediate uveitis.[1, 9, 35, 36] However, most of these studies have been carried out in university referral centers, and their results cannot be applied to the general public. In these settings, a higher proportion of patients with posterior and pan-uveitis and a lower proportion of those with anterior uveitis are expected to be comparable.[4, 37]

The pattern of uveitis can be influenced by several epidemiologic factors; therefore, any comparison should consider these differences. The regional-based epidemiological studies can be useful for both diagnostic and therapeutic guidance. This may be more important in developing countries such as Iran because of its resource constraints and a higher prevalence of the disease in some uveitic entities (compared to developed countries), and its complications, especially blindness.[4, 22, 38–40]

This study has some limitations. First, this study was limited by the inclusion and exclusion criteria of the studies reviewed; for example, all studies considered traumatic uveitis as exclusion criteria,

while Das *et al* reported a prevalence of 5%.[35] Second, reports on the epidemiology of uveitis in Iran have covered different time periods that may be difficult to compare. Even in a single community, the pattern of uveitis can change over time for several reasons such as emerging diseases, advances in laboratory equipment, and changes in diagnostic criteria. However, when comparing studies from different cities, some factors such as the socioeconomic level of the region, can change the face of the disease. In under-resourced areas, an underrepresentation of mild or moderate cases of uveitis is expected because of limited access to medical facilities.[4, 22, 38–40] Third, this study was limited by the inclusion of all types of uveitis and different age ranges; considering the heterogeneity in the selected studies and the non-representative population, aggregate estimates for the prevalence of uveitis could not be made in the current review. However, according to the survey in the Iranian population, the heterogeneity of patients in terms of racial factors compared to other global studies was minimal. Finally, the survey of the referral centers may have been influenced by referral bias; therefore, they do not reflect an appropriate view of the disease pattern in society or in general practice. Therefore, subsequent analysis focusing on homogeneous age groups can provide more accurate results regarding the pattern of uveitis. In addition, future epidemiologic studies are recommended in the general population and in the field of general ophthalmology.

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Conflicts of Interest

There are no conflicts of interest.

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Review Article

Ocular Manifestations of COVID-19: A Systematic Review and Meta-analysis

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Abstract

Several studies have reported the characteristics of Coronavirus disease 2019 (COVID-19), yet there is a gap in our understanding of the ocular manifestations of COVID-19. In this systematic review and meta-analysis, we investigated the prevalence of ocular manifestations in COVID-19 patients. We searched Pubmed, Embase, Scopus, Web of Science, and medRxiv from December 1, 2019 to August 11, 2020. Two independent reviewers screened the articles, abstracted the data, and assessed the quality of included studies in duplicate. Thirty-eight studies were eligible after screening of 895 unique articles, with a total of 8,219 COVID-19 patients (55.3% female; *n* = 3,486 out of 6,308 patients). Using data extracted from cross-sectional studies, we performed random-effects meta-analyses to estimate the pooled prevalence of ocular symptoms along with 95% confidence interval (CI). The prevalence of ocular manifestations was estimated to be 11.03% (95% CI: 5.71–17.72). In the studies that reported the details of observed ocular symptoms, the most common ocular manifestations were dry eye or foreign body sensation (*n* = 138, 16%), redness (*n* = 114, 13.3%), tearing (*n* = 111, 12.8%), itching (*n* = 109, 12.6%), eye pain (*n* = 83, 9.6%) and discharge (*n* = 76, 8.8%). Moreover, conjunctivitis had the highest rate among reported ocular diseases in COVID-19 patients (79 out of 89, 88.8%). The results suggest that approximately one out of ten COVID-19 patients show at least one ocular symptom. Attention to ocular manifestations, especially conjunctivitis, can increase the sensitivity of COVID-19 detection among patients.

Keywords: Conjunctivitis; COVID-19; Meta-analysis; Ocular Manifestations; Systematic Review

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially detected in late

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2019 in Wuhan, China,[1] and Coronavirus disease 2019 (COVID-19) swiftly spread across the globe, and was declared a pandemic on March 11, 2020.[2] By August 14, 2020, 21,092,096 people were infected with SARS-CoV-2, 757,727 of whom passed away due to COVID-19 or its adverse health consequences.[3]

COVID-19 may pose challenges in clinical diagnosis because there is no pathognomonic symptom to detect the disease. Several clinical symptoms have been frequently reported among COVID-19 patients including but not limited to cough, fever, fatigue, sore throat, nasal obstruction, shortness of breath, headache, sputum production, and hemoptysis.[4] Moreover, while some patients show a wider range of gastrointestinal symptoms such as diarrhea, abdominal pain, low appetite, and vomit,[5] others have shown renal and ocular symptoms.[6]

Most clinical research about SARS-CoV-2 have focused on respiratory manifestations; however, a growing body of evidence has raised concerns about the ocular complications caused by SARS-CoV-2.[7] The reported ocular manifestations of the infection vary greatly and include dry eye, foreign body sensation, itching, blurring of vision, conjunctivitis, chemosis, and photophobia.[8] Some studies have even reported conjunctivitis as an early sign for COVID-19 diagnosis.[9] Knowing the prevalence and type of ocular manifestations of COVID-19 can help physicians diagnose the infection better and sooner in the course of the disease. Therefore, we aimed to summarize the relevant published literature on the ocular manifestations of the COVID-19 patients.

METHODS

We completed our systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (See Supplementary file S1 for PRISMA checklist).[10]

For this systematic review and meta-analysis, we searched Pubmed, Embase, Scopus, Web of Science, and medRxiv preprint server from December 1, 2019 to August 11, 2020 for studies published in English (See Supplementary file S2 for a sample search strategy). We also searched the reference lists of related systematic reviews for potentially eligible studies.

Inclusion Criteria and Study Selection

We included empirical observational studies including cohort, case-control, cross-sectional, case-reports, or case-series that reported about ocular manifestations in COVID-19 patients. We excluded editorials, commentaries, letters to editors, and reviews. Two reviewers (NN and HSH) independently, and in duplicate, screened the titles and abstracts of identified citations, and assessed the full-text of potentially eligible studies for inclusion in the data synthesis. The reviewers resolved the disagreements on the process of study selection through feedback and discussion with the senior author (ASH).

Data Collection

Two authors (NN and AB) independently, and in duplicate, extracted data from each eligible study, including study characteristics (e.g., first author, publication date, study type, location, and total sample size) and patients' information (e.g., age, sex, and ocular manifestations such as conjunctival hyperemia, clear secretions, conjunctivitis, follicles, petechia, and chemosis).

Quality Assessment of the Evidence

Two independent reviewers evaluated the quality of included studies duplicate using the Joanna Briggs Institute critical appraisal tool.[11] The criteria suggested by Joanna Briggs to assess quality include eight items for case-report studies, nine items for cross-sectional studies, and ten items for case-series. Reviewers resolved the disagreements by adjudication or feedback from the senior author.

Statistical Analysis

Data were presented using descriptive statistics (i.e., mean, median, and standard deviation [SD] for continuous variables and frequency and percentage for categorical variables). To assess the proportion of patients with a particular manifestation, we calculated the sum of the patients with a particular manifestation in different papers and divided them to the number of included patients. To account for the different study designs included in the study, we only

considered cross-sectional studies in our meta-analysis. Using random-effects meta-analysis, we calculated the pooled estimated prevalence and 95% confidence interval (95% CI) of ocular manifestations, using *metaprop* command in Stata version 14.2. We also assessed the heterogeneity among the included studies using I^2 and the Q-statistic. A value of ≥50% of I^2 and a *P*-value of <0.1 for the Q-statistic was perceived as considerable heterogeneity. We then ran a meta-regression to assess the potential sources of heterogeneity. The following variables were included in the meta-regression: Method of COVID-19 diagnosis (polymerase chain reaction [PCR] or computed tomography scan [CT scan] vs clinical signs), the quality of studies (quality score < 4 vs quality score ≥ 4), the mean age of patients (age ≤ 45 years vs age > 45 years), the method of examination by ophthalmologist (standard ophthalmic exam vs non-standard ophthalmic exam), and the recruited sample size (sample size > 500 vs sample size ≤ 500). Based on the reported information in the papers, we also aimed to assess whether the reported ocular manifestations preceded or followed the presence of systemic symptoms. To do so, we calculated the lag between ocular manifestation and systemic disease as well as the lag between systemic disease and ocular manifestation. All statistical analyses were performed in Stata version 14.2 and all comparisons were two-tailed, with a threshold *P*-value of 0.05.

RESULTS

Out of the 895 unique publications that were assessed, 38 studies[12–49] were included in this review (Figure 1). Overall, 13 studies were case reports,[37–49] six were case-series study,[13, 15, 18, 25, 28, 36] and the remaining 19 studies were cross-sectional.[12, 14, 16, 17, 19–24, 26, 27, 29–35] Twenty-four studies reported aggregate-level[12–35] and fourteen[36–49]reported individual-level information about ocular manifestations. Out of the 38 studies, 1 study[16] was conducted among healthcare providers (see Supplementary file S3 for type of study, sex, mean age, and main ocular manifestations; Supplementary file S4 for location, publication data, patient population, and chronic disease). Moreover, out of the 38 included studies, 32 (3,719 out of 8,219 patients) were among inpatients, four among outpatients (2,353 out of 8,219 patients), and two included outpatient and inpatient individuals, simultaneously (2,147 out of 8,129 patients).

Demographic and clinical characteristics of COVID-19 patients included in the reviewed studies are presented in Table 1. A total of 8,219 patients with COVID-19 were enrolled in the included studies. Across all COVID-19 studies, 6,308 reported sex distribution, 1,532 reported other comorbidities with COVID-19, and 1,021 were at the individual level and reported ocular symptoms and signs. The number of enrolled patients in the included studies ranged from 1 to 1,452, most patients were female (*n* = 3,486 out of 6,308 patients, 55.3%), and the mean age of the participants ranged between 7 and 65.8 years. The diagnosis of SARS-CoV-2 was confirmed in 4,039 (49.1%) and 4,180 (50.9) patients using clinical signs and CT scans. The most detected comorbidities in patients were hypertension (593 out of 1,532), diabetes mellitus (294 out of 1,532), respiratory diseases (219 out of 1,532), and cardiovascular and cerebrovascular diseases (188 out of 1,532).

Quality Assessment of Included Studies

Joanna Briggs Institute's critical appraisal scores ranged from 2 to 6 for case reports (out of 8 possible points), and 0 to 5 for prevalence (cross-sectional) studies (out of 9 possible points), and 3 to 7 (out of 10 possible points) for single case-series included in the review. Quality assessment tools were different based on study design; therefore, scores could not be directly compared (See Supplementary file S5).

The Pooled Prevalence of Ocular Manifestations

We included 19 cross-sectional studies corresponding to 7,300 individuals for meta-analysis of ocular manifestations among patients with COVID-19. The pooled prevalence of all ocular manifestations among COVID -19 patients was 11.03% (95% CI: 5.71 to 17.72) (Figure 2), The most prevalent ocular manifestations were dry eye or foreign body sensation (*n* = 138, 16.0%), redness (*n* = 114, 13.3%), tearing (*n* = 111, 12.8%), itching (*n* = 109, 12.6%), eye pain (*n* = 83, 9.6%), and discharge (*n* = 76, 8.8%). The most prevalent ocular disease was conjunctivitis (*n* = 79, 88.8%).

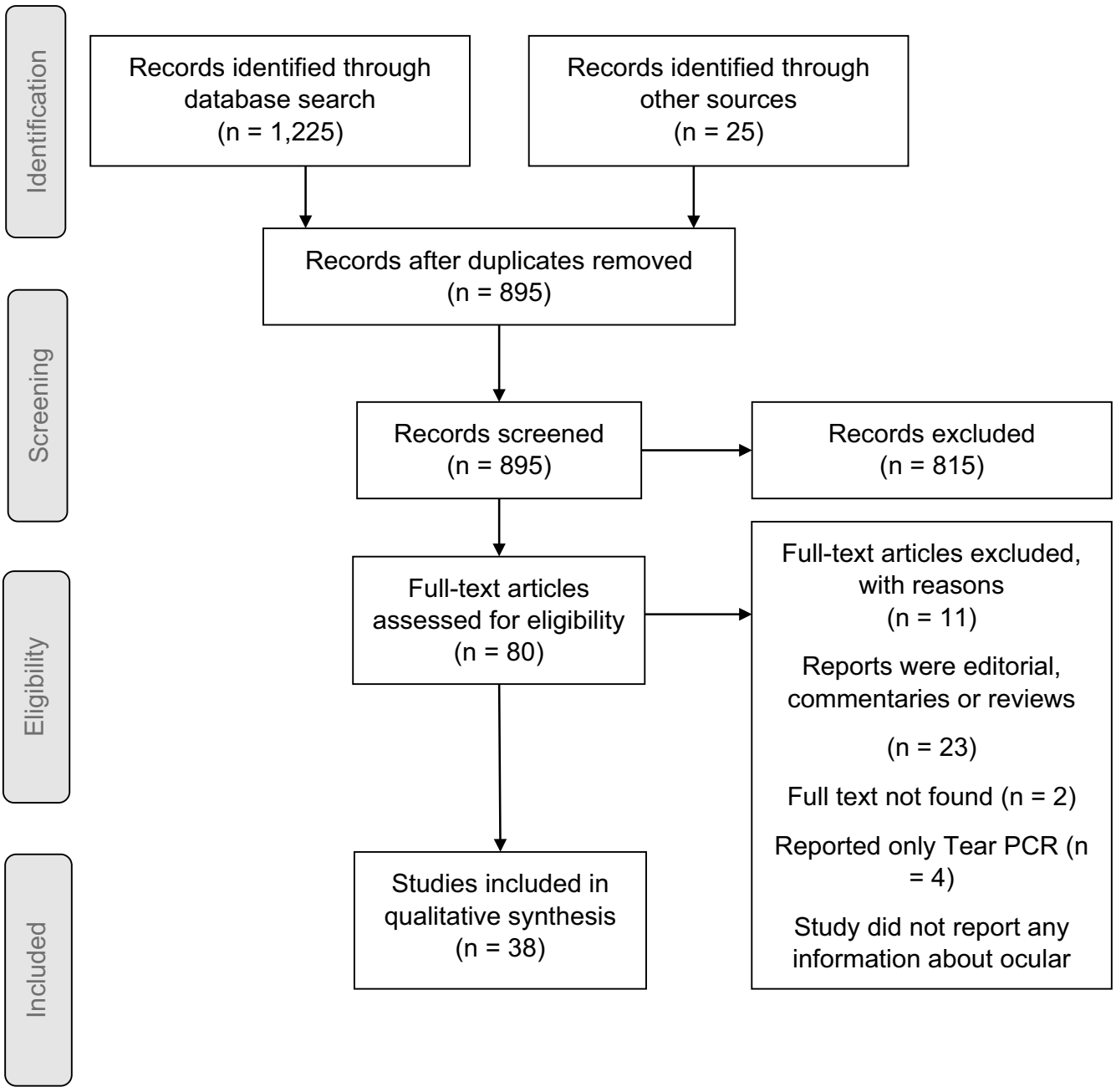

Figure 1. Flowchart of studies included in the systematic review of COVID-19 ocular manifestation

Other rare conditions such as keratitis (*n* = 2, 2.2%), episcleritis (*n* = 2, 2.2%), keratoconjunctivitis (*n* = 2, 2.2%), hordeolum (*n* = 2, 2.2%), pingueculitis (*n* = 1, 1.1%), posterior ischemic optic neuropathy (*n* = 1, 1.1%) were also reported (Table 2). No significant source of heterogeneity from the included variables in the meta-regression was detected (Table 3).

Five studies reported the lag between ocular manifestation and systemic disease; however, nine studies reported the lag between systemic disease and ocular manifestation. Weighted mean between onset ocular manifestations and systemic disease was 0.04 days (range, 1 to 3 days). However, weighted mean between systemic disease and ocular manifestation was 1.5 days (range, 2 to 21 days).

DISCUSSION

This systematic review and meta-analysis included 38 studies with a total of 8,219 COVID-19 patients.

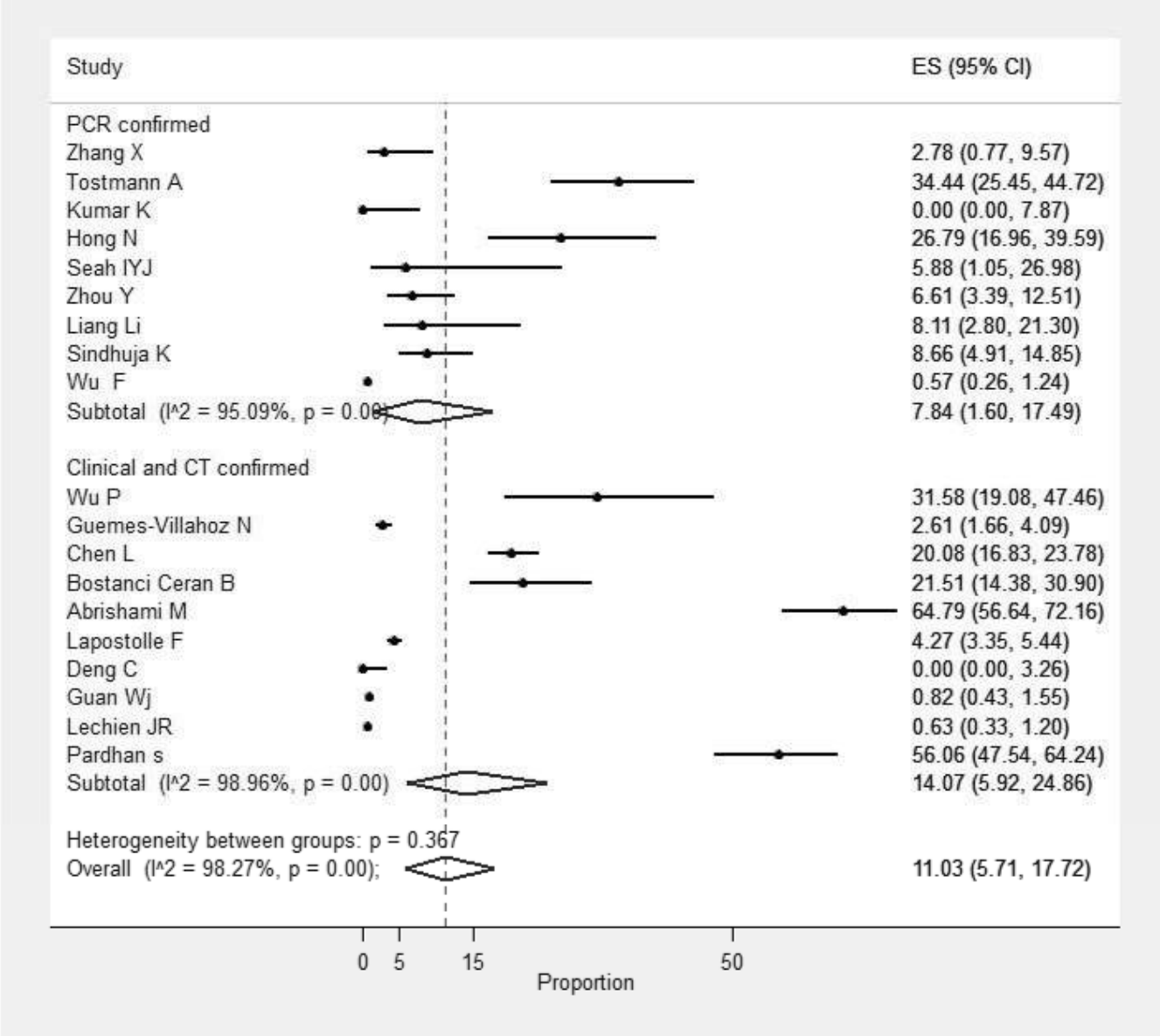

Figure 2. Pooled prevalence of ocular manifestation among patients with COVID-19

Based on the existing evidence, we found the pooled prevalence of all ocular symptoms to be 11.03% (95% CI: 5.71 to 17.72) among COVID-19 patients. Dry eye or foreign body sensation was the most common reported ocular symptoms (16.0%), followed by redness (13.3%) and tearing (12.8%). The most prevalent ocular disease was conjunctivitis (88.8%).

This study showed that approximately one out of ten COVID-19 patients included in this study showed at least one ocular manifestations. Although these manifestations may not be frequent, they should not be overlooked by physicians and ophthalmologists.[50] These findings are comparable with the findings of previous studies on COVID-19 or other coronaviruses. For example, Vabret *et al* in a study in a French hospital, from November 2002 to April 2003, reported that ocular manifestations were 16.7% (3 out of 18) in patients diagnosed with human coronavirus NL63.[51] Moreover, Ulhaq *et al* in a systematic review study up to April 4, 2020 reported that ocular manifestations in COVID-19 patients were 5.5%.[52] The reason for ocular manifestations among patients diagnosed with COVID-19 and other coronaviruses could be related to the presence of ACE2 receptor, the cell receptor for coronaviruses and SARS-CoV-2, in

Table 1. Demographic and clinical characteristics of COVID-19 infection included in the reviewed studies

Characteristics	N (%)
Diagnostic approach (n = 8,219)	
Only clinical signs and CT Scan	4,180 (50.9)
PCR laboratory confirmed	4,039 (49.1)
Sex (n = 6,308)	
Male	2,822 (44.7)
Female	3,486 (55.3)
Comorbidity with COVID-19 (n = 1, 532)	
Hypertension	593 (38.7)
Diabetes	294 (19.2)
Respiratory system disease	219 (14.3)
Cardiovascular and cerebrovascular diseases	188 (12.3)
Cancer	60 (3.9)
Disease of immune system	59 (3.9)
Hepatitis	54 (3.5)
Liver disease	33 (2.1)
Kidney disease	32 (2.1)

the eye cells.[8] Transmission of SARS-CoV-2 by tear is not unlikely,[53] and the eye can be a way for entering the infection droplets to the body.[54] Therefore, protecting eyes is essential for people, especially for healthcare providers to protect themselves against SARS-CoV-2.

The most important ocular manifestations in COVID-19 patients were dry eye or foreign body sensation, redness, tearing, itching, eye pain, and discharge. The mechanism of dry eye or foreign body sensation is unclear in COVID-19 patients and may not be directly associated with SARS-CoV-2. Indeed, the occurrence of dry eye during the COVID-19 epidemic could be due to wearing face masks and directing the expiratory air current toward eyes, especially when masks are loose against the face and nose. The stream of air against ocular surface causes accelerated evaporation of the tear and may create dry eye symptoms. In persons with pre-existing dry eye or poor-quality tear film, the symptoms can be more common and prominent. Limitation of access to lubricating agents in fear of contamination of hands and drug containers also deteriorates dry eye manifestations.[55, 56] Furthermore, since the beginning of the pandemic, people spend more time looking at screens that may exacerbate dry eye sensation.[57, 58] While screen watching, the rate and intensity of blinks is significantly diminished, exacerbating the dry eye symptoms. Loss of follow-up visits and reduced seeking care in patients with previous dry eye condition could be other factors that may have contributed to increased dry eye symptoms during the pandemic.[55, 56]

Conjunctivitis was the most common eye disease in patients. Conjunctivitis could be developed by certain viruses (e.g., *Haemophilus influenzae* and *Herpes simplex*), bacteria (e.g., *Staphylococcal* species*, Streptococcus pneumoniae*, and *Neisseria gonorrhoeae*), and allergies (e.g., pollen and animal dander).[59] Conjunctivitis could also be developed by coronavirus and SARS-CoV-2.[60, 61] In a study in Iran among 142 COVID-19 patients, the most prevalent ocular finding was conjunctival hyperemia (44 persons; 31%); however, the most prevalent ocular manifestation among ICU-admitted patients was chemosis (17 out of 28 admitted to ICU; 60.7%), and 50.0% of the patients admitted to ICU (14 of the 28) showed conjunctival hyperemia.[23] Scalinci *et al* in a study among five Italian COVID-19 patients reported that conjunctivitis remained through the course of the disease among COVID-19 patients.[38] Hong *et al* in a study in China showed that some

Table 2. Symptoms and diseases of ocular in COVID-19 infection included in the reviewed studies (*n* = 1,021)

Characteristics	N (%)
Symptom and sign (n = 932)	
Dry eyes or foreign body sensation	138 (16.0)
Redness	114 (13.3)
Tearing	111 (12.8)
Itching	109 (12.6)
Eye pain	83 (9.6)
Discharge	76 (8.8)
Blurred vision or decreased vision	71 (8.2)
Photophobia	62 (7.2)
Chemosis	42 (4.9)
Irritation	21 (2.4)
Gritty feeling	14 (1.6)
Burning sensation	8 (0.9)
Lid edema	8 (0.9)
Subconjunctival hemorrhage	3 (0.3)
Pseudomembrane and hemorrhage	2 (0.2)
Pseudodendrite	1 (0.1)
Subepithelial infiltrates	1 (0.1)
Water secretion	1 (0.1)
Disease (n = 89)	
Conjunctivitis	79 (88.8)
Keratitis	2 (2.2)
Episcleritis	2 (2.2)
Keratoconjunctivitis	2 (2.2)
Pingueculitis	1 (1.1)
Hordeolum	2 (2.2)
Posterior ischemic optic neuropathy	1 (1.1)

Table 3. Meta-regression analysis of the effect of the factors on the ocular manifestations of the COVID-19 patients

Variables	Multivariable meta-regression		
	Coefficient	***P*-value**	**[95% conf. Interval]**
Quality of the included papers (quality ≥4 vs quality < 4)	0.02	0.59	–0.07 – 0.11
The mean age of the patients (≤ 45 years vs > 45 years	–0.11	0.29	–0.35 – 0.13
Clinical examination (standard ophthalmic exam vs non-standard ophthalmic exam	0.12	0.33	–0.17 – 0.42
Diagnostic method (PCR vs CT Scan and clinical signs)	–0.22	0.09	–0.50 – 0.05
The recruited sample size (sample size > 500 vs sample size ≤ 500)	–0.22	0.13	–0.52 – 0.09

conf., confidence

patients reported conjunctivitis after admission for treatment of COVID-19.[19] Chen *et al* in a cross-sectional study in Wuhan China reported that some patients had conjunctivitis as their first symptom and others reported conjunctivitis after the clinical symptom of COVID-19 had begun.[21] In a study in Canada, an association between conjunctivitis with corneal subepithelial infiltrations, corneal epithelial defects, development of tender preauricular lymphadenopathy, and conjunctival follicular reaction was observed among COVID-19 patients.[44] Navel *et al* reported tarsal hemorrhage mucous filaments and tarsal pseudomembranous in one COVID-19 patient. They observed the eyelids were irritated by numerous sticky secretions accumulating around the eyelashes, and described mucous filaments, tarsal pseudomembranous, and superficial punctuate keratitis.[39]

Assessing and observing the symptoms and ocular manifestations of COVID-19 patients could improve clinicians' diagnosis of the disease. During the ongoing pandemic, ophthalmologists should consider COVID-19 as a potential diagnosis when observing ocular manifestations and conjunctivitis, especially with other manifestations of COVID-19-like respiratory signs or fever.[60] Incidence of ocular symptoms may happen a few hours or days before the onset of COVID-19 systemic signs such as fever and cough.[18, 19, 36]

Ophthalmologists are at a high risk for SARS-CoV-2 given their close contact with patients. Although the transmission of SARS-CoV-2 via tear is not unlikely[53] and the mechanism is uncertain,[8, 62] there exists a risk of transmission,[54] and ophthalmologists and other healthcare providers should adhere to recommendations about wearing eye protective gears in addition to face masks and other protective devises during clinical examinations.[63] This is particularly important when it comes to interactions with asymptomatic COVID-19 patients.[1]

We acknowledge the limitations of our study. First, ocular manifestations were measured by an ophthalmologist in some studies and through patient self-reports in others. Second, given the significant variations between the studies, we could not merge the results of different study designs. Third, most studies had a low sample size, and the quality of the included studies was low, and most were case reports and cross-sectional studies. Lastly, most COVID-19 patients are asymptomatic, but all patients enrolled in studies were symptomatic which could overestimate the infection's manifestations.

SUMMARY

Attention to ocular manifestations in combination with other COVID-19 manifestations could help improve COVID-19 diagnosis. The main ocular manifestations were dry eye, tearing, itching, redness, eye pain, and foreign body sensation. It is recommended that healthcare providers especially ophthalmologists who are in close contacts with patients wear eye protective goggles in addition to other recommended protective equipment.

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Conflicts of Interest

There are no conflicts of interest.

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Perspective

Need for Nurse Practitioner Fellowships in Ophthalmology in the USA

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Abstract

Medical attention to vision impairment and associated eye care complications are a vital component of daily living and overall well-being. In the United States today, the physician to patient deficit places great strain on the availability of medical attention tenable to patients nationwide; in terms of specialty medicine, this deficit is even more widespread. The field of ophthalmology faced the same physician to patient deficit in 2020, a grim reality that has left many states void of ophthalmic care, rending millions of aging individuals without domestic eye care. The implementation of trained, ophthalmic nurse practitioners (NPs) can fill the needs of this deficit; however, efficient, accredited, and board-approved American ophthalmic fellowships and residencies that secure proper ophthalmic NP transitions from academia to clinical practice are non-existent. Though scant, evidence-based literature presents sound findings that support the efficacy and benefit for superior patient outcomes with care provided by ophthalmic-trained NPs, offering a viable, long-term solution to the need for ophthalmic medical providers across all states without mitigating patient care, emphasizing the great need for the implementation of ophthalmic NP residencies and fellowships to ensure the continuity of impeccable ophthalmic care for all populations.

Keywords: Fellowships; Nurse Practitioner; Ophthalmology; Post-graduate Training; Residency; United States

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INTRODUCTION

To date, there exists a severe shortage of eye care providers that perpetuates unnecessary vision impairment and blindness in developing and developed countries worldwide.[1] In the United States (US) and according to the Association of American Medical Colleges (AAMC), America will observe a physician shortage of approximately 122,000 by the year 2032.[2] The current physician shortage is pragmatic in primary care services, which is projected to rise due to the ever-growing population and increasing population

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age, estimated to account for 81% of the total population from 2010 to 2020.[3] Specialty shortages also form a significant disparity in provider healthcare, where the projected medical specialist dearth rates are projected to fall between 1,900 and 12,100; the projected surgical specialist shortage is approximated to fall between 14,300 and 23,400, while other specialists like neurologist, pathologists, psychiatrists, and radiology specialists can anticipate a shortage of 20,600 to 39,100 by the fiscal year of 2032.[2] Specifically, a total deficit of 45,400 primary care physicians and 46,100 medical specialists, a grand total of 91,500 medical doctors will be needed in the fiscal year of 2020 alone.[4] Recent data acquired in 2020, post onset of the COVID-19 pandemic, projects the physician shortage to dramatically worsen by 2033; in (i) primary care, the physician shortage will range from 21,400 to 55,200 physicians, (ii) in non-primary care specialties, the shortage will fall between 33,700 and 86,700 physicians, (iii) in surgical specialties, the shortage will be between 17,100 and 28,700 physicians, (iv) in medical specialties, the shortage will be between 9,300 and 17,800 physicians, and finally (v) in other specialties such as radiology, pathology, and psychiatry, there will be a 17,100 to 41,900 physician shortage.[5, 43] The cumulative need for physicians in the US emphasizes the roles of primary care Nurse Practitioner (NP) and Physician Assistant (PA) workforces, which is anticipated to grow at a greater rate compared to physician supply; the supply of the primary care NPs is expected to see a 30% increase, where primary care PAs are expected to increase by 58% through 2020.[3] More recently, the 2019 role of the NP has grown by over 270,000 in the US, as patients are now benefiting more than ever from comprehensive, high-quality, patient-centered healthcare services governed and provided exclusively by NPs.[2] Additionally, an AAMC study analyzing the effective use of the NP and PA workforce to compensate for the growing healthcare provider paucity projected a potential physician shortage decrease of 42,600 to 121,300 by 2030.[6]

Through the effective integration of Advanced Practice Clinicians (APCs) in the medical field, the projected deficit of primary care physicians can decrease to 6,400.[3] Studies conducted by Spetz *et al*[7] and Hoff *et al*[8] illustrate the positive patient perception and care provided by APCs in diverse patient populations including primary care and medical specialties. Comparative studies conducted by Jiao *et al*[9] detail the relative comparability of ambulatory prescribing among physicians and APCs alike. While Hooker *et al*[10] delineates the different characteristics among APCs, NPs have been specifically noted to fully utilize their APC skills, practice to the maximum capacity of their legal scope, are satisfied with their careers, and plan to stay in their jobs log-term, all while reporting greater practice autonomies.[7] In specialty fields, trends assessed by Ray *et al*[11] acknowledge the lack of research addressing APC involvement in medical specialties. It was concluded that patient visits involving APCs in surgical and medical specialties increased from 3.3% between 2001 and 2003 to 6.9% between 2010 and 2013, lending credit to the effectiveness and increasing need of APC visits in specialty medicine.[11, 12] Effective use of APC practice in specialties are further bolstered and defined by the implementation of APC fellowships and residencies, facilitating adequate transition into specialized medical care. Additionally, education and training not only strengthen and develop the capabilities of global eye healthcare and the World Health Organization Development Goals in a sustainable way, but they also direct focus and bolster the skills and efficacy of ophthalmic providers in the US to ensure quality and precision care, while addressing the need for qualified and superiorly trained specialty eye care providers, a void that can be fulfilled by ophthalmic NPs.[1] The purpose of this article is to draw attention to the need for Nurse Practitioner Fellowships in the US with specific attention to NP fellowships and residencies in specialty medicine like ophthalmology.

The Importance of NP Fellowships in the US

The terms fellowship and residency are used synonymously in APC literature.[13] Generally, medical and pharmacy fellowship and residency programs serve to provide adequate transition of the new healthcare practitioner from academia to clinical practice; the APC transition is no different, especially in specialty practices.[14] Both PA and NP accreditation bodies have established postgraduate training models governed by the (i) Accreditation Review Commission on Education for Physician Assistant (ARC-PA) and

(ii) the American Nurses Credentialing Center (ANCC) and National Nurse Practitioner Residency and Fellowship Training Consortium, respectively.[15] As of 2007, 60 APC postgraduate training programs were functional in the US, with primary attention toward surgical specialties.[15]

As of 2019, there existed 145,585 certified NPs in the US; clinical areas of field certification include acute care, adult care, adult psychiatric-mental health, gerontology acute care, gerontology primary care, diabetes management, family medicine, pediatrics, psychiatric-mental health across lifespan, school NPs, and emergency medicine.[16] While the NP scope of practice is discussed at length by Hudspeth and Klein,[17] it is important to underscore the recent legislative changes that now enable more NPs to practice autonomously in the majority of the states in the US. According to Park *et al*,[18] greater NP practice autonomy was attributed to full, independent prescriptive authority, whereas having independence governing medical diagnoses and treatment regimens only moderately affected prescriptive independence. Such results indicate that expanded state NP practice regulations correlated with an increase in NP supply and greater access to care among rural and underserved populations deprived of a decrease in care quality.[19] Recent literature directly affirms and correlates NP autonomy and favorable relationships with leadership improves teamwork in the clinical provider workforce.[42] Additionally, there is a clear correlation between interdisciplinary teams and better patient outcomes; interdisciplinary teams within clinical practice effectively facilitates teamwork, inter-collegiality, and superior clinical provider and leadership relationships, which yield better care outcomes.[21–23] Finally, a study conducted by Poghosyan *et al*[20] also affirms and provides tangible evidence that NP–physician teamwork directly affected clinician job satisfaction, intent to leave, and perceived quality of care within a given medical practice.

Though there are many facilitators and barriers that both aid and negate effective and confident NP workforce transition, the implementation of NP fellowships can serve as a platform to sustain effective shifts from the academic to clinical platform; facilitators like the establishment of mentorship, social support, meaningful work, and work–life balance as well as barriers to NP workforce transition such as lack of support, role ambiguity, and workload exists have been founded to impede and bolster this process, a challenge that can be resolved by NP fellowship implementation.[24] According to Bryant and Parker,[25] participation in a nurse practitioner fellowship instills greater confidence, job satisfaction, and increased job retention through the transition from novice to expert clinician; as a result, continued provision of NP fellowships facilitate superior clinical practice leading to greater patient outcomes provided by NPs. While NPs are noted to deliver cost-effective, high-quality medical care that addresses the need for medical providers, graduate education often lacks specialized postgraduate fellowships, resulting in the acquisition of on-the-job training.[26] With emerging research highlighting the need for NP fellowships across US specialty disciplines, Kesten and El-Banna[27] found that over 90% of program directors state an increase in NP recruitment and retention following NP fellowship implementation. Additionally, the majority of decision-makers favor NP fellowship implementation with few to no barriers and 84% of physician and administrative support and favor fellowship/residency acquisition.[27]

NP Fellowships and Residencies in Specialties – What is known?

As of 2016, more than 30 postgraduate fellowships are available for masters and doctorly prepared NPs to enhance their teaching, clinical outcomes, advocacy, and research abilities.[13] A total of 68 active NP fellowships and residencies were identified by Martsolf *et al*[28] in the US, where 45.6% of programs were self-defined as residencies and 54.5% self-defined as fellowship programs. The average postgraduate NP fellowships varied from 12 to 24 months in duration and offered predominantly full-time status with competitive salaries and benefits.[28] NP fellowship salaries averaged $60,000 USD, with the highest noted at over $100,000 USD; some programs reported a salary of <$50,000 USD, whereas other fell within the $50,000 to $60,000 USD range.[28]

In terms of admission requirements, 79.4% of the 68 NP postgraduate programs required a state NP license, 67.7% required a discipline-specific certificate, 51.5% targeted new graduates,

22.1% required additional certification specific to the program, 51.5% required an NP specific degree such as pediatric or family NP, and 17.7% required a Drug Enforcement Agency number (DEA).[28] Performance and effect of increased ability, patient satisfaction, and quality of care are further evaluated in detail by Hoff *et al*[8], Kesten and El-Banna,[27] Sciacca and Reville,[13] and Spetz *et al*.[7] Examples of recent specialty NP fellowships successfully implemented within the last five years are depicted in Table I, in the fields of oncology,[26] palliative care,[29] emergency medicine,[30] and neurology.[31]

Predominant NP fellowship and residencies offered throughout the US to date are distributed disparately throughout each state, where some states do not offer any NP fellowship programs whatsoever. NP fellowships and residencies predominate in advanced practice, advanced practice nursing, acute adult care, cardiology, critical care, diabetes, dermatology, emergency medicine, family nurse practitioner, gastroenterology and hepatology, geriatric, neuroscience/neurology, oncology, orthopedic, palliative care, pediatrics, surgical, and wound reconstruction among other variations based on demographic and state need; however, there is no NP ophthalmology fellowship or residency available to date.[32]

Defining the Need for NP Fellowships in Ophthalmology

As a clear delineation circumscribes the countless benefits provided by NP health services in the medical profession in terms of physician deficit burden, patient outcomes, and quality of care, clinical efficiency is bolstered through the implementation of NP fellowships, especially in specialty medicine.[25, 27] To date, there is minute to no literature that supports the need to establish an NP fellowship in the specialty field of ophthalmology.

The Value of Advanced Practice Ophthalmology Nursing

While the physician to patient burden is prevalent in all medical disciplines, there is paralleled heightened urgency in the field of ophthalmology; by the year 2020 compared to 2000, the total population to ophthalmologist ratio has increased by 15% with a projected increase over time.[33] Such a shift in demand can be largely attributed to the increase in the elderly population, who heavily rely on ophthalmic services, drawing attention to the need for additional ophthalmology health providers.[33] As illustrated by Browning,[33] there are three predominant methods to address the need gap in ophthalmology care, namely (i) increase the number of ophthalmology providers, (ii) enable current and future ophthalmologists to work more hours, or (iii) institute and effectively utilize APCs in the field of ophthalmology. Historically, an average of 52 PAs were employed by ophthalmologists by 1990; that number has since increased to 70 as of the fiscal year 2015.[33] Established duties known to ophthalmology PAs include preoperative histories and physical exams for large cataract and refractive surgery; however, Browning[33] states that PAs can do more such as take call, conduct clinical work-in visits, perform intravitreal injections (IVTs) for retinal specialties, and operate dry eye clinics. As effective as PA duties are in ophthalmology, the role of the NP is even more so, making NPs an invaluable addition to the field of ophthalmology.

From a financial perspective, Moore and Barr[34] further define the potential resolution of bridging the ophthalmology physician deficit burden with the use of APCs, optometrists, faculty ophthalmologists, and resident ophthalmologists. Though a detailed overview approximated the average salary and benefit wages to be $126,797, $117,021, $338,233, and $71,210, respectively, the study concludes that while the use of ophthalmology residents to address the ophthalmologist shortage is more cost-effective, they do not directly produce work relative value; therefore, long-term implementation of resident ophthalmologists to address the need is not a viable long-term solution.[34]

Advanced practice NPs are educated to provide competent, independent, autonomous patient care; they have the ability to manage their own health clinics and provide adequate and efficient healthcare for their own governing patient populations.[35] Advanced practice NPs have the ability to adjust, expand, and integrate practical skills, and evidence-based research into patient care regimes to meet the demands and expectations of patients, governing bodies, and stakeholders.[35] In terms of ophthalmic medicine,

Table 1. Examples of US NP fellowships across medical specialties in the past 5 years

Citation	Country	Program Type	Model	Aim	Outcome
Alencar *et al*, 2018[26]	USA	ARNP Oncology Fellowship	ARNP Model	Define the need for ARNP Fellowship in Oncology	1. Structured ARNP fellowships in oncology facilitate training, mentorship, and retention 2. Implementing new NP oncology fellowship lead to increased patient care, job and staff satisfaction
Dahlin *et al*, 2019[29]	USA	Hospice & Palliative Care APRN Fellowship	HPNA APRN Fellowship Guidelines	Detail aspects of six Palliative APRN fellowships	1. APRN Fellowship improved patient outcomes
Hardeman & Hough, 2017[31]	USA	APRN and PA Fellowship in Neurology	ARNP and PA Model	Define need for advanced practice practitioner fellowship in Neurology	1. Need for APC in neurology backed by statistics that reflects high patient burden 2. APP Neuro fellowship will train, retain, and ease neuro clinician shortage 3. APP more cost-effective, better patient outcomes
Gaudio & Borensztein, 2018[30]	USA	ARNP Emergency Medicine Residency	ARNP Model	Define the need for ARNP Residency in Emergency Medicine	1. Increased ENP self and job satisfaction 2. Increased ENP competency 3. Stronger clinical foothold in EM

the benefits of ophthalmology NP implementation is no different.

Ophthalmic NP Duties

Ophthalmology NPs have the ability to evaluate, diagnose, treat, and discharge patients with ocular disorders.[35] They have the ability to manage care for referred patients from general and primary care providers, conduct baseline screenings, monitor disease development and outcomes, and treat chronic ocular conditions such as diabetic retinopathy, dry eyes, and glaucoma among other ocular disorders.[35] In terms of surgical care, ophthalmic NPs can conduct initial, follow-up, and discharge assessments and education for ophthalmic surgery patients diagnosed with cataract among other ocular disorders; they can also manage care on a broad spectrum, from children to adults to the older adults.[35] Additionally, ophthalmic NPs can perform minor ophthalmic procedures autonomously without physician supervision, such as adnexal surgery and assisting in ophthalmic surgeries like YAG laser capsulotomies.[35]

Tangible Evidence of Successful Ophthalmology NP Implementation

To date, there is currently one study that documents the successful implementation of a single PA into an ophthalmology consulting service in an academic setting; the purpose was to improve resident education with an outcome

of improved ophthalmic resident education facilitated by a PA overall.[36] The implementation of advanced practice NPs into an ophthalmology clinic dates back to 2007, a case study that documents an ophthalmology NP effectively providing NP-led consultation services to a diabetic retinopathy patient in Wales.[37] Harty[37] clearly delineates the value of the ophthalmic NPs in a patient's most vulnerable state and reiterates the fact that if no ophthalmic NP serves were provided, the patient would have suffered additional, unnecessary trauma and anguish potentially leading to blindness. A literature review complied by Drury *et al*[38] of Australia documents the effectiveness of advanced practice ophthalmology NPs, indicating that while the majority of nurse-led ophthalmology clinics are supervised by ophthalmologists, there are many autonomous clinical skills performed by the ophthalmic NP such as slit lamp examinations, fundus examinations via direct ophthalmoscope use, optic disc assessment, and anterior segment assessments.[38] Additionally, Drury *et al*[38] highlighted the variability in ophthalmic NP training, stating that two documented studies delineated the training of ophthalmic NP-led clinics who held a Master's degree with postgraduate training in pharmacology and extensive anterior segment training. Such services are meant not to facilitate replacement of the ophthalmologist yet render adjunct ophthalmic services to shorten waiting lists and allow providers to spend more time caring for complex patient needs.[38] Finally, in a Scottish study by Gallagher *et al*,[39] an advanced ophthalmic NP delineated the effective and suitable implementation of ophthalmic NPs in IVT clinics given their training and experience; demonstrating NP expansion in the ophthalmic discipline in terms of IVT, macular assessment and follow-up, and effective patient care and outcomes for those diagnosed with age-related macular degeneration, macular edema-associated diabetic retinopathy, and retinal vein occlusion. Findings of the study indicate that most of the polled ophthalmic population found the delivery of IVT provided by an ophthalmic NP to be more educating, receptive to questions, and patient centered.[39] Additionally, patients did not mind IVT delivery performance via a trained, ophthalmic NP versus a physician, and of those who objected to IVT via an NP over a physician cited concern for decreased training and experience to deal with consequential problems as the primary mode of concern.[39]

SUMMARY: US Ophthalmology NP Fellowships, It Is Needed. What Now?

To date, there are no established ophthalmology NP fellowships recorded within the past 10 years in the US. Given the increasing physician deficit to increased population burden that is echoed in the discipline of ophthalmology, the time for APC implementation in ophthalmology has arrived.[33] The importance of APC provider healthcare is boundless; with increased autonomy in the US for NPs across various states; NPs offer a cost-effective, efficient, and patient-centered option to providing medical care across demographics and socioeconomically challenged populations. In an effort to standardize and direct the role of the NP, the APRN Consensus Work Group and National State Boards of Nursing formed the 2008 Consensus Model, mandating NPs to obtain a proper education with a graduate degree or postgraduate certification from an accredited university among other requirements.[12] Over time, NP schooling requirements, clinical knowledge, and patient practicums have developed more rigorously to ensure efficacy of care provided.

While the acquisition of postgraduate APC fellowships or residences are sparse, participation in accredited programs bolster the skillset, mental acuity, and evidence-based care provided to the given, served population. They function to bridge the gap in clinical practice among APCs.[15] It is here that the APC learns to transition their academic knowledge to the clinical setting in a safe, supervised, and directed platform. Favorable outcomes of such programs have been noted to augment care, where patients feel reassurance in knowing that the APC underwent rigorous and accredited educational standards to ensure their privilege at the bedside as a medical care provider. As stated by Cosme,[14] continued growth of residency and fellowship programs for APCs are needed in order to meet the growing demand of healthcare needs in terms of patient safety and decreased reimbursement; continued growth will safeguard increased self-reflection and drive research that will better both medicine and healthcare consumers as a whole. Additionally, participating in a postgraduate NP

training program, residency, or fellowship aids in the creation of valuable members of the healthcare team that can function during rapid changes in the American healthcare system.[13] Moreover, participating in APC postgraduate residencies or fellowships aids to calm the anxiety associated with the transition from academia to clinical practice, all while obtaining supervised training and expert mentorship.[13]

Current ophthalmology statistics underscore the need and shortage of ophthalmologists, where 61% of Americans had no ophthalmologist in 2011; a shift in population distribution toward an aging population surmises the need for ophthalmic services across the country.[33] While there are many solutions to bridging the need for ophthalmic physicians such as working longer hours and expanding Medicare, the use of APCs can bridge the deficit.[33] Although initial studies emphasized the efficacy of trained PAs in ophthalmology, NPs are equally if not more viable in terms of trainability, clinical experience, cost, and clinical background, making NPs highly suitable for ophthalmic care following the successful completion of an accredited ophthalmology residency or fellowship.

In terms of ophthalmology APCs, studies prove that successful postgraduate training for advanced practice NPs in the field of ophthalmology enable efficient patient care in the various aspects of ophthalmic care.[37–39] As described by Drury *et al*,[38] following NP ophthalmic-specific training, nurse-led ophthalmic clinics successfully functioned to enable NPs to complete common ophthalmic practice such as slit lamp exams, direct ophthalmoscope fundus examinations, optic disc assessments, and anterior segment assessments among other critical techniques and practices needed for independent ophthalmic assessment, care, and treatment. Additionally, ophthalmology simulations offer cost-effective, heighted accessibility, objective ophthalmology training outcomes, and improved patient safety initiates to effectively train APCs with specific attention to NPs in the specialty field of ophthalmology.[1] As current practices in the US do not facilitate ophthalmic fellowships or residencies, the purpose of this article was to delineate the need and benefit for immediate implementation.

Although the NP workforce transition can be rigorous at times, there are many strategies that can facilitate the effective transition of the NP into a proper clinician and leadership role; self-initiative, mentorship, experiential learning, professional socialization, and interprofessional training are effective and proven methods that facilitate operative, sustainable, and substantial clinician–patient relationships in an effort to provide superior patient care, methods that are absolutely critical and effective in molding impeccable ophthalmic NPs.[40, 41] The primary objective of specialized postgraduate ophthalmic NP fellowships would be to educate and train NPs to be fast, logical thinkers under pressure and during emergent situations; decisions should compile assessment and utilization of prior studied information for accurate situation evaluation, all while rationalizing best patient outcomes, just as US physicians undergo in post-medical school residencies.[35] As Martsolf *et al*[28] describes, the need to establish NP ophthalmology fellowships coincides with the Institute of Medicine's seminal report that urges the state boards of nursing, accrediting bodies, the federal government, and healthcare organizations to enact methods that support nurses' completion of a transition-to-practice program, such as a residency or fellowship, after completing prelicensure, advanced practice degrees, or when transitioning into new clinical practice areas. The need for ophthalmology NP fellowships in the US is clear; the time for establishment is now.

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Conflicts of Interest

There are no conflicts of interest.

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Case Report

Surgical Management of Glaucoma Secondary to Bilateral Acute Iris Transillumination: A Role for Gonioscopy-assisted Transluminal Trabeculotomy

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Abstract

Purpose: We report a case of bilateral acute iris transillumination (BAIT) in a young woman associated with ocular hypertension which eventually progressed to glaucoma that was treated with gonioscopy-assisted transluminal trabeculectomy (GATT).

Case Report: A 37-year-old otherwise healthy female presented with intermittently red and inflamed eyes and blurred vision. She was treated with oral moxifloxacin months prior to presentation. Iris transillumination defects, a pigmented anterior chamber reaction, the absence of keratic precipitates, and a history of upper respiratory infection treated with an oral fluoroquinolone prompted the diagnosis of BAIT. Intraocular pressure (IOP) remained uncontrolled on multiple glaucoma medications. Following the development of new visual field defects, indicating progression to glaucoma, GATT with cataract extraction was performed.

Conclusion: Although surgical intervention is rare with BAIT, our case demonstrates that GATT may be used effectively in those patients needing better IOP control before considering incisional glaucoma surgery.

Keywords: Bilateral Acute Iris Transillumination; Fluoroquinolone; Glaucoma; Ocular Hypertension; Gonioscopy-assisted Transluminal Trabeculotomy

J Ophthalmic Vis Res 2021; 16 (1): 122–126

INTRODUCTION

Bilateral acute depigmentation of the iris (BADI) and bilateral acute iris transillumination (BAIT) are recently described clinical diagnoses of uncertain etiology that tend to occur in young women and may be associated with viral illness and/or fluoroquinolone use.[1, 2] BADI consists of a predominantly pigmented anterior chamber (AC) reaction and bilateral, usually symmetric, depigmentation of the iris stroma without transillumination defects (TIDs). It tends to be

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self-limited with resolution of iris depigmentation and no effect on intraocular pressure (IOP).[1, 3, 4] BAIT also produces pigment in the AC but is characterized by TIDs, variable pupillary sphincter paralysis, and an increased likelihood for IOP elevation.[2] Seventy-nine cases of BAIT have been reported in the literature since the first description of the syndrome in 2004.[5] We present a case of BAIT with secondary open-angle glaucoma and uncontrolled IOP that was ultimately managed with gonioscopy-assisted transluminal trabeculotomy (GATT), which to our knowledge is unprecedented.

CASE REPORT

A 37-year-old otherwise healthy female was referred to our glaucoma clinic for uncontrolled IOPs in the setting of bilateral hypertensive uveitis. Her initial symptoms included intermittent red and inflamed eyes accompanied by blurred vision. She was managed by several ophthalmologists for five months prior to presenting at our clinic. She had been diagnosed with bilateral hypertensive uveitis, for which she was placed on and off topical steroids and glaucoma drops. Her symptoms notably began shortly after taking a 10-day course of oral moxifloxacin (Avelox) for sinusitis. Initial and maximum recorded IOPs were 30 mmHg in the right eye and 17 mmHg in the left eye. At presentation to our clinic, visual acuity was 20/60 and 20/25 with –2.25 sphere and –1.50 sphere in the right and left eyes, respectively. Both pupils were poorly reactive to light, and the left pupil was noted to have an oval shape [Figure 1A–D]. IOPs by Goldmann Applanation Tonometry were 19 mmHg and 9 mmHg in the right and left eyes, respectively, on topical latanoprost and fixed-combination dorzolamide-timolol in both eyes, brimonidine in the right eye, and oral methazolamide. Lids and lashes were unremarkable. Cornea exam revealed a bilateral, diffuse endothelial pigmentation. The AC was deep in both eyes and showed trace flare in the right eye and rare pigmented cell without flare in the left eye. Gonioscopic exam was open scleral spur with a flat iris contour and heavy pigment deposition in both eyes [Figure 1E–F]. The irides demonstrated diffuse, patchy TIDs in both eyes. There was trace nuclear sclerosis with a 1+ posterior subcapsular (PSC) cataract in the right eye, and a trace nuclear sclerosis cataract in the left eye. On dilated fundus examination, the right and left optic nerves had cup-to-disc ratios of 0.4 and 0.1, respectively, with sloping of the superior rim of the right optic nerve. The remaining fundus exam was unremarkable.

Optical coherence tomography of the retinal nerve fiber layer (OCT-RNFL) demonstrated mild thinning in the right eye with a corresponding superior nasal step on 24-2 Humphrey visual field (HVF) [Figure 2A]. The OCT-RNFL and HVF in the left eye were within normal limits [Figure 2B]. A prior work-up with a uveitis specialist yielded negative results for syphilis, Lyme, and HLA-B27 antigen.

The patient's acute presentation associated with heavy AC pigmentation, diffuse iris TIDs, prior upper respiratory infection (URI), and oral fluoroquinolone use led to the diagnosis of BAIT.

IOPs were initially maintained on her presenting medical therapy. During follow-up visits, the patient experienced intermittent redness and photophobia, which were treated with topical steroids. The AC reaction remained predominantly pigmented with an absence of keratic precipitates. IOPs were labile but remained well-controlled on and off oral acetazolamide. Five months following her initial diagnosis, the IOP of the right eye was 28 mmHg despite maximum medical therapy. A repeat HVF revealed significant progression of the field defects in the right eye [Figure 2C]. The pressures remained controlled with full fields in the left eye [Figure 2D]. The PSC cataract had worsened, and her best-corrected visual acuity had declined to 20/100.

Due to the visually significant cataract and elevated IOP uncontrolled with medications, a combined cataract extraction and gonioscopy-assisted transluminal trabeculotomy (GATT) was performed in her right eye using a fiberoptic microcatheter (iTRACK, Ellex, iScience Inc., Fremont, CA) as previously described by Grover and colleagues [Figure 3].[6] IOP on the first postoperative day improved to 12 mmHg on dorzolamide-timolol and pilocarpine. Following resolution of inflammation with tapering doses of topical steroids, pilocarpine was discontinued at the one-month follow-up. IOP remained controlled in the mid-teens. At her final follow-up eight months after the surgery, IOP was 9 mmHg in the right eye on dorzolamide-timolol alone and 10 mmHg in the left eye.

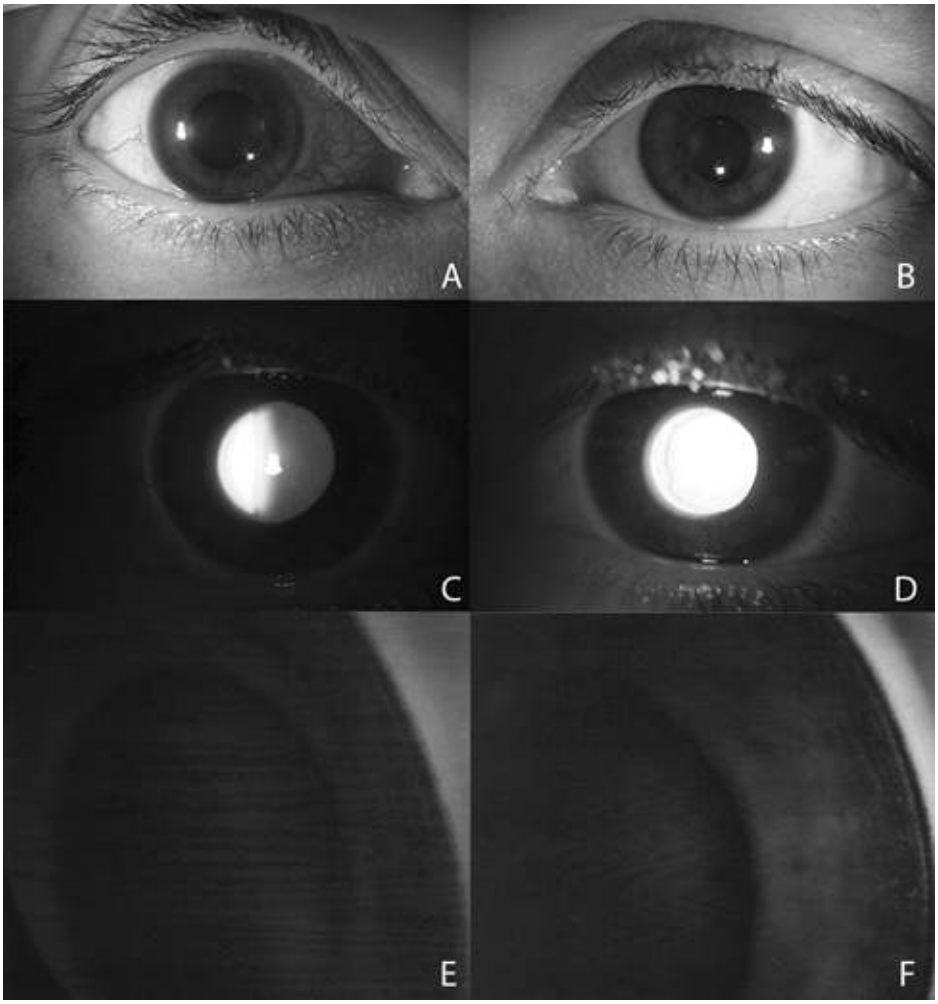

Figure 1. (A & B) External photos of the right and left eyes. The right eye has a mydriatic pupil with pupillary sphincter paralysis and nasal conjunctival injection. (C & D) Retroillumination photos of the right and left eyes. The right eye has a reduced red reflex, likely due to a more significant cataract. Visible in the left eye are diffuse, moth-eaten transillumination defects. (E & F) Gonioscopy photos of the right and left eyes showing open angles with dense trabecular meshwork pigmentation.

DISCUSSION

The differential diagnosis for anterior segment pigmentation and ocular hypertension is limited. Common diagnoses include pigment dispersion syndrome, herpetic uveitis, pseudoexfoliation, Uveitis-Glaucoma-Hyphema syndrome, and trauma. Less common diagnoses include iris/ciliary body melanomas, irradiation-induced depigmentation, and finally BADI/BAIT. Pigment dispersion syndrome was certainly considered, but the patient lacked the classic findings of posterior iris bowing and mid-peripheral TIDs. Furthermore, Krukenberg spindles, which signify a more indolent and chronic depigmentation process, were notably absent. This, in addition to the acuity of onset, severe and diffuse iris pigment loss, inflammatory symptoms, and preceding URI with oral fluoroquinolone use led to the unusual diagnosis of BAIT.

BAIT was first described in a series of five patients who presented with bilateral photophobia and injection 10 to 14 days after taking oral moxifloxacin.[7] In the largest case series to date, all 26 patients examined presented with photophobia. Most had pigmented cells in the AC, bilateral diffuse iris TIDs, and mydriasis with poor pupillary sphincter function. Nearly three-quarters of the patients had a preceding URI, and nearly half of this subset had taken oral moxifloxacin.[2] Our patient has many clinical features consistent with BAIT. The more patchy and milder TIDs than those described in other reported cases may be partly due to media opacity from the cataract in her right eye.

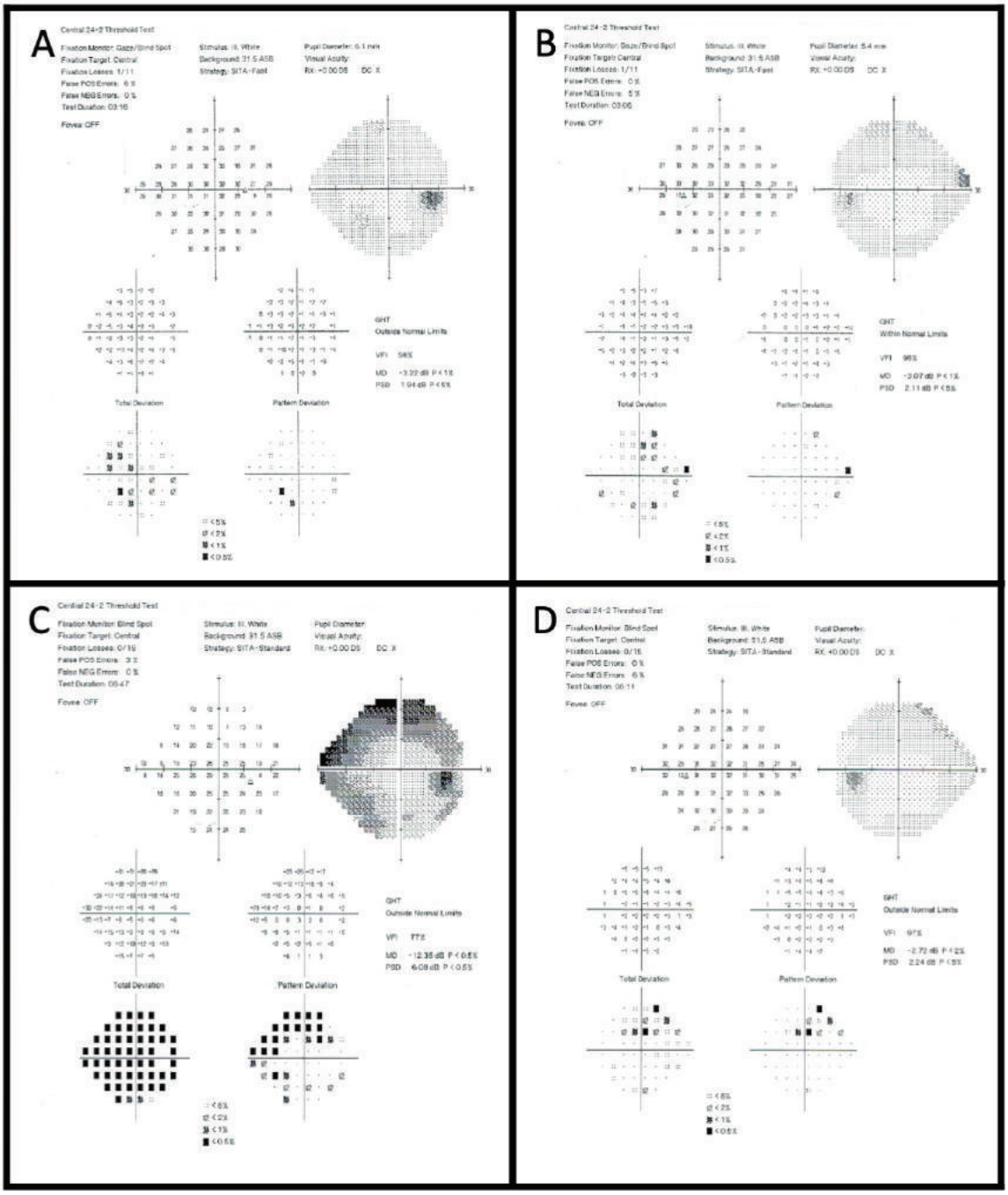

Figure 2. (A & B) 24-2 Humphrey visual field of right and left eyes at initial presentation. (C & D) 24-2 Humphrey visual field of right and left eyes five months after initial presentation to our clinic showing superior arcuate and inferior nasal defects in the right eye.

BADI is another rare, female-predominant clinical entity potentially linked to a prior URI and/or moxifloxacin use. Like BAIT, BADI typically presents with photophobia, bilateral involvement, and a pigmented AC reaction. The iris findings, however, are drastically different. Unlike BAIT, there is depigmentation of the iris stroma, yielding a greyish, granular appearance, a lack of TIDs, and a normal pupil.[1] Another distinguishing feature between BAIT and BADI is the incidence of elevated IOP. Tugal-Tutkun and colleagues showed that 54% of patients with BAIT developed elevated IOP during their disease course, with 27% requiring oral acetazolamide and 8% requiring bilateral trabeculectomies with mitomycin C.[2] In contrast, only one patient (4%) in the BADI cohort

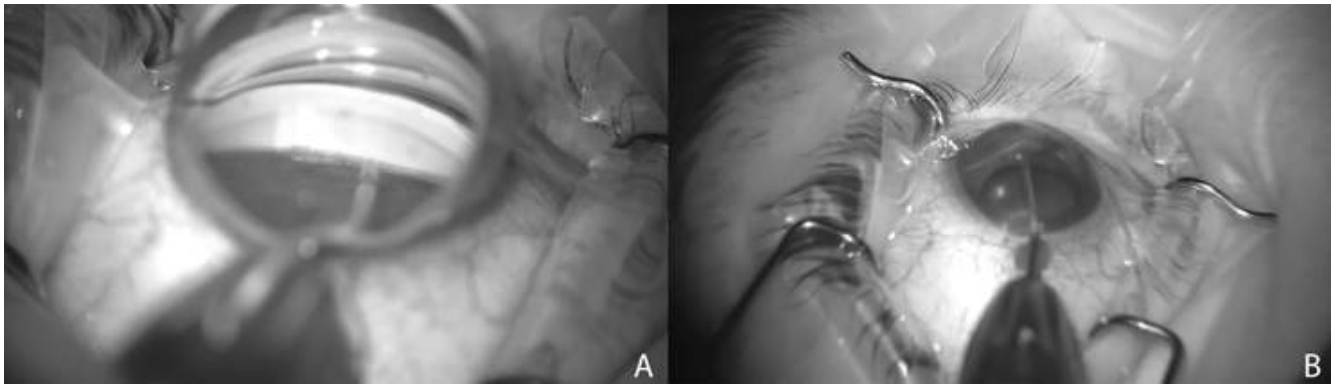

Figure 3. (A) Intraoperative gonioprism view demonstrating insertion of microcatheter into Schlemm's canal using microsurgical forceps via a goniotomy at the nasal angle. (B) The microcatheter has a red light at its proximal end, which is visible through the sclera as the microcatheter passes through Schlemm's canal. Once it has been passed for 360 degrees, the proximal end is held in place while the distal end is externalized to create a 360-degree trabeculotomy.

demonstrated elevated IOP. Gonioscopic findings were similar for both diseases, demonstrating heavy angle pigmentation, especially inferiorly.

Ocular hypertension is a common complication of BAIT.[2, 8–10] Patients with BAIT often receive topical steroids, which may contribute to the rise in IOP. However, ocular hypertension with BADI is rare despite steroid use, and elevated IOP in the setting of BAIT has been reported in the absence of steroids, suggesting a mechanism for ocular hypertension intrinsic to the disease.[1, 2, 8] Surgical management in this condition is rare; early cases involved bilateral trabeculectomies.[2] More recently, Trabectome was the first micro-incisional canal-based procedure to be utilized in the setting of BAIT.[8] Unlike Trabectome, which is limited to the nasal angle, GATT allows for a circumferential treatment. This provides a theoretical advantage by exposing more collector channels and improving the likelihood for treatment success. GATT has been utilized in patients with secondary open-angle glaucomas and has shown a high success rate and robust IOP reduction through 24 months of follow-up.[6] Our patient has demonstrated excellent IOP control after GATT.

In summary, to the best of our knowledge, this is the first reported case of GATT used to treat glaucoma secondary to BAIT. Although surgical intervention is rare with BAIT, our case demonstrates that GATT may be used effectively in those patients needing better IOP control before considering incisional glaucoma surgery.

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Case Report

Heads-up Digitally Assisted Surgical Viewing with Intraoperative Optical Coherence Tomography for Myopic Schisis Repair

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Abstract

Purpose: To describe the surgical approach with a screen-based heads-up, three-dimensional (3-D) digital viewing with intraoperative optical coherence tomography (I-OCT) for the successful repair of a myopic macular schisis (MMS) case.

Case Report: A 62-year-old woman with vision loss in the left eye was scheduled for pars plana vitrectomy (PPV) and MMS repair. Surgery was performed using the NGENUITY® system for surgical viewing, and foveal-sparing internal limiting membrane (fs-ILM) peeling was performed without gas tamponade, after confirming the absence of iatrogenic macular hole with I-OCT. There were no intraoperative or postoperative complications. Visual acuity improved to 20/40 and the subfoveal macular thickness improved from 706 µm (preoperative) to 221 µm after seven months of follow-up.

Conclusion: Heads-up digitally assisted viewing technology with I-OCT may be useful or preferred for patients requiring vitreoretinal surgery in the setting of MMS.

Keywords: Heads-up surgery; 3-D; Intraoperative Optical Coherence Tomography; Myopic Macular Schisis; Foveal-sparing Internal Limiting Membrane Peeling

J Ophthalmic Vis Res 2021; 16 (1): 127–130

INTRODUCTION

Myopic macular schisis (MMS) is a pathology that is typically seen in high myopic patients, which is distinguished by progressive secession of the neurosensory retinal layers. Many articles have shown that pars plana vitrectomy (PPV), with or without internal limiting membrane (ILM) peeling and gas tamponade, is a successful treatment for this condition.[1–4] Here, we describe an MMS case treated with PPV and foveal-sparing internal limiting membrane (fs-ILM) peeling [Figure 1], without gas tamponade, using intraoperative optical coherence tomography (I-OCT) and digitally-assisted vitreoretinal three-dimensional (3-D) viewing.

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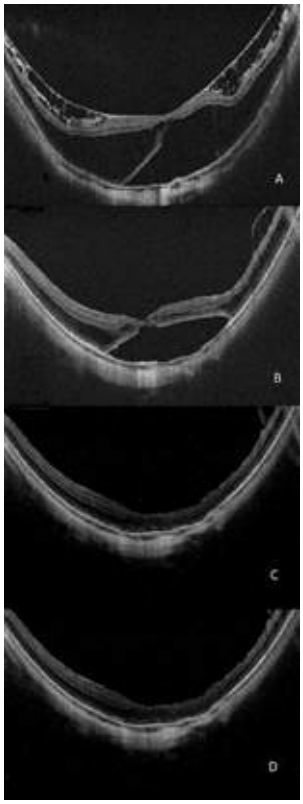

Figure 1. Intraoperative snapshot showing fs-ILM peeling using 3-D surgical viewing.

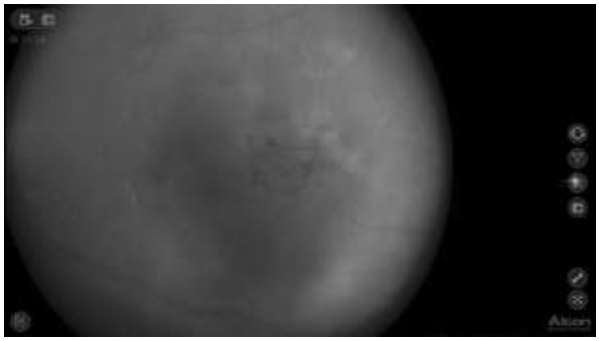

Figure 2. Intraoperative snapshot showing fs-ILM peeling using 3-D surgical viewing and I-OCT. The I-OCT shows no evidence of any iatrogenic complication.

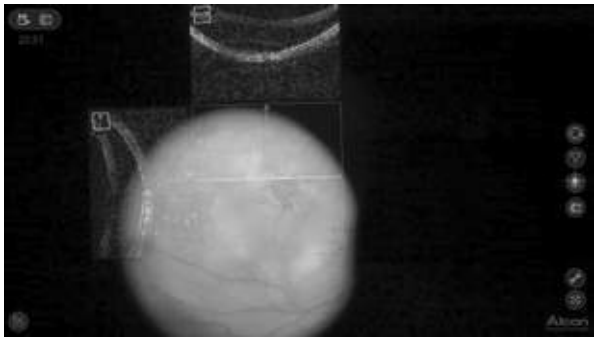

Figure 3. (A) Preoperative appearance, (B) partial resolution of the macular schisis one month postoperatively, and complete resolution of the schisis (C) four and (D) seven months after the surgery. Visual acuity improved from 20/200 to 20/40 and subfoveal macular thickness improved from 706 to 221 µm after seven months of follow-up.

CASE REPORT

A 62-year-old woman with MMS in the left eye of few month duration underwent a complete ophthalmologic examination that included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, fundus examination, and applanation tonometry. Spectral domain optic coherence tomography (SD-OCT) images were obtained with Cirrus HD-OCT (Carl Zeiss AG, Oberkochen, Germany) at baseline and at all follow-up visits (one, four, and seven months). Subfoveal macular thickness was 706 micrometers (μm), vision was 20/200, and PPV was scheduled. The patient had a history of phacoemulsification in the left eye.

The anesthetists performed sedation and a retrobulbar block. The NGENUITY® digitally assisted vitreoretinal surgery system (Alcon, Inc., Fort Worth, TX) was connected to replace the oculars of the microscope. The 3-D high definition real-time video was displayed on the NGENUITY®4K 3-D flat-panel placed at 1.3 m from the surgeon. To be able to see in 3-D, the surgeon wore polarized glasses. Traditional vitreoretinal techniques, with the Constellation Vision System (Alcon, Inc, Fort Worth, TX), were performed without obstacles, including core vitrectomy, posterior hyaloid detachment, and peripheral vitrectomy. Brilliant blue G (DORC, Zuidland, the Netherlands) was used to stain the ILM and the surgeon performed fs-ILM peeling using disposable 25-gauge end-grasping forceps under I-OCT [Figure 2]. The I-OCT also proved that there were no iatrogenic lesions [Video 1], so it was decided not to perform gas tamponade. The subfoveal macular thickness improved from 706 μm (preoperative), 540 μm (after one month), 214 μm (after four months) to 221 μm (after seven months) [Figure 3] and the visual acuity improved to 20/40 after seven months of follow-up.

DISCUSSION

In the current case, a 62-year-old woman was scheduled for PPV and MMS repair in the left eye, using the 3-D system. Foveal sparing ILM peeling was performed, without gas tamponade, after confirming the absence of iatrogenic macular hole with I-OCT.

MMS has already been described by many authors, showing a wide variety of therapeutic interventions. In most reported cases in which PPV was performed, ILM peeling was advised to completely remove residual traction on the retina, enabling the inner surface to adjust to the mold of the posterior staphyloma.[2] It is still a surgical challenge to measure accurately the dimensions of ILM sparing intraoperatively.

With the development of 3-D system[5] with I-OCT, real-time visualization of vitreoretinal interface, definition of the various plans of epiretinal membranes (ERM) and macular holes (MH), and visualization of ILM undulation after successful peeling can help in unequalled exactitude in an otherwise assumptive surgery.[6] Visualization of resolution of traction following vitrectomy and ERM removal can also help determine the surgical termination. Addition of such an advance would further improve management of MMS to very small precision.[3] In the current case, similar to Kumar et al,[3] fs-ILM peeling was performed under direct I-OCT visualization of the requisite area of sparing to prevent intraoperative deroofing of the cysts and MH formation.

Gas tamponade has been used in the treatment of MMS, provoking retinal repositioning by pushing the retina back. However, it remains unknown whether gas tamponade is necessary and its efficacy has not been established. Kim et al[4] showed resolution of MMS in six of the eight eyes (75.0%) after PPV and ILM peeling without gas tamponade. On the other hand, Figueroa et al[2] achieved resolution of MMS in 93% of 30 patients after PPV with ILM peeling and gas tamponade.

Our case demonstrates that heads-up digitally assisted viewing with I-OCT was suitable and effective to manage these challenging retinal disorders.

Financial Support and Sponsorship

None.

Conflicts of Interest

There are no conflicts of interest.

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Case Report

Optical Coherence Tomography Findings in Nodular Anterior Scleritis due to Poststreptococcal Syndrome

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Abstract

Purpose: To report a case of nodular anterior scleritis due to poststreptococcal syndrome using optical coherence tomography imaging.

Case Report: A 41-year-old woman with a history of acute rheumatic fever presented with a nodular anterior scleritis. Common causes were excluded. Optical coherence tomography of sclera showed enlarged vessels, inflammatory infiltrates, separated fibers, and a serous detachment. Laboratory investigations showed an elevated erythrocyte sedimentation rate, raised anti-streptolysin O titer, and the presence of group A streptococcus in the throat. The scleritis rapidly improved with penicillin treatment.

Conclusions: Poststreptococcal syndrome should be considered in the etiology of non-necrotizing anterior scleritis.

Keywords: Scleritis; Optical Coherence Tomography; Poststreptococcal Syndrome

J Ophthalmic Vis Res 2021; 16 (1): 131–134

INTRODUCTION

Poststreptococcal syndrome (PSS) includes all nonsuppurative complications of infections with group A streptococci.[1, 2] It appears as an immune-mediated reaction in any tissue of the body.[1] Acute rheumatic fever and acute glomerulonephritis are the common entities of PSS which most frequently involves young patients.[1, 2] Ocular involvement of PSS is uncommon and rare.[1, 2] More precisely, PSS is not considered among the common causes of scleritis.[3, 4] Scleritis is an inflammatory condition characterized by ocular pain and redness of the sclera.[3] It can threaten vision in severe cases.[3] Previous studies reported that optical coherence tomography (OCT) showed different changes in the sclera within each grade of active scleritis.[5, 6] Our aim is to describe a rare case of nodular anterior scleritis due to PSS using OCT imaging.

CASE REPORT

A 41-year-old woman had a history of an acute rheumatic fever (ARF) treated with penicillin in childhood. She presented with a two-day history

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of redness and pain in her left eye. Symptoms occurred few days after an acute pharyngitis. She reported a history of a similar episode in her right eye a year ago. Best-corrected visual acuity was 20/20 in both eyes. Slit lamp examination revealed a nodule in the superior sclera with hyperemia and chemosis around it [Figure 1]. Ocular examination and funduscopy excluded all forms of uveitis or suppurative infections. B-scan ultrasonography showed no abnormalities in the posterior segment of the left eye. Spectral Domain OCT (3D OCT-1Maestero; Topocon, Japan) of the sclera showed enlarged vessels, inflammatory infiltrates (hyporeflective spaces), separated fibers, and a serous detachment between them [Figure 1]. The scleral thickness at the level of visible layers was 659 µm on the nodular area and 555 µm around it. A surgical punch biopsy of conjunctiva and Tenon's tissue was performed at admission. Histopathologic exam revealed mild and nonspecific inflammation and excluded bacterial or parasitological infections. Investigations showed negative results for tuberculosis, syphilis, and rheumatoid arthritis (chest X-ray, throat culture, tuberculin skin testing, syphilis serology, antinuclear antibodies, rheumatoid factor). Laboratory tests showed high erythrocyte sedimentation rate (35 mm in the first hour), raised anti-streptolysin O (ASO) titer of 545 units/ml, the presence of group A *Streptococcus* in the throat culture, C-reactive protein of 1 mg/l, a white blood count of 5600/mm^3 (lymphocytes: 51%), and normal levels of blood electrolytes, glycemia, and azotemia. The patient received benzathine benzylpenicillin (extencilline: 1.2 million units intramuscularly twice monthly for three months). Examination showed rapid improvement within six days and remarkable resolution of signs after two weeks [Figure 1]. OCT demonstrated accumulation of the liquid in the sub-Tenon's space after 6 days and improvement of the fibrous structure of the sclera after 15 days. Recurrence of signs was observed in the right eye after 22 days [Figure 1]. The patient declared that she had not received the second dose of extencilline. OCT revealed hyporeflective areas due to an inflammatory fluid in the right sclera [Figure 2] and normal findings in the left eye. Extencilline treatment was administrated with the same doses in addition to oral corticosteroids. Complete recovery of signs was noticed after one week [Figure 2]. Normal level of ASO titers was reached after two months.

DISCUSSION

In this report, we described an uncommon case of nodular anterior scleritis induced by presumed PSS. Findings supporting the diagnosis of PSS scleritis were the history of ARF, pharyngitis, biopsy results, the high erythrocyte sedimentation rate, the raised ASO antibody titer, the evidence of streptococcal infections, the rapid response to penicillin, the early recurrence when the patient stopped penicillin treatment, and the negative results for all main diseases responsible for scleritis.[1, 6–8]

Reported cases of an ocular involvement of PSS include scleritis, in addition to uveitis, and rarely episcleritis, conjunctivitis, Brown's syndrome, optic disc edema, posterior scleritis, and glaucoma.[2, 7–12] However, previous studies reported PSS as an uncommon cause of uveitis or scleral inflammation.[2] To our knowledge, PSS was not figured among the possible causes of nodular anterior scleritis.[3, 4] Anamnesis, clinical examination, and laboratory investigations were helpful to exclude causes of necrotizing forms of scleritis and to suggest PSS. Biopsy may be helpful in establishing the diagnosis in cases of scleritis, but cannot rule out special scleral diseases especially in cases of non-necrotizing scleritis.[6]

According to the anatomo-clinical classification of scleritis, there are two forms of scleritis: anterior and posterior.[6] Anterior scleritis is divided into nodular, diffuse, and necrotizing scleritis. The nodular scleritis has two forms: necrotizing and non-necrotizing forms. OCT is useful to show the scleral changes and to classify the scleral inflammation. Moreover, this tool is helpful in distinguishing all forms of anterior scleritis and monitoring them.[5, 6] The common scleral changes in anterior scleritis were separated fibers, dilated vessels, hyporeflective spaces and high thickness of sclera.[5, 6] Although thickening of the episcleral layer was observed in both episcleritis and anterior scleritis, scleral layers were not affected in episcleritis.[13] OCT imaging is useful for distinguishing between non-necrotizing and necrotizing anterior scleritis. In the cases of

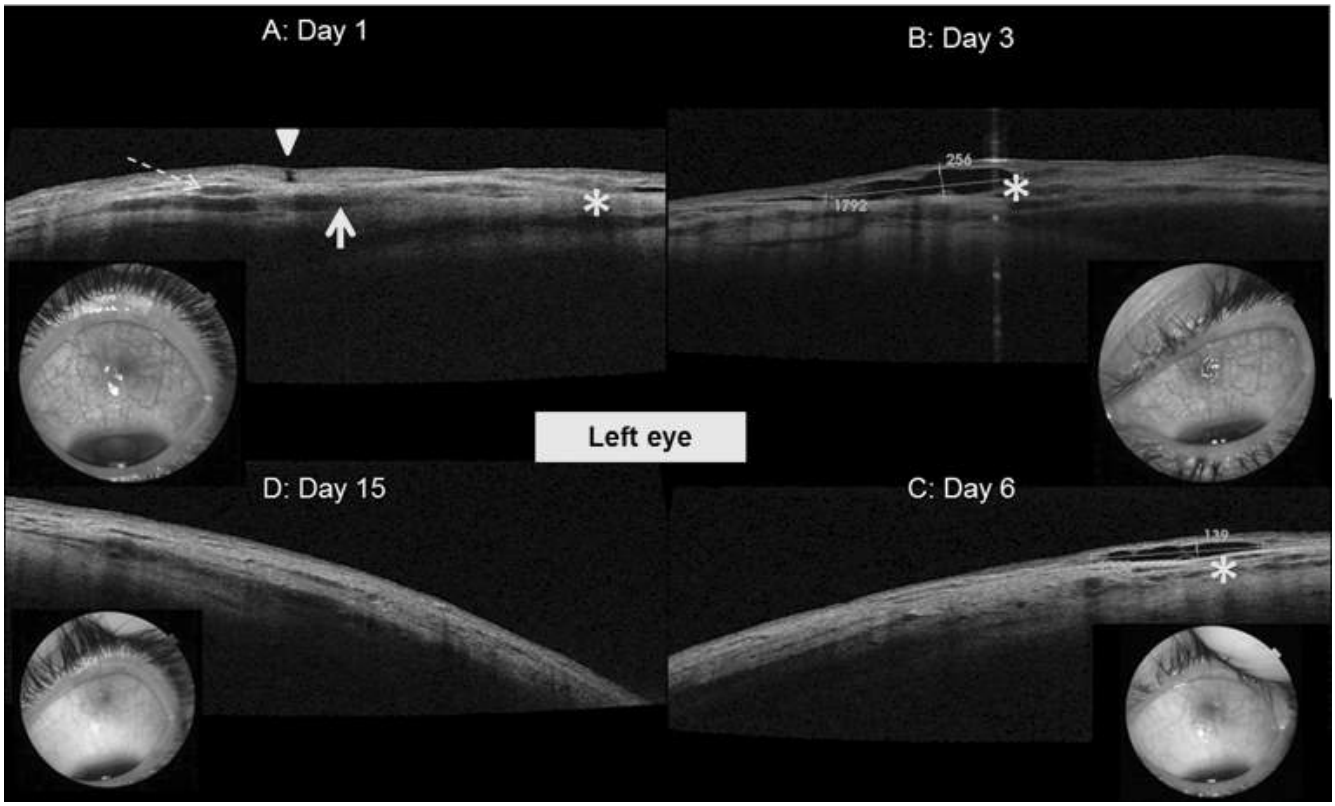

Figure 1. (A) Optical coherence tomography images of the left eye showed separated fibers (dashed arrow), enlarged vessels, inflammatory infiltrates (solid arrow), serous detachment between them (asterisk), and the site of conjunctival biopsy (arrow head). (B, C, D) Evolution after penicillin treatment.

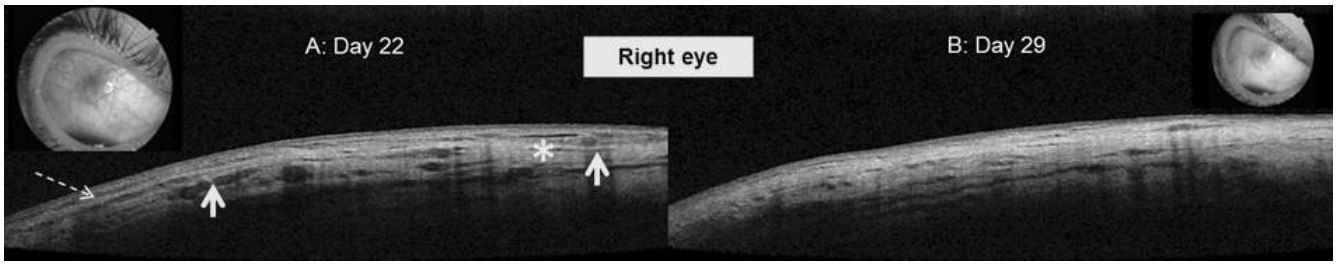

Figure 2. (A) Optical coherence tomography showed separated fibers (dashed arrow) and inflammatory infiltrates (solid arrow) due to recurrence of anterior scleritis in the right eye. (B) Resolution of signs in the final examination.

non-necrotizing scleritis, the collagen fibers were simply separated and associated with an extracellular fluid without necrosis of tissue. In the second form, scleral OCT showed destructive changes, in which any hyporeflectivity of the deep layers of the nodule corresponded to liquified tissues.[2, 5, 6, 10, 13] In addition, this tool is useful to grade anterior scleritis from mild to severe when the activity signs reach the deeper sclera and the suprachoroidal space.[5] In this case, OCT findings strongly suggested non-necrotizing form of nodular scleritis as described in the previous reports.[1, 6–8, 13]

Sometimes, OCT can suggest the etiology of anterior scleritis. Common associated diseases were rarely found in the cases of non-necrotizing noninfectious scleritis.[6] However, OCT was helpful in suggesting the etiology in some cases of necrotizing anterior scleritis. This tool showed destructive changes that involved the cornea, limbus, and the adjacent sclera in the case of a systemic vasculitis. However, the adjacent sclera was normal in the case of an idiopathic and rheumatoid-associated sclero-keratitis. The characteristic changes in rheumatoid arthritis are those of a venular

occlusive scleritis affecting the vessels of the episcleral plexus.[5, 6, 10]

In this patient, presumed PSS scleritis rapidly improved with just penicillin. Such a finding have been previously reported.[8] Penicillin prophylaxis is needed to prevent PSS complications and recurrence.[1, 7, 8, 12] Presumed PSS scleritis may be among refractory cases to standard corticosteroid treatment and may require penicillin for treatment.[7] The fluid space, that has been seen at admission (before the biopsy) and that has been increased at the follow-up examination of the left eye, seemed to be a new clinical event.

In conclusion, PSS should be considered in the etiology of nodular anterior scleritis. ASO titer should be performed in any patient suffering from anterior scleritis and having a history of streptococcal infections. OCT may be helpful in the diagnosis and follow-up of scleral lesions.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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Photo Essay

Crystalline Lens Staining with Intracameral Phenylephrine During Cataract Surgery

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PRESENTATION

During intracameral use of low concentration phenylephrine in several consecutive routine phacoemulsification cases, we have consistently observed a "spikes" pattern of staining in the crystalline lens structures; however, it was not entirely clear whether this involved just the capsule, the cortex, or both (Figure 1). Although it appears that the staining occurs largely at the level of the anterior capsule, some very faint staining could possibly be seen on the anterior lenticular surface as well. The formulation of intracameral phenylephrine (Minims® Phenylephrine Hydrochloride, Bausch & Lomb UK Ltd.) that is routinely used in our practice consists of 0.5 ml of 10% phenylephrine preservative free minims mixed with 0.5 ml of 2% lidocaine and 1 ml of Balanced Salt Solution with adrenaline. This mixture (0.2 ml) was injected in the anterior chamber.

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DISCUSSION

Phenylephrine is an α-adrenergic agonist regularly used as a dilating agent in the form of eye drops prior to intraocular surgery such as cataract surgery. It is also frequently used as an intracameral injection in conditions such as floppy iris syndrome to assist with pupillary dilation as well as to increase the iris tone.[1, 2]

No evidence of capsular staining was observed in our patients at postoperative visits. There were no reported or observed cases of toxic anterior segment syndrome or other systemic or vision-threatening complications intraoperatively or during the postoperative period. Although Lockington *et al* reported the possibility of toxicity associated with the presence of free radicals in intracameral phenylephrine formulations, we report no relevant deviations from routine practice in our patients.[3]

Lens staining was consistent in all cases where the intracameral phenylephrine formulation was used. It began to appear in 20 sec, peaking at around 1 min after the intracameral injection (Figure 2). We believe that the resulting appearance of the crystalline lens can facilitate capsulorrhexis in routine as well as in cases of borderline visibility

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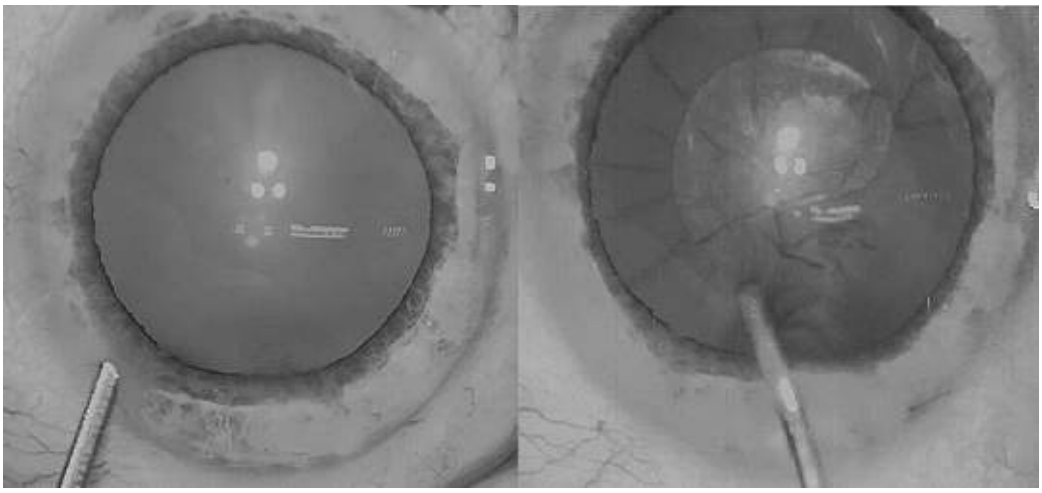

Figure 1. Spike-like staining of the crystalline lens (arrows) following intracameral injection of phenylephrine hydrochloride.

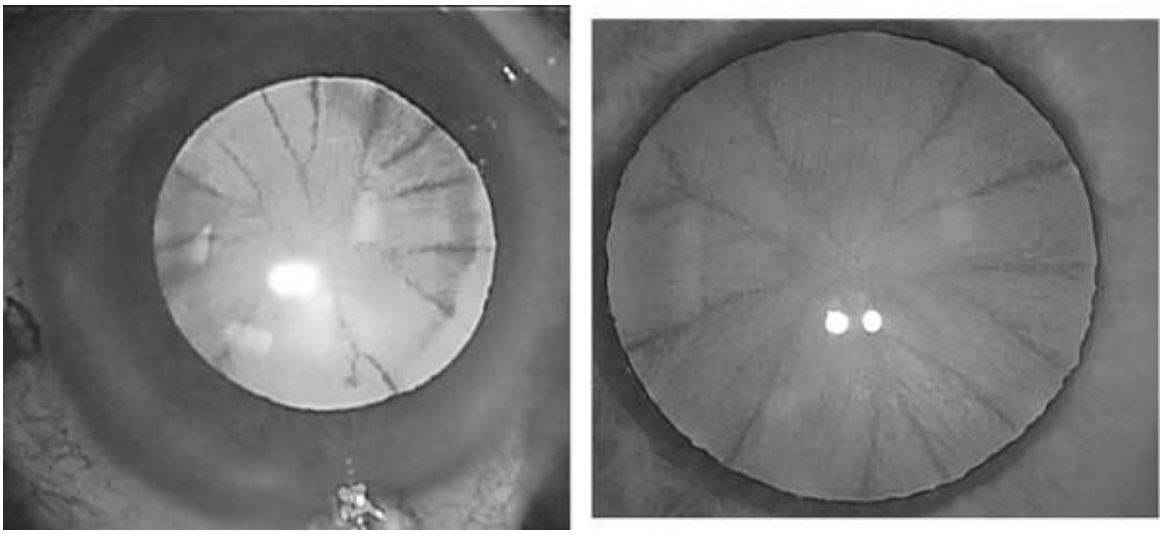

Figure 2. Early (left) and late (right) staining of the crystalline lens following intracameral use of phenylephrine hydrochloride in two different patients.

where usually a staining agent such as trypan blue is considered by the surgeon. Thus, no extra provisions need to be made resulting in reduced cost of surgery as well as less logistical burden on the operation theatre.

Furthering our understanding on the cause of crystalline lens staining related to intracameral phenylephrine and its implications will hopefully enable us to use this agent more effectively as a mydriatic and to facilitate capsulorrhexis in routine as well as complicated cases.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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Photo Essay

Oguchi Disease Associated with Keratoconus

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PRESENTATION

A 22-year-old female came to a cornea specialist in our center to do refractive surgery. The best-corrected visual acuity was 20/20 in both of her eyes with the following refraction: OD: –4.5–0.75 x 180 and OS: –4.75–2.00 x 110. Scissors motion was obvious in her left eye during refraction. In funduscopic evaluation, an abnormal yellow to brown sheen was obvious in her both eyes (Figure 1, right column). Other ocular examinations were within normal limits and patient had no history of any other systemic or ocular disease. Drug history and family history of ocular diseases were negative. Due to scissors motion and abnormal Pentacam (Figure 2), she has been diagnosed with keratoconus, her refractive surgery has been held, and corneal cross linking (CXL) was suggested to her. Both eyes optical coherence tomography (OCT) were completely normal but due to abnormal yellow sheen in her both eyes funduscopy, she was referred for further evaluation to us before CXL. She denied any night blindness or decreased vision in her both eyes. Oguchi disease diagnosis was made with presence of obvious Mizuo-Nakamura phenomenon (Figure 1) and was confirmed with genetic testing. Her electroretinography (ERG) was done based on the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol (Metrovision, Pérenchies, France). Due to rapid loss of dark adaptation by a short light exposure, dark adapted fundus photo and ERG have been done in different visits but with same instruments. Fundus photos have been captured by Canon CR-2 AF Retinal Camera. There was not any abnormality in her both eyes OCT angiography (OCTA) by Optovue OCTA (Fremont, CA, USA).

Genetic testing has shown a homozygous mutation in SAG (NM_000541.5) gene, variant c.874C>Tp.R292 which is compatible with type one Oguchi disease.

DISCUSSION

Oguchi disease is a type of congenital stationary night blindness (CSNB) with autosomal recessive inheritance. Patients usually have normal visual acuity and do not complain from night blindness. The disease is very rare and around 50 cases have been reported up till now. Most of the cases are from Japan and Pakistan.[1] Patients have an abnormal fundus color that is described as having yellow to brown sheen or metallic appearance.

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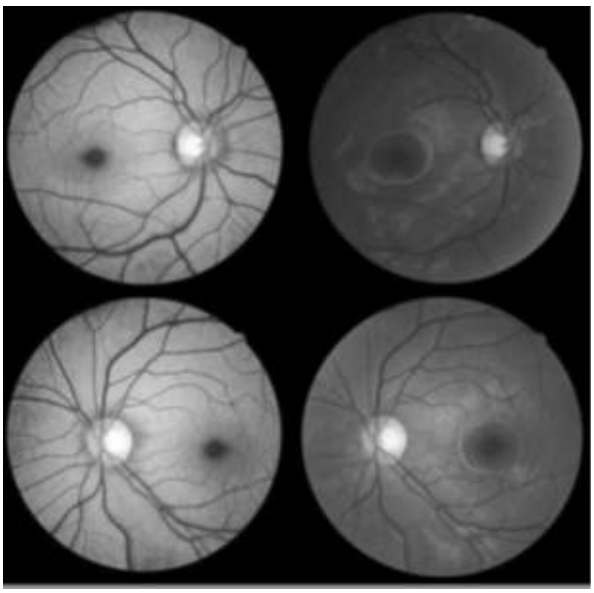

Figure 1. Mizuo-Nakamura phenomenon. Fundus photo of right and left eyes before (left column) and after (right column) 6 hr of overnight dark adaptation. All photos have been taken in normal illumination. Abnormal yellow sheen disappeared after dark adaptation.

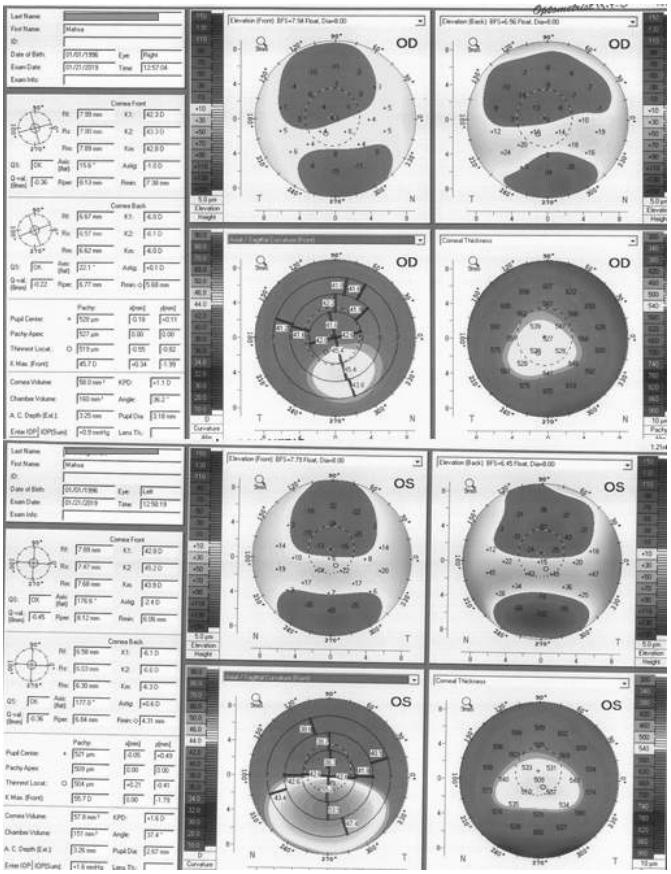

Figure 2. Pentacam of right (upper row) and left (lower row) eyes. Right eye Pentacam shows inferior steepening, high I-S value, posterior elevation, and inferior displacement of the thinnest point. Pentacam of left eye shows significant inferior steepening, increased keratometries, anterior and posterior elevation, and inferior displacement of the thinnest point that is compatible with keratoconus diagnosis.

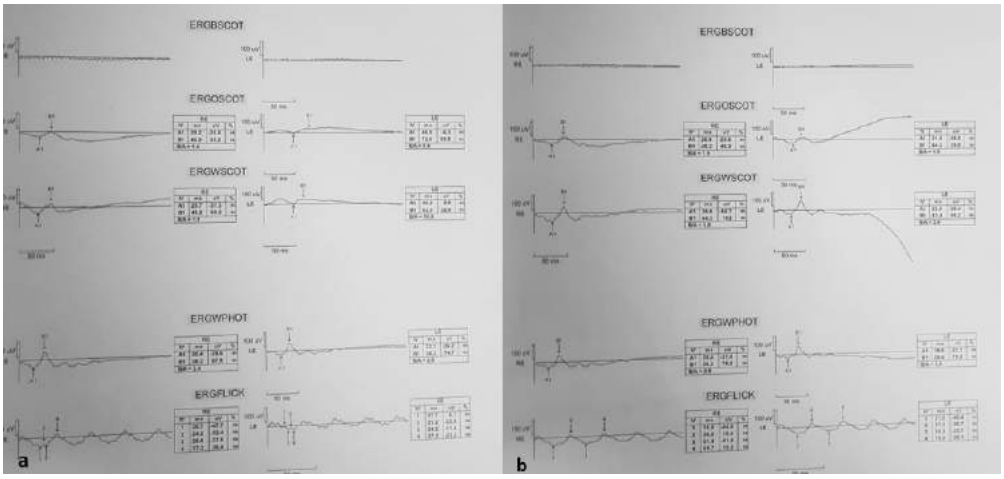

Figure 3. ERG before (a) and after (b) 6 hr of dark adaptation. Her first ERG (a) was performed after 30 min of dark adaptation which showed a severely reduced b-wave amplitude with a mild reduction of the a-wave that improved after 6 hr of overnight dark adaptation (b).

Prolonged dark adaptation can recover rhodopsin and re-normalize fundus color (Mizuo-Nakamura phenomenon).[2–4]

Oguchi disease has been reported in association with retinitis pigmentosa[4] and diabetic retinopathy,[1] but there is no report of its association with keratoconus or any other corneal abnormality up till now. However, there was a report of X-linked CSNB associated with keratoconus in 2006 from UK by Nguyen *et al*.[5]

Here, we report the first case of association of this disease with keratoconus in the world. To the best of our knowledge, this is the second case of Oguchi reported from Iran[1] but the first genetically proven Oguchi disease type 1 of Iran and Middle East.

The other case from Iran has shown negative ERG in photopic state with near flat ERG in scotopic condition.[1] Another case of Oguchi disease was reported by Francois *et al* with absent scotopic waves in 1956.[1]

In conclusion, Oguchi disease can be seen with keratoconus. Although it could be accidental due to high prevalence of keratoconus in our population, further reports in future may suggest a pathogenic linkage between them.

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Conflicts of Interest

There are no conflicts of interest.

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Photo Essay

An Unusual Presentation of Vogt–Koyanagi–Harada Disease Without An Overt Serous Retinal Detachment and With Severe Diffuse Alopecia

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PRESENTATION

In February 2018, a 21-year-old otherwise healthy female patient was diagnosed with a bilateral anterior uveitis by her local physician at a small rural hospital and was treated accordingly with topical prednisolone acetate drops. The patient also complained of a severe headache. However, no further investigation was carried out at that time. Severe alopecia ensued in March and June 2018, the patient was examined by us due to the recurrence of bilateral anterior uveitis. Her visual acuity was 20/25 OU. Bilateral (++) anterior chamber cells, non-granulomatous in nature, and a few pigmented iris clumps were observed on the anterior lens capsules. According to the SUN criteria, grade 0.5+ cells were noted in the vitreous bilaterally.[1] Fundus examination revealed mildly blurred disc margins and numerous scattered yellowish-gray, round spot-like changes scattered 360° throughout the fundus OU (Figures 1A and 1B). Fluorescein angiography revealed lesions exhibiting early venous hyperfluorescence with late staining associated with mild bilateral disc leakage (Figures 1C, 1D, 1E, and 1F). An indocyanine green angiogram (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) exhibited hypocyanesence of these lesions throughout the angiography sequences (Figures 1G and 1H). Most notably, no signs of serous retinal detachment were present (Figures 1I and 1J). On the other hand, diffuse type of alopecia areata was evident (Figure 2A) and the patient was referred to the dermatology and rheumatology departments. Meticulous laboratory and imaging examinations were carried out. Laboratory results showed that the erythrocyte sedimentation rate (ESR) and cytoplasmic reactive protein (CRP) were normal. Anti-nuclear antibody (ANA) was positive (homogeneous pattern; 1/100–1/320 with dilution). Tests for HLA B27, rheumatoid factor (RF), anti-citrullinated peptide (anti-CCP), extractable nuclear antigen (ENA) panel, anti-neutrophil cytoplasmic antibody, and anti-phospholipid antibody were negative. Serum protein electrophoresis results

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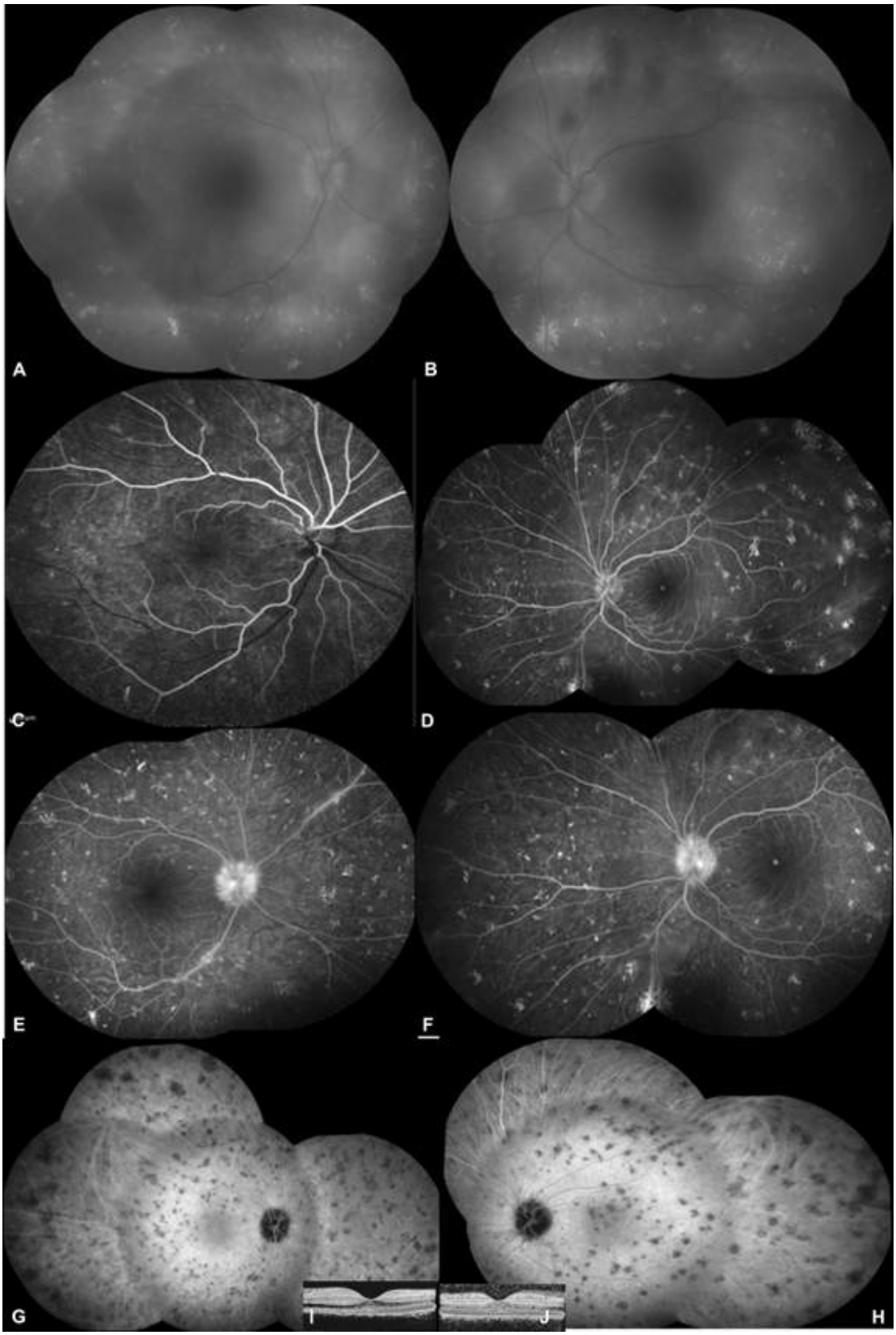

Figure 1. Composite of color fundus showing 360° scattered yellowish–gray spot like aggregates, (A) right eye, (B) left eye. Early venous phase of composite fluorescein angiographic picture exhibiting staining of these spot-like lesions, (C) right eye, (D) left eye. Late venous phase of composite fluorescein angiographic picture showing leakage from the optic disc, (E) (right eye), (F) left eye. Mid-phase of composite indocyanine green picture demonstrating the hypocyanescent widespread spot-like opacities, (G) right eye, (H) left eye. Normal foveal contour on optical coherence tomography, (I) right eye, (J) left eye.

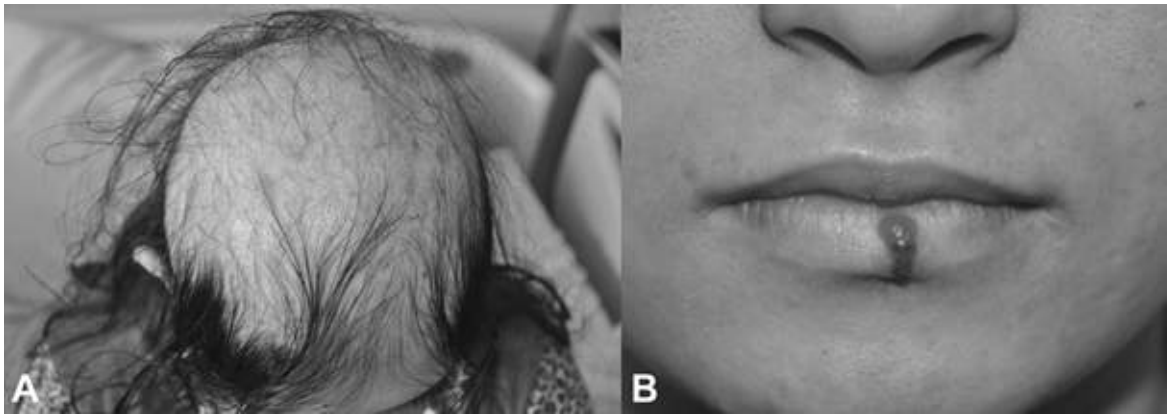

Figure 2. (A) Appearance of hair scalp from above depicting the diffuse alopecia. (B) Colored picture of coexistent Herpes Labialis.

and complement levels were normal. Furthermore, cranial and orbital MRI with contrast, chest X-ray imaging, and abdominal ultrasonography were all normal. No systemic treatment was administered as the patient had developed primary herpes labialis (Figure 2B) at the systemic evaluation phase and topical steroid treatment seemed sufficient to control the anterior chamber inflammation. In October 2018, the patient experienced a bilateral non-granulomatous anterior uveitis attack without any further posterior segment changes. Optical coherence tomography angiography and en-face OCT (Figures 3A, 3B, 3C, and 3D), as well as swept source-OCT were performed (Triton, Topcon Inc., Oakland, New Jersey, USA). This revealed that the subfoveal choroidal thickness was 512 and 498 μm in the right and left eyes, respectively (Figures 3G and 3H). At this time, oral azathioprine 50 mg daily was prescribed together with topical prednisolone acetate eye drops. This case was diagnosed as incomplete Vogt–Koyanagi–Harada (VKH) syndrome[2] without overt serous retinal detachment and a significant decrease in vision. The disease progressed to the convalescent stage of VKH syndrome (with alopecia, depigmentation of fundus, and peri-papillary atrophy) as no systemic treatment was given early in the course of the disease.

DISCUSSION

In the present case, we found that VKH syndrome can have some unusual clinical manifestations such as no initial visual loss and no overt serous retinal detachment together with the occurrence of relatively early-onset severe alopecia. As the correct diagnosis was not made by her local physician, high-dose systemic steroids and immunosuppressants were not prescribed early at the early stages of disease presentation.

Alopecia areata is a chronic, inflammatory disorder of the hair follicles that results in non-scarring, patchy hair loss of the scalp. Histopathologically, alopecia areata associated with VKH disease is characterized with prominent pigment release, suggesting that the primary target is melanocytes and that keratinocytes might also be involved.[3] However, there was a very short time lapse of one month between the occurrence of bilateral uveitis and severe alopecia in the present case. In a recent study, alopecia was present in 38 of the 261 VKH patients (13.9%) in the early disease stages, whereas in 187 of the 373 VKH patients (49.6%) it occurred in the late stages.[4]

The presence of serous retinal detachment can be considered as a hallmark of VKH disease. In the acute disease stages of VKH, serous retinal detachment has a positive predictive value of 100.[5] Yang *et al*[4] reported that serous retinal detachment was present in 87.9% of their patients during the early stages of the disease. Remarkably, serous retinal detachment was not detected in any visits during the disease course in our case and we believe that this is very unusual in VKH disease.

Systemic high-dose corticosteroid is the first-line treatment for VKH as posterior segment involvement is almost always severe at the initiation.[6] However, we examined the patient four months after the first episode of bilateral anterior uveitis. During the second anterior uveitis attack, the disease was in the convalescent stage. We decided to withhold systemic steroid and immunosuppressive therapy due to the presence of coexistent herpes labialis and the relative inactivity of the posterior segment lesions.

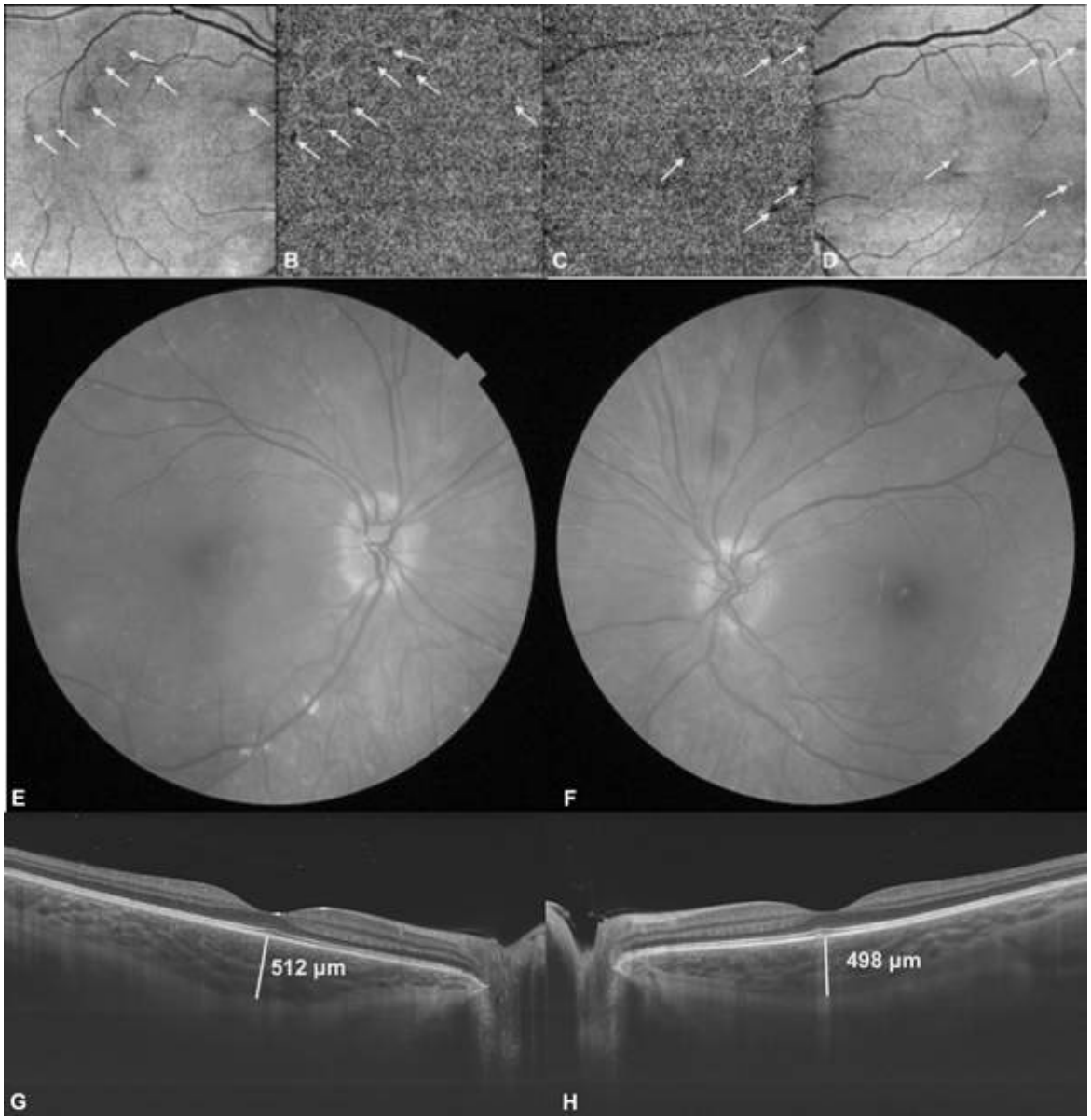

Figure 3. (A&B) Choriocapillaris slab of montage optical coherence tomography angiography and en-face OCT image of the right. (C&D) Left eyes revealing the patchy ischemia of choriocapillaris (arrows). Color fundus pictures taken at the last visit showing slightly blurred disc margins with less apparent old scars with no new lesion. (E) Right eye and (F) left eye. (G) Swept source optical coherence tomographic subfoveal choroidal thickness was 512 µm in the right eye and (H) 498 µm in the left eye.

Systemic azathioprine was prescribed four months after our initial evaluation as soon as the patient experienced the third attack of bilateral anterior uveitis.

In summary, this report presents an unusual case of VKH disease with early onset severe alopecia and the lack of overt bilateral serous retinal detachment during the early stages.

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Conflicts of Interest

There are no conflicts of interest.

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Letter to Editor

Topical Umbilical Cord Serum for Corneal Epithelial Defects after Diabetic Vitrectomy

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Dear Editor,

I have read with great interest the article by Moradian et al on "Topical Umbilical Cord Serum for Corneal Epithelial Defects after Diabetic Vitrectomy."[1] They have performed the study to investigate whether topical umbilical cord serum (TUCS) has any beneficial role in healing corneal epithelial defects (CED) after diabetic vitrectomy. However, I have a few concerns about the study.

Firstly, the postoperative intraocular pressures (IOP) were not mentioned in both groups. Elevated IOP (which is common after a vitreoretinal surgery) is known to cause corneal edema and increase the risk of corneal complications such as epithelial defect and non- healing epithelial defect.[2] It would be more informative if the authors had provided IOP measurements in both groups, as it could influence the healing pattern of the epithelial defects.

Secondly, it is mentioned that all 80 eyes underwent deep vitrectomy but it is not mentioned what type of intraocular tamponade agent such as air, Sulphur hexafluoride (SF6), perfluoropropane (C3F8), or silicone oil was used during the surgery. Intraocular tamponade of long-acting expansile gases may induce corneal endothelial cell toxicity. The loss of corneal endothelial cells has also been reported to be significantly greater in eyes with C3F8 than in those with SF6.[3] This endothelial damage especially in a diabetic eye can lead to corneal edema and loose adhesions between the Bowman's layer and stroma which delays the epithelial healing mechanism.

Thirdly, even though the authors have admitted for the absence of dry eye testing in these eyes, they should have performed simple corneal sensations. It is well-known that diabetic eyes have corneal hypoesthesia due to peripheral neuropathy. The development of diabetic keratopathy has been suggested to be related to loss of nerve-derived trophic factors following a decrease in corneal sensation. This reduced corneal sensations can lead to neurotrophic keratopathy which can lead to disturbance in the healing of the epithelial defects. Diabetic keratopathy may be associated with neuropathic keratitis in patients with a persistent corneal epithelial defect, and dry eyes may occur secondary to a reflex decrease of tear secretion due to corneal

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hypoesthesia and/or secondary to reduced tear and mucin secretion due to efferent nerve dysfunction.[4]

Also, the risk of allergies and possibilities of transmitting parenterally transmitted organisms must also be kept in mind when using TUCS apart from the legal and ethical issues. A routine testing of the mothers and a rapid test on the sera for viral contaminants is required. When the event to the time between the testing of the mother for HIV and the preparation of cord serum from the placental blood is more than six months, HIV testing should be undertaken again at the time of serum delivery to account for the window period of the infection.[5] In consideration of the window period of HIV infection, additional HIV testing with a shortened window period, such as p24 antigen detection method, should be performed before the use of the TUCS.

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Letter

Authors' Reply

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Dear Editor,

We would like to thank Dr Arjun Srirampur for his interest in our work. Below please notice our replies:

1. All of our diabetic patients were operated upon due to proliferative diabetic retinopathy (PDR) complications such as non-clearing vitreous hemorrhage and traction retinal detachment but there was no case of rhegmatogenous retinal detachment; therefore no tamponade was used during surgery.

2. None of our patients had uncontrolled IOP during the short follow-up period (two weeks) after surgery in both groups. The corneal epithelial defect (CED) was improved in all eyes except three; and in those three eyes, lateral tarsorrhaphy and application of a lubricant ointment resulted in healing of the CED less than one month after surgery.

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