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Editor in Chief
Dr. Sunil Ganekal, MS, DNB, FRCS

From Editor's Desk

This issue of journal of visual sciences (JVS) highlights recent advances like Gene therapy,Genetic testing, Artificial intelligence, Ocular pathology, newer developments in artificial cornea and collaborative research.This issue also includes number of articles on ocular imaging written by many eminent ophthalmologists covering various ophthalmic subspecialities, interesting case reports, surgical pearls, Post graduate corner and controversies.Do feel free to write to me regarding any suggestions and feedback at editorjvsjournal@gmail.com.

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Editorial

Artificial intelligence in ophthalmology

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Introduction

Artificial Intelligence (AI) is playing an increasingly prominent role in medicine because of advances in computing power, learning algorithms, and the availability of large datasets (big data) sourced from medical records and wearable health monitors.[1] While AI is being used in other medical specializations such as radiology, pathology, and cardiology, the use of AI-based approaches has expanded in ophthalmology due to widespread availability of ophthalmic imaging. In particular, the AI subfields of machine learning (ML) and deep learning (DL) are currently being used in ophthalmology practices to revolutionize vision care. This paper aims to investigate the role of AI-based systems in performing medical work in each subfield of ophthalmology and evaluate the progress made in this area along with challenges.

Machine learning and deep learning

AI is a subfield of computer science that aims to create intelligent machines.[2] ML is a subset of AI which focuses on the learning feature of intelligence and imitates the neural structure of the nervous system through the creation of artificial neural networks (ANNs), responsible for signal processing. ANNs are limited in that they require large amounts of image data for pattern detection and a descriptive label for each image during the training phase. DL is an improvement over ANN, consisting of more layers that permit higher levels of abstraction and improved predictions from data. The basic idea is that a neural network, instead of just acting as a classifier, can also serve as the feature extractor as well.[2] Therefore, a single deep neural network performs both tasks and can learn to both extract features that are suitable for a given classification problem and to classify them.[2]

✦ Advances in the use of AI in ophthalmology

The application of AI in ophthalmology has focused on diseases such as diabetic retinopathy (DR), age related macular degeneration (AMD), cataract, and glaucoma. DR is the primary cause of blindness and visual loss amongst working-age men and women in the United States, with cataract and glaucoma as leading causes of blindness worldwide. The wide prevalence of these diseases as well as the availability of imaging make these areas attractive for the application of AI-based approaches. This extensive imaging has provided the large data sets (big data) for such applications. Big data when combined with AI allows for the detection of subtle associations that would be missed with smaller scale datasets.[3]

Retinal disorders

The immediate impact has been observed in the field of retinal diseases where colour fundus photography and optical coherence tomography (OCT) are widely used.[4] Since interpreting such large sets of imaging data is very time intensive for the ophthalmologist and can lead to delays in care for patients facing treatable eye conditions, AI tools that could be trained to interpret OCT scans as accurately as humans provide a path forward. This has the potential to reduce the burden of the ophthalmologist, giving them a better chance to treat sight-threatening diseases. Point-of-care DR screening using autonomous AI is now available and provides immediate results in a primary care setting. As a significant number of patients with diabetes do not get annual diabetic eye exams, autonomous systems such as IDx-DR (Digital Diagnostics, formerly IDx) have the ability to create a large impact in primary care settings.[5,6] IDx-DR, developed by Dr. Michael D. Abràmoff, is an autonomous, FDA-approved AI system designed to detect DR and diabetic macular oedema (DME) .[6] IDx-DR was validated against clinical outcomes, including OCT, and demonstrated promising results, with an observed 87% sensitivity and 90% specificity for detecting more-than-mild DR.[6,7] Similarly, Shah et al. in[8] validated a DL algorithm based on deep convolutional neural networks as a tool for screening to detect referable DR with an overall sensitivity and specificity of 99.7% and 98.5% for any DR detection.

Various DL-based systems have been designed with the intent to diagnose and track the progression of AMD and other associated retinal conditions. In particular, Faes et al. developed DL algorithms to detect drusen, neovascular AMD, and DME after training with 101,418 OCT images of the retina from 5761 patients with a sensitivity of 97.3%, a specificity of 100%, and a positive predictive value (PPV) of 97.7%.[3,9] Schlegl et al. in[10] developed a DL-based system to automatically detect and quantify intraretinal cystoid fluid (IRC) and subretinal fluid (SRF). This system accurately characterized the pattern of intraretinal fluid in patients with wet AMD or retinal vein occlusion (RVO) and distinguished between intraretinal cysts and SRF.[10] The authors conclude that DL in retinal image analysis provides an accurate means "for the differential detection of retinal fluid types across the most prevalent exudative macular diseases and OCT devices" .[10]

Cataract

The use of AI systems is now extending beyond retinal diseases and has numerous applications in the field of cataract management, including diagnosis, referral, and the prediction of refractive outcomes. Wu et al. utilized DL using residual neural network (ResNet) to establish a 3-step sequential AI algorithm for the diagnosis and referral of cataracts.[11] Per the authors the performance in three-step tasks was robust as follows: (1) capture mode recognition [area under the curve (AUC) 99.28%–99.71%], (2) cataract diagnosis (normal lens, cataract, or postoperative eye with AUCs of 99.82%, 99.96% and 99.93% for mydriatic-slit lamp mode and AUCs >99% for other capture modes) and (3) detection of referable cataracts (AUCs >91% in all tests).[11]

AI has additionally shown great promise in the prediction of refractive outcomes and is currently utilized by several intraocular lens (IOL) formulae.[12] In particular, Sramka et al. found the prediction accuracy of two ML-based algorithms [the Support Vector Machine Regression model (SVM-RM) and Multilayer Neural Network Ensemble model (MLNN-EM)] to compare favourably to that of traditional clinical methods.[12,13] Prediction accuracy of the Hill-radial basis function (RBF) calculator, a system of ANNs which implements pattern recognition and sophisticated interpolation to analyse big data, has compared favourably to traditional methods but unfavourably to newer IOL formulae (Kane, EVO 2.0, and VRF-G IOL formulae) .[12,14,15]

Glaucoma

AI systems may be used to diagnose or monitor the progression of glaucoma. AI systems are being developed to diagnose glaucoma based on measurement of the retinal nerve fibre layer (RNFL) thickness and assessment of the visual field (VF).[16] Systems are also employing AI strategies to detect glaucomatous damage (*i.e.*, optic nerve head abnormalities) from a dataset of fundus photographs.[17] Two ML-based systems – which utilized neural network classifiers and multiclass support vector machines (SVMs) to detect glaucoma from 61 to 100 fundus images – achieved 100% sensitivity, with specificity values of 80% and 87%, respectively.[18,19] In regard to disease progression, Yousefi et al. have introduced a ML-based index for glaucoma progression detection and concluded that ML analysis detects progressing eyes earlier than other methods consistently.[20]

Corneal diseases

While the integration of AI in ophthalmology has primarily focused on the subfields of retinal disorders, cataract, and glaucoma, AI systems are also being used to diagnose corneal diseases. Previous studies have shown AI-based systems can diagnose keratoconus and Fuchs' dystrophy based on Scheimpflug tonometry[21,22] and high definition OCT images,[23] respectively.

Challenges in using AI in Ophthalmology

One of the challenges with the use of AI based systems in medicine, including ophthalmology, has to do with the well-known 'black-box' problem. This has to do with physicians being unable to fully trust the decisions of such systems because the AI decision-making process is often-times opaque.[24,25] The algorithms used to arrive at a decision can be proprietary or difficult to understand. Hence the physician is unable to figure out how the AI system arrived at its conclusion.[24,25] For physicians to trust AI, systems must not lock their secrets inside a black box.

The limited screening scope of AI-based systems can be of concern to some physicians. An ophthalmologist will screen a patient for a range of eye diseases such as glaucoma, cataracts, diabetes, tumors etc.[6] However, AI systems can only screen for what they are trained. While this may be a concern, one can appreciate that not being screened at all is far worse for patient outcome.[6]

As mentioned by Krause et al. in[26] in their study of grader variability in ML models, most common discrepancies in grading DR were due to missing microaneurysm, artifacts, and misclassified hemorrhages. False positives are also possible if the fundus image has artefacts due to poor image capturing, though this cannot be attributed to the AI- algorithm itself.

Lee et al. point out some data-specific limitations that must be kept in mind before interpreting study results associated with big data in AI.[3] For example, statistical significance becomes less meaningful when handling millions of data points because even minor differences will show statistical significance.[3] Hence, the clinical significance is important when results are analysed. Secondly, physicians need an understanding of the data used to train AI algorithms because the resulting algorithm may not be generalizable to the targeted population.[3] Results of these studies need to independently validated.[3]

Complementary and alternative medicine

Worldwide use of complementary and alternative

medicine (CAM) has expanded as a result of greater resources, poor health, and unmet medical needs.[27,28] AI has been integrated into various CAM modalities and has shown great promise in the classification of herbal medicine prescriptions.[29,30] In the field of ophthalmology, AI models may be used to predict compounds to treat various ocular pathologies (DR, AMD, anterior uveitis, cataract, and glaucoma). Curcumin is a herbal remedy with widespread antioxidant and antifibrinolytic properties which may reinstate homoeostasis and slow the progression of glaucoma and/or other eye diseases.[31] Similarly, resve ratrol exhibits anti-inflammatory properties which can minimize the apoptosis and neuroinflammation commo nly observed in glaucomatous eyes.[32] Additional herbal medicines associated with glaucoma treatment include marijuana,[33] bilberry,[34] and gingko.[35,36] Future applications of AI in integrative medicine include the potential to explicitly screen for integrative techniques which can mediate the inflammatory response and vascularization resulting from several ophthalmological conditions.

Conclusions

Advances in computing power have prompted the worldwide exploration of AI-based systems in several medical subfields, including ophthalmology. Ophthalmic AI systems are advantageous in that they decrease time required to interpret image data, enable ophthalmologists to gain a greater understanding of disease progression, and assist with early-stage diagnosis, staging, and prognosis. Future directions include addressing the limited screening scope, false positives, and 'black box' problem associated with AI-based systems. Although more studies on patient outcomes are needed, based on the results seen thus far there is now the expectation that the use of AI in ophthalmology will improve patient outcomes across an increasing range of ophthalmic diseases.

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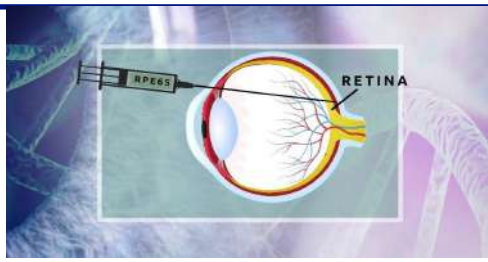
Review Article

Gene therapy - Current status and challenges



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Abstract

Inherited retinal disorders (IRDs) encompass a diverse group of disorders that primarily affect photoreceptors and are caused by various genetic mutations, with over 270 associated genes identified to date. Gene therapy has emerged as a promising method to correct or replace defective genes responsible for causing IRDs. Notably, the FDA's approval of Luxturna as the first gene therapy drug for the treatment of Leber congenital amaurosis caused by RPE65 mutations has instilled optimism within the research, clinical, and patient communities. The retina, with its anatomical and functional characteristics, is an ideal target for gene therapy, although the translation from preclinical models to human applications presents challenges. This review aims to illuminate the fundamental concepts of gene therapy, with a focus on various viral vector systems and delivery routes in this transformative approach. Additionally, the review explores the exciting potential of CRISPR-mediated gene editing in correcting genetic defects. Gene therapy stands as a dynamic and evolving field in medicine and ophthalmology, its success and applicability contingent upon disease-specific factors. At present, gene therapy is considered relatively safe, and we eagerly anticipate further advancements through ongoing clinical trials, offering hope for improved treatments and better outcomes in the future.

Introduction

Adeno-associated virus AAV viruses are among the smallest viruses, with an uncoiled icosahedral capsid of about 22 nm. An AAV is able to infect both dividing and nondividing cells and has a broad tropism that allows it to infect many cell types depending on the particular serotype. To date, over 100 AAV serotypes of different animal species have been isolated. The serotypes differ in the sequence of their capsid protein. The recombinant vectors of AAV (rAAV) used for gene therapy are mainly based on serotype 2 (AAV2); this was the first human serotype described and the best characterized AAV serotype. This was the first human serotype described and the best characterized AAV serotype. In 1969, AAV demonstrated its ability to package up to a 5kb genome, leading to the utilization of the first recombinant AAV2 (rAAV2) vector for gene transfer in mammalian cell culture. Subsequent studies extensively explored AAV genome biology, including aspects of trans-gene delivery, safety profile, immunogenicity, and persistent expression in various tissues such as the liver, retina, cardiac muscle, and central nervous system. In vivo applications were investigated in animal and human disease models. Over the course of more than five decades of research, AAV-based gene therapy products for inherited disorders affecting different tissues received approvals from the European Medicines Agency and the American Food and Drug Administration between 2012 and 2019[1]. Currently, rAAVs serve as a leading platform for delivering wild-type gene copies for in-vivo therapies. Despite the significant achievements and remarkable progress made in gene therapy during the 21st century, there remain several critical questions that demand answers. Ongoing and forthcoming clinical trials (Table 1) are providing valuable insights, but gaining a deeper understanding of the pathophysiology and optimal delivery methods is essential for the development of more effective gene therapy products.

Advantages of using the eye as an end-organ for gene/cell therapy

Accessibility: Localized delivery of gene or cell therapies can be achieved through simple and non-invasive procedures, such as intravitreal injections or subretinal injections.

Immune privilege: This immune privilege reduces the risk of immune rejection, allowing gene and cell therapies to have a better chance of survival and effectiveness within the eye.

Small target tissue: This small target area facilitates precise delivery of therapeutic agents, minimizing off-target effects and potential side effects.

Quick feedback on efficacy: The capability to noninvasively monitor the response to therapy using advanced imaging systems. The evaluation of efficacy and safety can be monitored in one eye while using the untreated eye as an ideal control[2].

Table: 1 Active and completed retinal gene therapy trials

Target disease	Target	Vector	Delivery	Phase	Sponsor	NTC NO.
Achromatopsia	CNGA3	AAV2/8	Subretinal	I/II	MeiraGTx	03758404
	CNGA3	rAAV	Subretinal	I/II, active	STZ eyetrial	02610582
	CNGA3	rAAV2tYF	Subretinal	I/II	AGTC	02935517
	CNGB3	AAV2/8	Subretinal	I/II I/II (5 year f/u)	MeiraGTx, EMAS	03001310 03278873
	CNGB3	rAAV2tYF	Subretinal	I/II	AGTC, NEI	02599922
Choroideremia	REP1	AAV2 (Gemini)	Subretinal	II III	Nightstar	03507686 03496012
	REP1	AAV2	Subretinal	II	Oxford, UCL	02407678
	REP1	AAV2-hCHM	Subretinal	I/II, active	Spark	02341807
	REP1	rAAV2	Subretinal	II, active	STZ eyetrial	02671539
	REP1	rAAV2	Subretinal	I/II, active	Alberta, Ian MacDonald	02077361
	REP1	AAV2	Subretinal	II, completed	BPEI, B. Lam	02553135
	REP1	rAAV2	Subretinal	I/II, completed	Oxford	01461213
LCA	RPE65	AAV5	Subretinal	I/II I/II (5 year f/u)	MeiraGTx	02781480 02946879
	RPE65	AAV2 (Luxturna)	Subretinal	I/II, active (follow-on)	Spark	01208389
	RPE65	AAV2 (Luxturna)	Subretinal	III, FDA approved	Spark, CHOP, Ulowa	00999609
	RPE65	AAV2 (Luxturna)	Subretinal	I/II, active (LTFU)	Spark	00516477
	RPE65	rAAV2	Subretinal	I, active	UPenn, NEI	00481546
	RPE65	rAAV2/4	Subretinal	I/II, completed	Nantes	01496040
	RPE65	rAAV2	Subretinal	I, completed	Hadassah	00821340
	RPE65	rAAV2	Subretinal	I/II, completed	AGTC	00749957
	RPE65	rAAV2	Subretinal	I/II, completed	UCL	00643747
LHON	ND4	rAAV2 (Reverse)	Intravitreal	III, completed III (5 year f/u)	GenSight	02652780 03406104
	ND4	rAAV2 (Rescue)	Intravitreal	III, active III (5 year f/u)	GenSight	02652767 03406104
	ND4	rAAV2 (Reflect)	Intravitreal	III	GenSight	03293524
	ND4	rAAV2	Intravitreal	I/II, active	GenSight	02064569
	ND4	rAAV2	Intravitreal	II/III, active	Huazhong, Shiyan	03153293
	ND4	rAAV2	Intravitreal	I/II, completed	Huazhong	01267422
	ND4	AAV2	Intravitreal	I	BPEI, NEI	02161380
Retinitis pigmentosa	RLBP1	rAAV8 (CPK850)	Subretinal	I/II	Novartis	03374657
	PDE6B	AAV2/5	Subretinal	I/II	Horama S.A.	03328130
Advanced RP[a]	ChR2	AAV2 (RST-001)	Intravitreal	I/II	Allergan	02556736
Autosomal dominant RP[b]	RHO	QR-1123 (Aurora)	Intravitreal	I/II	ProQR Therapeutics	04123626
Mertk-associated RP	MERTK	rAAV2	Subretinal	I	King Khaled, Fowzan	01482195
Non-syndromic RP	ChrR-tdT	rAAV2.7m8	Intravitreal	I/II	GenSight	03326336
Stargardt disease	ABCA4	Lentivirus (SAR422459)	Subretinal	I/II I/II (15 year f/u)	Sanofi	01367444 01736529
Usher type-1B	MYO7A	Lentivirus (UshStat)	Subretinal	I/II I/II (15 year f/u)	Sanofi	01505062 02065011
Usher type-2A[b]	USH2A	QR-421a (Stellar)	Intravitreal	I/II	ProQR Therapeutics	03780257
XLRP	RPGR	AAV2/5	Subretinal	I/II	MeiraGTx	03252847
	RPGR	rAAV2tYF	Subretinal	I/II	AGTC	03316560
	RPGR	AAV8	Subretinal	I/II/III	Nightstar	03116113
XLRS	RS1	rAAV2tYF	Intravitreal	I/II, active	AGTC	02416622
	RS1	AAV8	Intravitreal	I/II	NEI	02317887

AGTC, Applied Genetic Technologies Corp; BPEI, Bascom Palmer Eye Institute; CHOP, Children's Hospital of Philadelphia; FDA, U.S. Food and Drug Administration; Hadassah, Hadassah Medical Organization; Huazhong, Huazhong University of Science and Technology; King Khaled, King Khaled Eye Specialist Hospital; LCA, Leber congenital amaurosis; LHON, Leber hereditary optic neuropathy; LTFU, long-term follow-up; LUXTURNA, voretigene neparvovec-rzyl; Nantes, Nantes University Hospital; NEI, National Eye Institute; Oxford, University of Oxford; RP, Retinitis pigmentosa; Shiyan, Shiyan Taihe Hospital; UCL, University College, London; Ulowa, University of Iowa; UPenn, University of Pennsylvania; XLRP, X-linked retinitis pigmentosa; XLRS, X-linked retinoschisis.
[a]Indicates optogenetics-based gene therapy.
[b]Indicates use of antisense oligonucleotides (AONs) as gene therapy modality.

Approach to gene delivery:

Adenovirus, lentivirus, and adeno-associated virus (AAV) are three commonly employed recombinant virus vectors used to deliver the normal gene into target cells. The success of gene therapy hinges on the selection of an appropriate vector. The ideal vector should possess key attributes, including prolonged transgene expression, low immunogenicity, non-integration into the host genome, and cellular specificity to ensure targeted transduction in the desired tissue, cell, or organ[3].

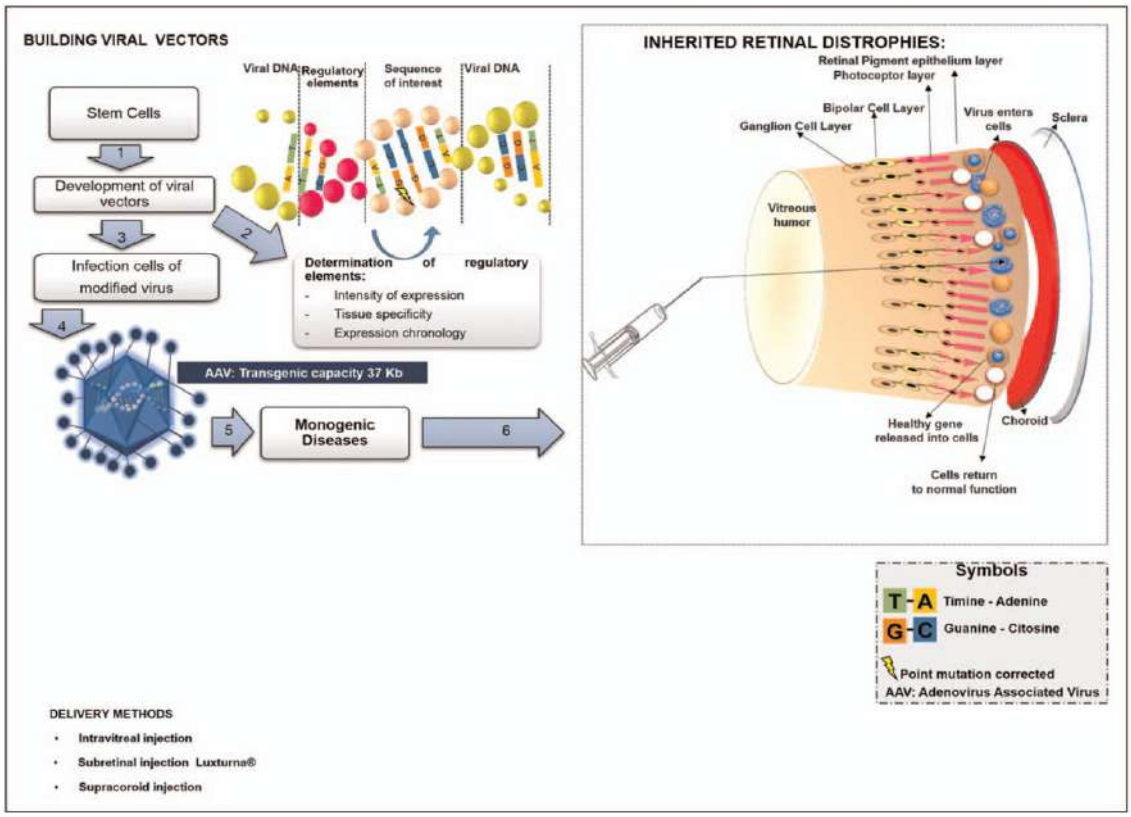


Figure 1. **Overview of viral vector production:** The key steps involved in the production of recombinant adeno-associated virus (rAAV) viral vectors for gene therapy applications. The process begins with the selection of a suitable host cell line, followed by the introduction of the rAAV vector plasmid containing the therapeutic gene of interest. Transfection or co-transfection with helper plasmids is employed to initiate viral replication and packaging. Subsequently, viral particles are harvested, purified, and titered to obtain high-quality rAAV vectors ready for in vivo or ex vivo gene delivery. The successful generation of rAAV viral vectors is crucial for the development of effective and safe gene therapy treatments for various genetic diseases.

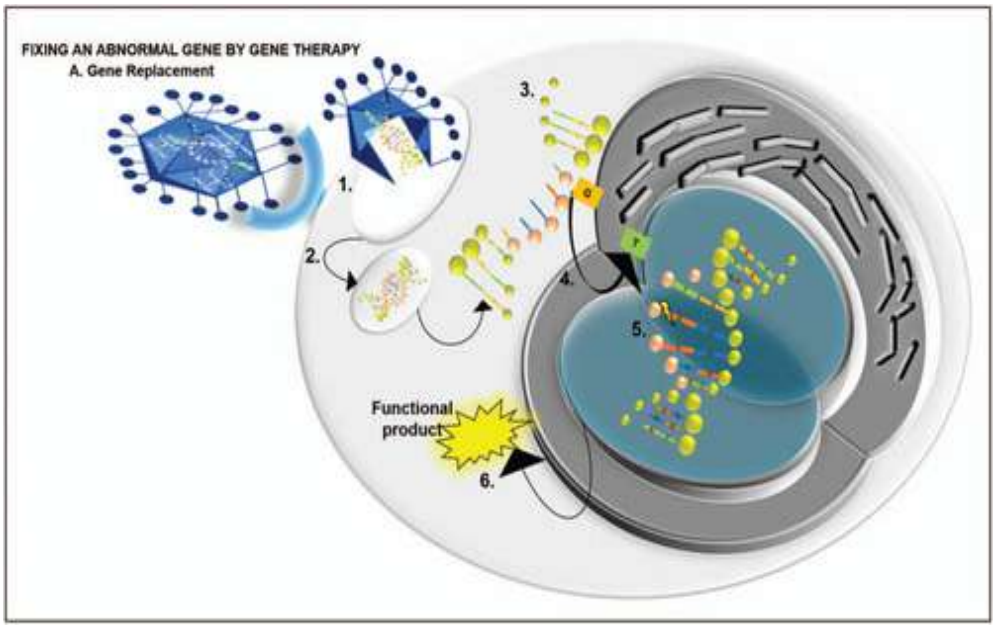


Figure 2. **Gene replacement**: Gene replacement involves introducing a functional copy of a defective gene into the patient's cells. The vector used for gene delivery contains the normal gene sequence, which can be a cDNA or a modified version of the gene. Once inside the target cells, the therapeutic gene is unwinding from capsid and remains episomal, leading to the expression of the functional protein, thereby correcting the genetic defect.

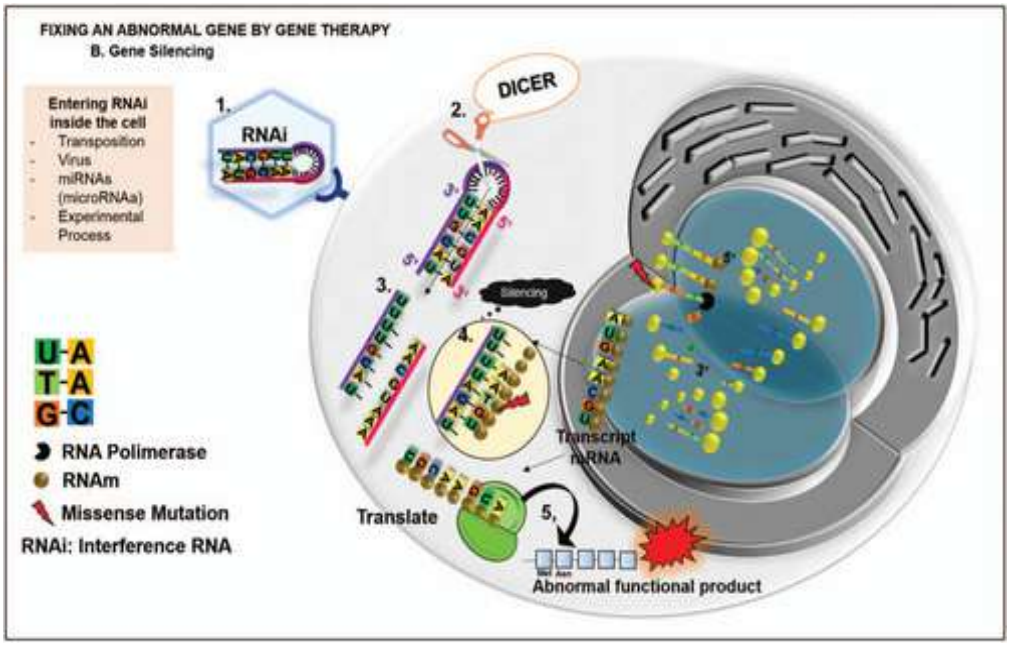


Figure 3: Gene Silencing by RNA Interference: Gene silencing through RNA interference is a mechanism used in gene therapy to interrupt the expression of a specific mutation. The process begins with the introduction of RNA interference via lenti viral vector (1). Once inside the cell, a ribonuclease called DICER cleaves the viral RNA strands, resulting in the production of the antisense strand (2 and 3). Within the cell nucleus, the nuclear DNA is undergoing transcription and may encounter errors. Subsequently, the nuclear DNA can take two different paths. In the first scenario (4), it is complemented by the antisense strand of RNA interference, effectively silencing the expression of the targeted gene and enabling the production of corrected functional products. In the second scenario (5), the sequence continues to produce a nonfunctional product within the cell. Gene silencing through RNA interference offers a promising approach in gene therapy for selectively modulating gene expression and correcting mutations.

Adenovirus

Adenoviruses are widely utilized as gene therapy vectors due to their ability to efficiently transduce a variety of cell types and achieve high levels of transgene expression, independent of the cell cycle stage, owing to their capacity to carry relatively large genetic material (up to 48 kb). However, a significant drawback of using adenovirus in gene therapy is its immunogenicity. As common viruses that naturally infect humans, many individuals may have pre-existing immunity to adenoviruses. Consequently, when adenovirus vectors are used in gene therapy, the immune system may recognize and mount an immune response against the virus, hampering the therapy's effectiveness. This immune reaction can lead to the swift clearance of the viral vector from the body, restricting the duration of gene expression and hindering the achievement of long-term therapeutic benefits. Moreover, challenges such as contaminating helper viruses, vector instability, and the occurrence of replication-competent adenoviruses have also been reported in certain instances, necessitating cautious consideration of these factors in the application of adenovirus-based gene therapy[4].

Adeno associated virus:

Adeno-associated virus (AAVs) was discovered from contaminant of adenovirus preparations in human tissues by Atchison. It is member of *Parvoviridae* family; belongs to genus of dependovirus. It is replication defective that depends on the presence of a helper virus, such as adenovirus or herpes viruses, hence for effective and productive replication in mammalian cells. Preliminary investigation shown, AAV life cycle does not cause any disease in mammals. AAV has a single-stranded DNA genome, which is small compared to other viruses, allowing it to carry only limited genetic material (about 4.7 to 5.0 kb)[5,6].

Lentivirus (LVs)

LVs are RNA viruses of the retrovirus family and able packaging ~8–10 kb that possessing a reverse transcriptase through which they are able to integrate their retrotranscribed proviral DNA into the chromosomes of host cells. Although these RNA vectors have been shown to facilitate long-term gene expression due to its genome integrative nature, they likewise may exhibit greater safety concern due to the unpredictability of integration and theoretical risk of cancer mutagenesis[7,8].

Prominent Approaches for Gene Therapy Product Delivery into the Eye

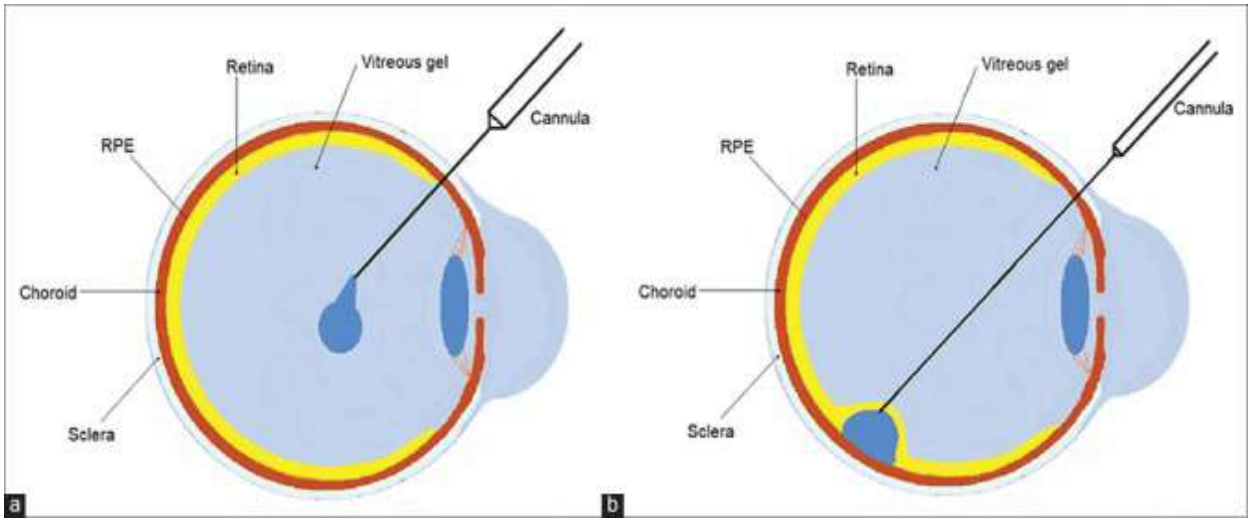
The success of gene therapy relies not only on the specific vector but also the appropriate gene delivery route. Early investigations used viral-vectors to deliver genes systemically to every cell in the body, which repeatedly spawned catastrophic immunologic reactions and multiorgan failure. Resultingly, gene delivery has shifted in design to administer specific genes to rather specific target cells. Among ocular diseases, gene therapy predominantly employs intravitreal, subretinal and suprachoroidal injection, with the target cell type a necessary consideration to properly guide the selected route of administration. In general, intravitreal injection can be used to target the inner retina, whereas subretinal injection is preferred to deliver genes to the outer retinal cells and retinal pigment epithelium (RPE) cells[3].

Intravitreal injection is a relatively well tolerated, non-operative delivery method to target retinal ganglion cells and muller ganglion cells, with slight propensity to target photoreceptors and the RPE[9]. Despite the greater ease of administration, intravitreal delivery has had less success compared with subretinal injection likely due to the physical barriers posed by the vitreous cavity and inner limiting membrane. Conversely, subretinal injection, which requires a pars planavitrectomy, is the most direct access to the RPE and photoreceptors and has resultingly emerged as the most popular gene delivery technique in inherited retinal dystrophies (IRDs), despite the risks inherent to the operative procedure[10]. This is evidenced by the recent FDA-approved drug Luxturna (voretigeneneparvovec-rzyl) which is delivered subretinally to treat patients with LCA type-2 (LCA2; NCT00999609). Lastly, suprachoroidal injection via retinotomy has garnered recent interest as an alternative to subretinal delivery when a less invasive procedure is desirable.

Subretinal injection: This involves a parsplanavitrectomy, followed by raising a subretinal bleb close to the macula with the genetic material/cells being injected directly into the subretinal space. Although this creates a temporary retinal detachment, this has the advantage of direct delivery to the cells of interest. Procedural complications include potential retinal detachment, epiretinal membrane formation, and other complications associated with vitrectomy.

Intravitreal injection: This involves a direct injection into the vitreous cavity, without the need for a vitrectomy. Although the procedure is simpler and associated with lesser complications, the availability of genetic material/cells to the subretinal space is difficult. In addition, an induced humoral response to the intravitreally delivered material may occur, which has not been noted in subretinal injections. Intravitreal injection allows a more widespread distribution of the therapeutic agent over the retina than subretinal delivery, using a less challenging and less-invasive procedure. However, several physical barriers, such as the vitreous, the internal limiting membrane, and the inner retina, limit the diffusion of the therapeutic agent to the PR and RPE after intravitreal delivery.

Suprachoroidal approach: This involves approaching the subretinal space through a specialized suprachoroidal delivery system (Eg: Orbit delivery system, Gyroscope therapeutics). The advantages include precise delivery and lack of reflux of therapeutic material into the vitreous cavity. Disadvantages include the need for a specialized delivery system and potential suprachoroidal or subretinalhemorrhage.



Schematic diagram identifying ocular structures and location of (a) intravitreal injection and (b) subretinal injection

Gene therapy in systemic disease

Before Luxturna had exploded into the market as the first gene therapy to treat any genetic disease, Kymriah (*tisagenlecleucel*), sponsored by Novartis, had set the stage in 2017 as the first FDA-approved gene therapy available in the United States (NCT02435849). Designed to treat children with B-cell acute lymphoblastic leukemia, this therapeutic innovation and its approval are a direct result of the preliminary work and initial successes first observed in children with ADA-SCID in the early 1990s. Kymriah is a chimeric antigen receptor T-cell therapy (CAR T-cell therapy), a unique treatment that removes a patient's autologous T-cells which are then genetically-modified to express a special receptor (CAR). These specialized cells are replaced back into the patient's circulation to act as antibody-like immune cells that then specifically target cancer cells [11].

Another milestone in gene and cell therapy was achieved with the approval of Zolgensma (*onasemnogeneabeparvovec-xioi*) in 2019, the first gene therapy approved to treat children less than 2 years of age with spinal muscular atrophy type-1 (SMA1), a rare genetic neuromuscular disease and leading cause of infant mortality (NCT02122952). This AAV vector-based gene therapy is a one-time intravenous injection that delivers a fully-functional copy of the *SMN* gene into the target motor neuron cells [12]. Results demonstrated increased survival, superior achievements of motor milestones and improved muscle function following a single infusion in patients with SMA1.

These historical landmarks and approvals demonstrate the continued momentum of this pioneering area of medicine, as well as the promising potential that other once-incurable diseases can finally be treated with gene therapy in the future.

Types of gene therapy and application in ophthalmic disease

The decision to pursue gene therapy is far from a simple choice. Physicians must understand not only the disease pathophysiology but also the underlying mechanism of each type of gene therapy.

Gene replacement therapy (also referred to as gene 'addition' or 'augmentation') remains the most common and straightforward technique to treat genetic diseases. As this technology delivers a normal gene copy into desired cells to replace the diseased DNA (Fig.2), gene replacement is most suitable to treat biallelic loss-of-function recessive diseases. Numerous recessive IRDs are being targeted by gene replacement, such as RPE-mediated LCA2, choroideremia and MERTK-associated retinitis pigmentosa via AAV-vectors, as well as Stargardt disease and Usher syndrome using EIAV-based lentiviral vectors [13]. However, as gene replacement requires that the non-functional target cells still remain alive, this option is most advantageous for early disease states and often incompatible for treatment of advanced retinal degeneration [14].

In diseases caused by gain-of-function mutations, such as in rhodopsin-linked autosomal dominant retinitis pigmentosa (RHO-adRP), a combined approach is often warranted. One common strategy utilizes both gene suppression and replacement therapies, in which an AAV is used to initially deliver an RNA interference (RNAi)-based gene suppressor to down-regulate and inactivate the target (Fig.3), at which point a separate AAV-vector can then deliver the functional, codon-modified replacement gene over the RNAi target site [15].

Gene editing has recently become an attractive and emerging approach to fill the void left by gene replacement in diseases associated with dominant mutations or large causative genes. The innovative CRISPR technology (*clustered regularly interspaced short palindromic repeats*) has sparked widespread excitement with the ability to 'cut' and remove the target cell's genome and simultaneously add the desired functional gene with precision, affordability and relative ease [16]. Promising animal studies have recently inspired several clinical trials to utilize CRISPR to target a variety of retinal diseases, including CEP290-associated LCA (LCA10), RHO-adRP and wet age-related macular degeneration.

Notably, optogenetics has become an exceptional gene therapy approach to address the limitations of traditional gene therapy options. Unlike most other retinal gene therapies, this treatment can be utilized in diseases with significant photoreceptor loss, as seen in the early clinical trial using channelrhodopsin-2 to treat advanced retinitis pigmentosa [17]. With a single injection, this technology delivers light-activating 'optogenes' that convert the remaining inner retinal cells into photosensitive cells, essentially behaving as artificial photoreceptors. In addition, this gene-independent approach does not rely on specific genetic mutations and thus lends great potential to treating a wide variety of retinal diseases.

Challenges in gene therapy

Driven by encouraging scientific innovations and the successes of completed and ongoing trials, gene therapy has rapidly become an important treatment consideration. However, several key issues and challenges must first be addressed in order for this new technology to reach clinical practice.

IRDs represent a collection of ultra-rare blinding diseases. With over 220 genes implicated in its pathogenesis [18], proper genetic testing is imperative to recognize patients as potential candidates for treatment. Yet this does not come without its challenges. In fact, only a small handful of these genes are currently being targeted by gene therapy, thus excluding the vast majority of patients who are simply not eligible for present-day gene therapy options. In addition, apart from optogenetics, most gene therapy treatments, including Luxturna, are applicable only to a select patient population with remaining, viable retinal cells. This reiterates the necessity to identify patients at early stages of disease via timely genetic testing, so that patients may at least have the opportunity to consider this treatment option.

There are a variety of other issues that raise concern for the future implementation of gene therapy, with none more paramount than the associated safety risks. Unlike biological agents or small molecule drugs, the effects of gene therapy are difficult to halt once the treatment is delivered [19]. Gene therapy requires viable cells and hence will not be effective in advanced stages of IRDs with severe PR degeneration. Cell therapy is more viable in the advanced stages of the disease. It is not definite that gene/cell therapy can prevent the progression of retinal degeneration. Gene therapy is gene-specific, and treatment for each gene has to go through all the steps of drug development including animal studies, clinical trials, and regulatory processes. The ability to deliver genes to PR is limited by the cargo capacity of viral vectors. Potential presence/development of anti-AAV antibodies in the eye that may reduce the efficacy of gene therapy. Mutations in genes such as rhodopsin that cause autosomal dominant RP are associated with dominant-negative effects. Treatment of these conditions necessitates the disruption of the mutated allele along with the insertion of a functional copy of the gene. Cell therapy requires systemic immunosuppression for prolonged periods of time with associated side effects.Although short-term data is promising, long-term safety concerns have yet to be established. Further, in contrast to most FDA-approved drugs, most gene therapy treatments for IRDs often requires a surgical procedure, such as a pars planavitrectomy which is an unavoidable and necessary technique for proper subretinal gene delivery. Patients thus face the additional risk of surgical complications including macular holes, retinal tears, cataracts and, rarely, permanent vision loss [20]. This treatment therefore inherently limits the volume of providers that can administer gene therapy, which relies on complex skills and special training required to perform such surgical procedures.

Lastly, although modalities like CRISPR and optogenetics are offering promise towards a more affordable gene therapy option, Gene therapy is very expensive; Luxturna remains our only current option at nearly $4 50 000 per eye. In fact, Luxturna is not the only FDA-approved gene therapy option with a steep price tag and a potential barrier to opportunity, as demonstrated in Table 2.[21] Thus, in light of the limited long-term safety and efficacy data, along with the heavy financial burden on both the patient and healthcare system, gene therapy is work in progress but certainly represents an inspirational future.

Table 2: FDA-approved gene therapy

Product (Company)	Technology	Target Disease	Price*
Zolgensma (Novartis)	AAV vector	Spinal muscular atrophy	$2000 000
Luxturna (Spark Therapeutics)	AAV vector	RPE65-mediated retinal dystrophy	$850 000
Kymriah (Novartis)	CAR T-cell therapy	Acute lymphoblastic leukemia	$475 000
Yescarta (Gilead)	CAR T-cell therapy	Nonhodgkin lymphoma	$373 000

*Price not confirmed, based on analytic predictions. AAV, adeno-associated virus; CAR, chimeric antigen receptor.

Future prospects

Science is on the cusp of being able to treat hitherto untreatable diseases. This is a major breakthrough for patients with IRDs. Future gene replacement therapy in IRDs will target patients at an early disease stage when the retinal architecture and function are still intact. Progress in retinal imaging including adaptive optics, microperimetry, and OCT-angiography should be able to identify clinical markers that identify diseases and their progression fairly early so that maximum functional vision is preserved.

Stem cell science is advancing, and although early, offers unprecedented opportunities for cell replacement strategies. Obtained from peripheral blood or a skin biopsy, iPSC offers an easy approach compared to ESC. Derivation and differentiation of human iPSCs into RPEs, PR, and retinal organoids *in vitro* provide exciting opportunities for cell-replacement therapy and screening small molecules for therapeutic potential. Gene therapy platforms may allow the development of multiple therapies, reducing costs considerably. The integration of gene-editing technologies, like CRISPR/Cas9, along with iPSCs to correct patient-specific mutations, signifies the dawn of a new era in precise and personalized medicine for our patients. This has several implications for the clinician. Current counseling of patients with IRDs should include information on current results of gene replacement/stem cell trials. Furthermore, genetic testing and identification of the underlying mutation should be used to support the clinical diagnosis. In addition, it is important to establish a database/registry of patients with confirmed genetic mutations to inform them of forthcoming gene/cell replacement therapies and offer them the possibility of participating in future trials.

Conclusion

The ever-promising field of gene therapy has taken remarkable strides in recent years. There are several approaches for gene therapy and each has different variables influencing its outcome. Hopefully, further context can be illuminated with the approval of additional gene therapy treatments in the near future. Until then, physicians should remain educated on the underlying disease pathophysiology and up-to-date on the current developments in gene therapy, because gene therapy may very well be the solution to a once-incurable, blinding disease.

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Review Article

Genetic Counselling in Inherited Ocular Genetic Disorders : Need of the hour

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Inherited ocular genetic disorders (IOGDs)

refer to a group of eye conditions caused by errors that are known as mutations or variations in specific genes[1,2,5]. These can be syndromic or non-syndromic. Non-syndromic disorders like retinitis pigmentosa (RP), Stargardt's disease, corneal dystrophy, etc., affect vision. These disorders can occur as early as childhood, in adolescence or late adulthood. In syndromic ocular diseases, other organs are affected along with the eyes. Some examples of syndromic ocular disorders are Usher syndrome, Bardet Biedl syndrome, Alstrom syndrome, etc[3]. These disorders are mostly monogenic and some are digenic (example: digenic RP). Monogenic disorders occur due to mutations in a single gene, whereas digenic disorders occur due to mutations in two different genes[4]. Retinoblastoma is an eye cancer of genetic origin affecting the retina and is caused by mutations in the RB1 gene. It can occur unilaterally or bilaterally[6].

Mutations causing IOGDs are mostly inherited in Mendelian inheritance patterns, such as autosomal dominant, autosomal recessive, X-linked and mitochondrial. Some mutations in the affected individuals can be sporadic and not inherited. Inherited retinal disorders (IRDs), an example of IOGDs, are genetic disorders of the retina. IRDs are genetically and clinically heterogeneous (figure 1). This means that, one gene can cause different clinical presentations and mutations in different genes can cause the same clinical presentation. Example, RP is caused by mutations in more than 80 different genes[3].

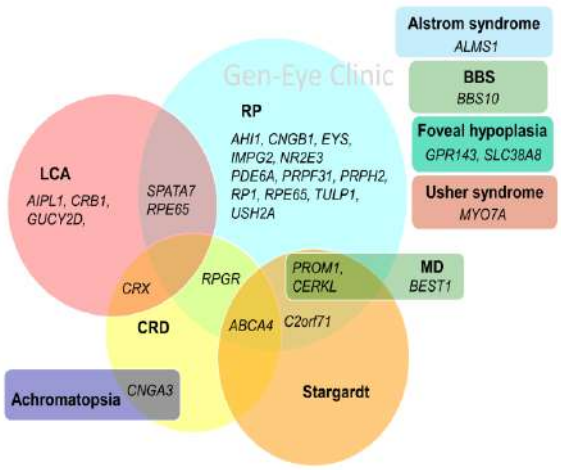

Figure 1: Summary of genotype–phenotype overlaps from clinical and genetic findings of 117 IRD cases. (Published manuscript: Inherited retinal disorders: a genotype-phenotype correlation in an Indian cohort and the importance of genetic testing and genetic counselling. Gopinath C et. al.)[3]

Genetic testing is of utmost importance in diagnosis of the disorder. It helps in identification of the mutation responsible for these genetic eye disorders, thereby enabling better prognosis and management. Knowledge of the genetic mutation and its inheritance helps identify the risk of passing it on to the next generation. There are different types of genetic tests. Karyotyping is used to determine the errors in chromosome number and structure. Next-generation DNA sequencing (NGS) is a molecular genetic test used to screen mutations in the genes. In NGS, blood sample of the affected person is collected and DNA is isolated and sequenced. The NGS reports can be either genetically solved or unsolved. Genetically solved cases aid the clinician in validating the clinical diagnosis and also helps the patient to understand the underlying cause. With the advent of technology and various upcoming diagnostic labs, the significance of genetic testing is not fully appreciated. Testing is done, but education is lacking to understand the impact of the finding in genetically solved or unsolved cases. The unsolved cases might leave the diagnosis unconfirmed and create a confusing environment for the affected patient and/or their family. In some cases clinicians can also get misled with the variant reported. The reported variation may not be causing the disease and further validations are required to arrive at a conclusion. Confirmed genetic and clinical findings require correlation. Only such patients can be ideal candidates for gene therapy. Unsolved clinical and genetic cases need revisiting for further assessments[3].

Genetic counselling at the Gen-Eye clinic:

Clinical and genetic heterogeneity, lack of awareness, unavailability of therapy, the societal stigma of carrying a genetic disorder added to the physical aspect of vision loss can be emotionally debilitating for the patient and their family. Genetic testing with appropriate genetic education and counselling is essential for better prognosis and management of IRD cases[7]. Clinically diagnosed IOGD patients are referred to a team of genetic counsellors and educators at the Gen-Eye clinic at Narayana Nethralaya (since 2014). When visiting the Gen-Eye clinic at Narayana Nethralaya, patients and families can expect a structured and comprehensive genetic counselling process to address their concerns. A detailed family history a.k.a. a pedigree (figure 2) is charted with information such as age, gender, marital status, occurrence of visual or non-visual medical conditions in family members and consanguinity.

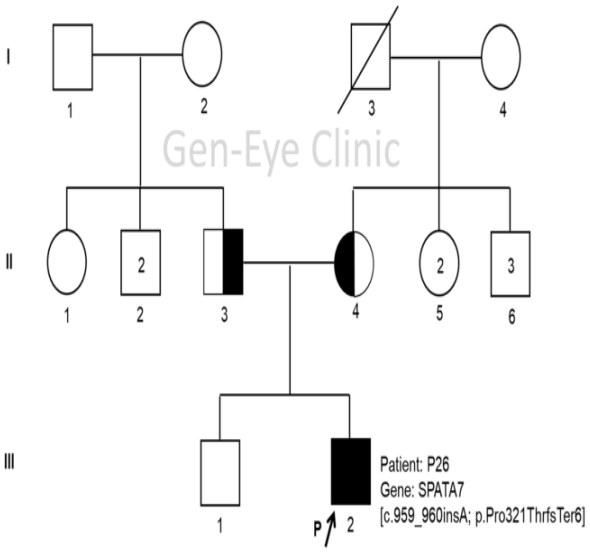

Figure 2: Example of a pedigree.(Published manuscript: Inherited retinal disorders: a genotype-phenotype correlation in an Indian cohort and the importance of genetic testing and genetic counselling. Gopinath C et. al.)[3]

The clinic provides a pre-test genetic counselling session for educating the patients and their family regarding the anatomical and molecular basis or the disorder, modes of inheritance and the choice of an appropriate genetic test. This empowers them to make an informed choice of the genetic test. The patient is provided with continued guidance not only through the genetic testing procedure, but also after arrival of the report through a post-test genetic counselling session to discuss the findings and understand the implications of the report. The reports are discussed with the diagnostic lab in case of any necessary clarifications. We encourage the patients to keep in touch with us in case of any further questions and/or to discuss updates on research and therapy. The test reports are also discussed with the respective clinician for correlation of the genetic finding with the clinical presentation. This holistic approach in genetic counselling enables patients and their families with knowledge to make decisions about their eye health, family planning, psychosocial wellbeing, and appropriate management strategies. With every incoming case, the Gen-Eye clinic has created a patient registry that serves as a representation of IOGD patients of Indian ethnicity. This becomes important from the point of view of accurate diagnosis and also for development of timely and precise therapy. Thus genetic counselling is a resource that serves as a bridge between patients, clinicians, diagnostic and research labs. (Figure: Workflow)

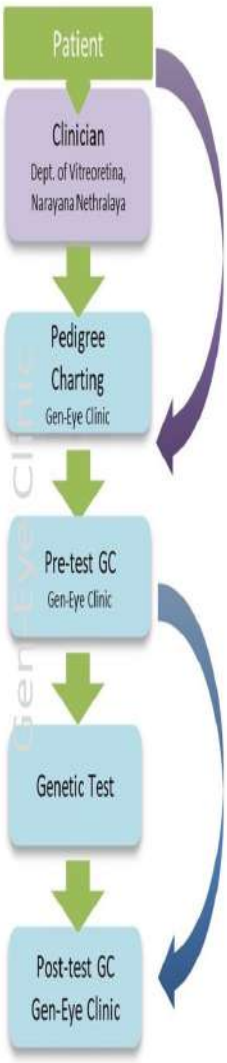

Figure 3: The Gen-Eye clinic genetic counselling workflow.

At the Gen-Eye clinic, Narayana Nethralaya in Bangalore, genetic counselling is provided for patients who have been diagnosed with ocular genetic disorders and seek guidance and support to understand the implications of their condition and the potential risks of passing it on to the next generation. Family members and relatives who may be at risk of developing heritable eye disorders also benefit from genetic counselling, as it helps them understand their risk and make informed choices.

At the Gen-Eye clinic, Narayana Nethralaya, genetic counselling and testing services are offered for various eye genetic disorders. These include conditions such as Retinal Dystrophies, Corneal Dystrophies, Optic Atrophy, Congenital Glaucoma, and Retinoblastoma. To schedule an appointment for genetic counselling at the Gen-Eye clinic, Narayana Nethralaya in Bangalore, please reach out via email at genetictest@narayananethralaya.com. Alternatively, appointments can be made by calling the clinic at the phone number 08066660715. Please visit the GROW (Genes, repair and regeneration at ophthalmic workstation) research laboratory's website www.nnf.org.in for additional information on genetic counselling and research.

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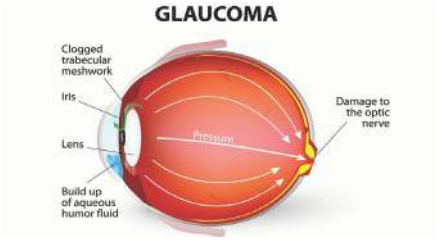
Review Article

Minimally invasive glaucoma surgery (MIGS) in Childhood glaucoma



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Abstract

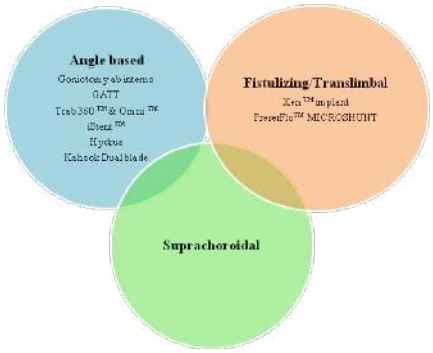
Purpose of review: Minimally invasive glaucoma surgery (MIGS) has been shown to be safe and effective in treatment of mild to moderate glaucoma in adults, but reports in childhood glaucoma are limited. We review the available data concerning MIGS and discuss its potential role in childhood glaucoma management.

Recent findings: Ab interno counterparts to circumferential ab externo trabeculotomy such as gonioscopy-assisted transluminal trabeculotomy (GATT) and Trab360 show promise in treatment of primary glaucomas as reported in a few retrospective case series. Kahook Dual Blade (KDB) and Trabectome have demonstrated mixed results in few published case reports in children. Small case series and reports suggest that the Xen gel stent can be a safer alternative to traditional filtration surgery, though data on long-term implant and bleb stability are unavailable. Newer devices are being investigated and early results are encouraging.

Summary: GATT and Trab360 seem to be safe, effective methods of achieving circumferential trabeculotomy in childhood glaucoma. KDB, Trabectome, and Xen gel stent have shown some success in selected cases with short-term follow-up. Surgeons must determine the risks and benefits of MIGS over more established methods of intraocular pressure reduction for each individual child. Further research is needed to validate initial findings regarding MIGS in childhood glaucoma.

Introduction

Childhood glaucoma is a heterogeneous group of diseases characterized by damage to ocular structures from elevated intraocular pressure (IOP) with age of onset younger than 17-18 years. The diagnostic criteria for childhood glaucoma place emphasis on the effects of elevated IOP on ocular structures such as optic disc cupping, Haab striae, buphthalmos, and progressive myopia.[1] The current International Classification System for childhood glaucoma (derived from the Childhood Glaucoma Research Network and World Glaucoma Association Consensus of 2013) represents a simplified, clinically relevant approach to diagnosis of childhood glaucoma. In brief, childhood glaucoma is classified as primary, which includes primary congenital glaucoma (PCG) and juvenile open-angle glaucoma (JOAG), or secondary. Secondary subtypes are further categorized as associated with nonacquired ocular anomalies, nonacquired systemic disease or syndromes, acquired conditions, and as glaucoma following cataract surgery (GFCS). The international classification system and its implications for collaborative research have been recently discussed. [1,2]



Management

There are many challenges to childhood glaucoma management including disease heterogeneity, diagnostic limitations,[1,3,4] and the long disease course for which multiple surgeries may be required over a patient's lifetime. The treatment is primarily surgical, but medications play an adjunctive role and may be particularly effective in certain types of glaucoma (e.g. traumatic, uveitic) and glaucoma suspects. Traditional surgical methods for childhood glaucoma such as goniotomy, trabeculotomy, trabeculectomy, glaucoma drainage device (GDD) implantation, cyclodestruction, and deep sclerectomy have been reviewed in recent years.[5-9] A limited but

growing body of data suggests a role for minimally invasive glaucoma surgery (MIGS) such as gonioscopy-assisted transluminal trabeculotomy (GATT), Trab360/OMNI surgical systems, Kahook Dual Blade (KDB), Trabectome, and the Xen gel stent in select cases of childhood glaucoma. Their use in childhood glaucoma is the subject of the current review. Updates specific to JOAG management are discussed separately [Meredith Klifto's article on JOAG updates].

Circumferential Ab interno trabeculotomy (Gonioscopy-assisted transluminal trabeculotomy and trab360/omni)

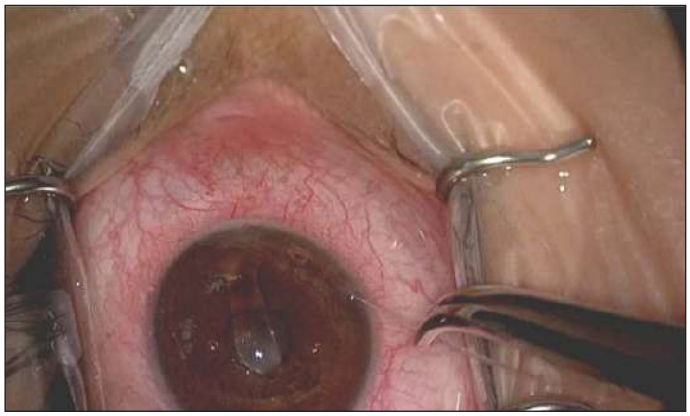
Promising results have been reported with GATT in PCG and JOAG. GATT is an ab interno technique for circumferential trabeculotomy that utilizes an illuminated microcatheter or suture to cannulate Schlemm canal via goniotomy incision within the anterior chamber.[10,11]

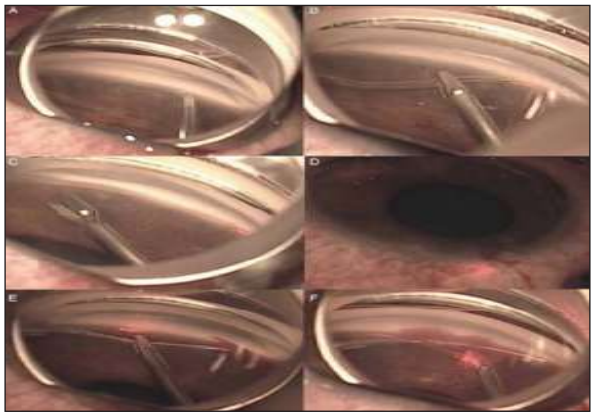
A retrospective consecutive case series including 115 eyes of 89 children with PCG reported comparable outcomes between GATT using an illuminated microcatheter (iTrack, Ellex, Menlo Park, CA) and ab externo microcatheter-assisted trabeculotomy (MAT). [12] Eighty-one percentage of 58 eyes in the GATT group and 73% of 57 eyes in the MAT group achieved the authors' definition of complete surgical success at 12 months. IOP reduction was similar at 54% for both groups (not statistically significant). The MAT group included more bilateral cases, female patients, and a larger number of catheterizations <180 degrees, suggesting a more severe phenotype that may have lowered the success rate in this group. Hyphema occurred in all eyes and required anterior chamber irrigation in 2 eyes in the GATT group and one eye in the MAT group within postoperative week one. Interestingly, more GATT eyes experienced postoperative IOP elevation compared to MAT. The authors suggest this was due to viscoelastic device retention in the GATT group and/or mild leakage through the scleral incision in the MAT group.

A retrospective case series of GATT as the initial surgical treatment in 14 eyes of 10 patients with PCG and JOAG reported a mean IOP reduction from 27.3mmHg to 14.8mmHg at an average follow-up of 20 months on a reduced mean number of glaucoma medications.[13]There were no reported intra- or postoperative complications other than hyphema in 5 eyes which all resolved by postoperative month one. The study included 3 PCG eyes of two children which maintained adequate IOP control off glaucoma medications at 12-21 months of follow-up. A small case series evaluated GATT as the initial surgery in 2 eyes of 2 infants and as additional surgery in both eyes of a 2-year-old child with history of multiple bilateral goniotomies. [14] All eyes achieved unmedicated IOP <20mmHg without signs of disease progression at follow-up of 30-48 months. GATT has also been used to successfully manage steroid-induced glaucoma in the right eye of an 8-year-old male through 2 years of follow-up.[15]. A case series reports the effectiveness of GATT in 59 eyes of 48 JOAG patients including those with severe disease and prior surgery.[16]

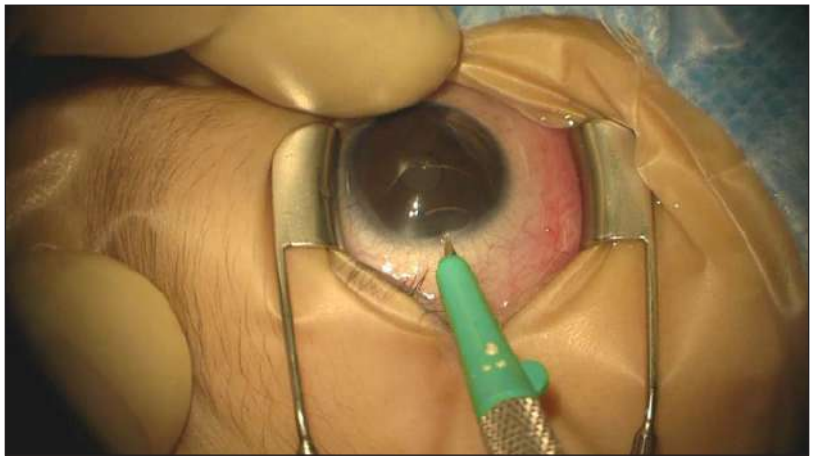
The Trab360 device (Sight Sciences, Inc., Menlo Park, CA) is a handheld instrument from which a nylon filament is advanced and cannulates Schlemm canal and subsequently tears through 180 degrees of trabecular meshwork (TM). The procedure is repeated in the opposite direction to complete up to 360 degrees of trabeculotomy. It was succeeded by the OMNI surgical system (Sight Sciences, Inc., Menlo Park, CA), which allows the surgeon to perform viscocanaloplasty prior to trabeculotomy. A multicenter retrospective case series evaluated the use of Trab360 in the treatment of 46 eyes of 41 patients with childhood glaucoma and reported similar success rates as standard methods of angle surgery.[17] Sixty-four percentage of all eyes, 70% of treatment-naive eyes, and 81% of PCG eyes achieved success at a mean follow-up of 16 months. There were poor success rates in glaucoma associated with a nonacquired systemic syndrome and nonacquired ocular anomalies. The authors caution about the risk of intraoperative cyclodialysis, which occurred in 2 secondary glaucoma eyes with peripheral anterior synechiae and which required subsequent repair. Hyphema frequently occurred and resolved without surgical intervention by postoperative month one. There is one reported case of stabilization of ocular enlargement and resolution of corneal edema in a 4-month-old patient with glaucoma associated with Sturge-Weber syndrome treated with the OMNI surgical system at 10 months of follow-up.[18]

The previously mentioned studies report the IOP-lowering effect and safety profiles of GATT and Trab360 to be comparable to ab externo approaches of circumferential trabeculotomy. [10-21] GATT and Trab360 may be advantageous in select cases due to sparing of the conjunctiva and avoidance of scleral dissection in buphthalmic eyes. They may be easier to complete than traditional goniotomy through smaller windows of clear cornea since these MIGS techniques require only a single point of entry into the TM. However, they may also be more challenging to perform in younger patients and eyes with indistinct landmarks, altered angle anatomy, hazier corneas, lower scleral rigidity allowing easier collapse of the anterior chamber, and/or shallow anterior chambers when compared to the ab externo approach. The current authors' typical practice with ab externo 360-degree trabeculectomy is to dissect conjunctiva and sclera inferotemporally, which limits scarring to a less favored region; i.e. preserving the inferonasal and superotemporal quadrants for future GDD implantation, and the superonasal quadrant for potential filtration surgery, as deemed necessary. Areaux *et al.* **provide an interesting costcomparison of various angle surgery methods**.[17]





GATT-Gonioscopy-assisted transluminal trabeculotomy



Trab360™ Circumferential Trabeculotomy

Partial Ab interno trabeculotomy (kahook dual blade and Trabectome)

Data on the use of KDB (New World Medical, Rancho Cucamonga, CA) in childhood glaucoma is sparse and limited by few cases, variable treatment extent, and short follow-up. The KDB, which consists of a pointed tip attached to a ramp that leads to two cutting blades, is designed to excise a strip of TM through an ab interno approach.[22] This contrasts with traditional goniotomy, which creates a single incision at the TM and is typically performed with a 25-gauge needle, goniotomy knife, or microvitreoretinal (MVR) blade [23]

The few case reports of KDB treatment as the first surgery in PCG are only modestly encouraging. KDB treatment of 4 clock hours achieved satisfactory IOP reduction in one PCG eye at 4 months postoperatively; both eyes of one infant underwent 4 clock hours of KDB treatment but underwent subsequent angle surgery at postoperative month 6 due to inadequately controlled IOP.[24] The left eye of a bilaterally treated 13-month-old male with PCG achieved satisfactory IOP lowering after a single 4-clock-hour KDB treatment at 7 weeks of follow-up. However, his right eye responded poorly to KDB, which was performed three times over 6 weeks. The patient was eventually scheduled for GDD implantation.[25] There are isolated reports of KDB use in other types of childhood glaucoma. An infant with GFCS who was treated bilaterally with KDB for approximately 100 degrees had adequate IOP reduction at a short follow-up of 7-10 weeks postoperatively.[26] KDB was used to treat 200 degrees of nasal and temporal angle in a treatment-naive eye of a 14-year-old patient with JOAG, resulting in IOP reduction from 28 to 15mmHg on no glaucoma drops at a follow-up of 18 months.[27]

The Trabectome (NeoMedix Corp., San Juan Capistrano, CA) is a handheld device with an electrosurgical ablation unit at the tip of the handpiece designed to selectively ablate TM and the inner wall of Schlemm canal via ab interno approach under gonioscopic view. The only published report of Trabectome use in childhood glaucoma is a prospective cohort study evaluating its efficacy and safety in JOAG.[28] Briefly, 60 eyes of 60 JOAG patients aged 12-40 years received 60-120 degrees of trabectome treatment. Mean IOP reduction at 12 months was 10mmHg with a nonsignificant reduction in glaucoma medications. Additional glaucoma surgery (trabeculectomy or GDD) was necessary in 15% of patients at 12 months. The study's authors concluded that Trabectome may be considered as a treatment alternative in JOAG but does not significantly

reduce dependency on glaucoma medications. The study was limited by a short follow-up period and poor follow-up to completion (41/60 eyes dropped out). Data on the Trabectome's safety and effectiveness in other types of childhood glaucoma are not currently available.

The proposed advantage of KDB and Trabectome over traditional goniotomy is based on the idea that the MIGS devices remove TM more completely without damage to adjacent tissues.[22,29] However, postoperative gonioscopic appearance suggests that only a limited trabeculotomy cleft may result from KDB and Trabectome. [27,29] Data on their use in childhood glaucoma are very limited and do not suggest that they reduce IOP better than more established and validated methods of angle surgery in childhood glaucoma, particularly PCG. Furthermore, there is growing evidence that circumferential angle treatment may be more effective than partial. [30,31,32,33]

XEN GEL STENT

The Xen gel stent (Allergan, Dublin, Ireland) is a 6 mm gelatin tube designed for translimbal implantation through an ab interno or ab externo approach to shunt aqueous fluid from the anterior chamber to a filtering bleb with or without subconjunctival mitomycin C (MMC) injection. A small case series of 3 eyes of 3 patients with refractory childhood glaucoma demonstrates the Xen gel stent's short-term safety and efficacy.[34] A 21-month-old patient with GFCS underwent ab interno Xen gel stent implantation with MMC combined with pupillary membrane removal in his right eye 14 months after failed ab interno trabeculotomy. Xen gel stent implantation resulted in a diffuse bleb and good IOP control off medications over 2 years of follow-up.[34] A second child with refractory PCG underwent Xen gel stent implantation with MMC and had inadequate IOP reduction at 5 weeks postoperatively. A second Xen gel was implanted through an ab externo approach adjacent to the initial one, which resulted in good IOP control at 6 months of follow-up. The distal end of the first Xen gel stent was found within tenon's capsule instead of the intended subconjunctival position, which was the suspected cause of its failure.[34] The third case was a 10-year-old girl with severe secondary angle-closure glaucoma who received a Xen gel stent with MMC (combined with phacoemulsification, intraocular lens implantation, and iridectomy) which successfully reduced IOP to the low teens through 2 years of follow-up.[34] None of the blebs required needling. Finally, Sousa *et al.* reported good results with sequential ab interno Xen gel stent implantation in both eyes of a 14-year-old girl with steroid-induced glaucoma, achieving IOP in the mid-teens in both eyes off glaucoma medications at a follow-up of 6 months.[35]

These reports offer Xen gel stent implantation as a viable alternative to traditional angle and filtration surgery in childhood glaucoma. Smith *et al.* report favorable bleb morphology with subconjunctival MMC injection at the time of Xen gel stent implantation [34] but acknowledge the risk of bleb-related complications associated with antimetabolite use in the pediatric population.[36-38] The final position of the distal end of the Xen gel stent within the subconjunctival space appears to be critical to the procedure's success. Thus, the ab externo approach may be preferred to ensure subconjunctival placement of the stent due to thicker tenon's capsule in children compared to adults. However, this approach would still require some amount of conjunctival dissection albeit not as extensive as for traditional trabeculectomy or GDD implantation. There are reports of stent degradation, intraluminal obstruction, and stent migration within months to a few years after Xen gel implantation in adults.[39-41] Surgeons should carefully consider the unknown long-term complications and outcomes of this device when contemplating its use in children.

Other Minimally invasive glaucoma surgery

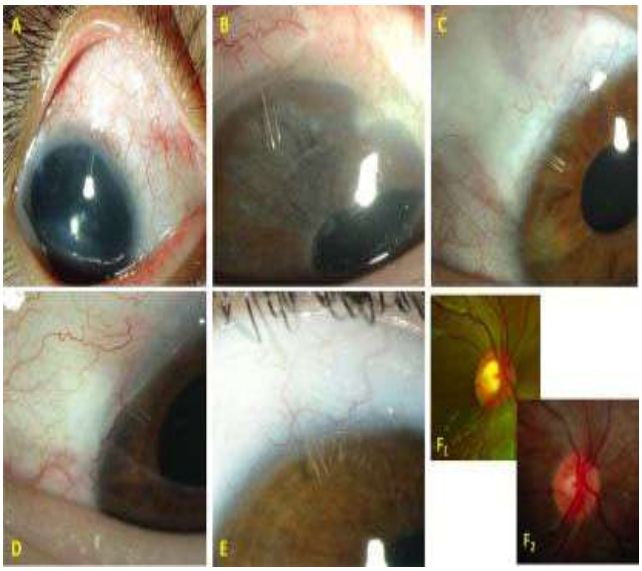
Endocyclophotocoagulation (ECP) is considered by some as a MIGS procedure.[42] This ab interno cyclodestructive technique utilizes a 19 or 20-gauge microendoscope (Endo Optiks Inc., Little Silver, NJ) to deliver laser energy to <=360 degrees of ciliary body processes under direct visualization. Published studies of ECP in childhood glaucoma demonstrate relatively good success in GFCS eyes when performed early or as primary glaucoma surgery compared to poor outcomes in eyes with advanced/refractory glaucoma.[43-45] ECP may have a special role in anatomically complex eyes with inadequate visualization of the anterior chamber or angle structures and when there is insufficient space for GDD implantation. Some consider it in aphakic and pseudophakic eyes which require additional IOP reduction in the setting of a patent GDD system. Severe complications such as retinal detachment, loss of vision, and chronic hypotony (particularly with subsequent outflow surgery) can occur with ECP. [43-46] Surgeons should exercise caution in high-risk eyes despite the 'minimally invasive' nature of this technique.

There are no published reports on iStent Trabecular Micro-bypass (Glaukos Inc, San Clemente, CA) or Hydrus Microstent (Ivantis, Inc., Irvine, CA) devices in childhood glaucoma. We do not recommend their use in children due to the relatively modest IOP reduction reported in adults with mild to moderate glaucoma.[47] and the potential risks of implanted intraocular metallic devices over a child's lifetime, presumably several decades. Additionally, these devices are approved only for use with cataract extraction in adults in the United States (though they can be used as standalone procedures elsewhere).

The CyPass Micro-stent (Alcon Laboratories, Inc, Ft. Worth, TX) is a polyimide device implanted between the anterior chamber and the supraciliary space. It was withdrawn from the market in 2018 due to increased endothelial cell loss which was directly related to the number of retention rings protruding into the anterior

chamber.[48] Other devices targeting suprachoroidal outflow seem promising, but their long-term efficacy and safety are yet to be determined. [49]

The PreserFlo MicroShunt (Santen, Osaka, Japan) is an ab externo translimbal device made from the same material as coronary stents. Like the Xen gel stent, the PreserFlo MicroShunt delivers aqueous fluid from the anterior chamber to a filtering bleb, but the material may be less prone to long-term degradation. It is currently being investigated in children with glaucoma with encouraging early results.[50]



Slit-lamp images of microshunts with adjacent blebs at various lengths of follow-up. A. Patient 2 at 3 months. B. Patient 4 at 14 months. C. Patient 5 at 14 months. D. Patient 7 at 4 months. E. Patient 9 at 14 months. Images F1 and F2 are optic disc images of patient 10 immediately before (false color wide-field scanning laser ophthalmoscope; intraocular pressure, 23 mm Hg) and 4 months after surgery (digital fundus camera; intraocular pressure, 8 mm Hg), demonstrating significant cupping reversal.

Conclusion

Current data on MIGS in childhood glaucoma is limited to few case series, cohort studies, and case reports. Most of the published experience has been with circumferential ab interno trabeculotomy (GATT and Trab360), which suggests similar safety and efficacy as circumferential ab externo trabeculotomy in treatment of primary types of glaucoma. Data on KDB, Trabectome, and the Xen gel stent are more limited, but there may be a role in selected cases. Future data may support use of newer MIGS, such as PreserFlo and/or CyPass-like devices, in selected cases of childhood glaucoma. The benefits of conjunctival sparing and potentially reduced risk of postoperative complications must be weighed against the uncertain longevity and long-term effects of each method. The learning curve, device availability, and relative cost for MIGS versus traditional surgical techniques should also be considered. MIGS has expanded the available tools for treating this challenging group of diseases; however, additional research with prospective and comparative study design, larger sample size, and longer follow-up are needed.

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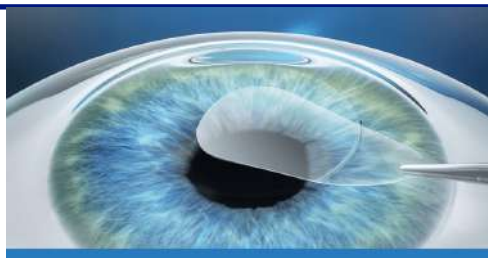
Review Article

Small incision lenticule extraction (SMILE) complications; Prevention and management



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Abstract

As a flapless procedure, SMILE brings benefits to refractive surgery, such as lower corneal biomechanical impact, less dry eye risk and less stromal bed exposure. However, the longer learning curve can be a risk factor for complications. This article aims to discuss SMILE complications and proposes a categorized analysis of occurrences, dividing into two groups: intraoperative and postoperative complications. Among intraoperative, we also suggest a subdivision between those related to the laser (lenticule construction), tissue separation (lenticule dissection) and tissue removal (lenticule extraction).The majority of SMILE complications are related to surgeon inexperience and reversible if precociously diagnosed and correctly managed. Intraoperative complications related to lenticule creation such as suction loss, opaque bubble layer and black spots, are correlated with later difficulties during lenticule dissection and removal, and may lead to unwanted situations, such as cap perforation, lenticule tear and cap-lenticule adhesion. Postoperative complications as dry eye, keratitis and ectasia should not be underestimated.

Analyzing what has been reported as major or unique among the complications with SMILE, and dividing them into subgroups, we aim to help refractive surgeons in becoming familiar with the things that can go wrong during SMILE. Early recognition and correct management will be fundamental for optimizing the final visual result.

Keywords: corneal refractive surgery; small incision lenticule extraction; SMILE

Introduction

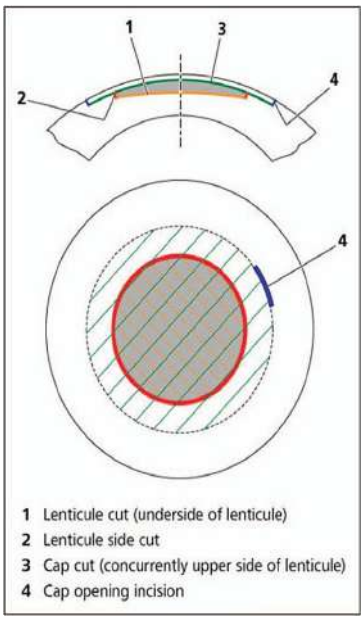
Since the earliest publications about SMILE in 2011, the concept of a refractive surgery performed through a small incision without the side effects associated with the flap creation, has led to an increased interest in the ophthalmologic field. Lower corneal biomechanical impact, less dry eye risk and less stromal bed exposure were some benefits this innovative technique had aroused. [1-7] As subsequent studies demonstrated stability, safety and efficacy in the treatment of myopia and myopic astigmatism, similar to FemtoLASIK. [8-11] it became suitable to consider SMILE as the next generation of laser vision correction.

Despite numerous benefits, the procedure has a longer learning curve than other techniques of refractive surgery, and it is mainly during this stage of skill development that a number of complications tend to occur. [9,12] Early recognition and management of complications are essential to achieve good results.

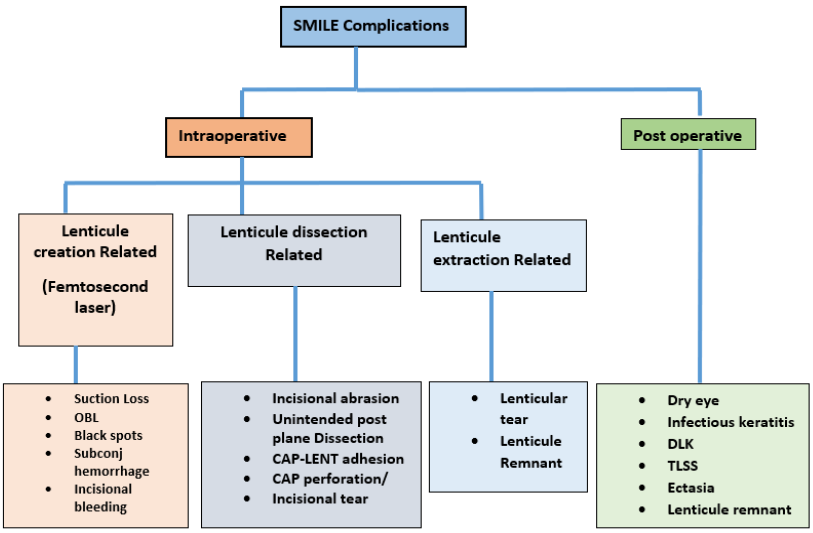
In considering the growing popularity of SMILE around the world, we have also observed an increase in the number of publications related to the subject in recent years. However, there are still relatively few publications analyzing the global scope of the complications related to this technique. Ivarsen *et al.* evaluated the rate of complications in 1800 eyes consecutively operated with SMILE between 2011 and 2013. Wang *et al.* published in June 2017 a series of 3004 SMILE cases evaluating the incidence and management of complications. Some of their findings will be discussed during this article.

Review of SMILE surgery and complications

Aiming for a better comprehension about SMILE complications, it is important the reader be aware about surgery steps. With topical anesthesia, the patient is positioned on Visumax platform (Carl Zeiss Meditec AG). The surgeon verifies the precise centering and initiates suction. The femtosecond laser lenticule cut is started obeying the sequence: posterior lamella, edge, anterior lamella and incision site (Fig.1). Once this step is completed, the surgeon initiates the lenticule dissection with the aid of a spatula, first on the anterior surface followed by the posterior one. Finally, the lenticule is extracted and inspected, followed by hydration and gentle stroking of the cap.



With the objective of organizing a step-by-step menu of possible SMILE complications, the following categorical chart is proposed to aid the surgeon in understanding and anticipating risk during and after the procedure (Fig 2). Although the two main groups, intraoperative and postoperative, are obvious, the intraoperative complications can be further subdivided into those involving the laser (lenticule construction), the dissection (lenticule separation) and the extraction (lenticule removal).



OBL=Opaque bubble layer, DLK=Diffuse lamellar keratitis, TLSS=Transient light sensitivity syndrome

Figure 2. Categorical chart of small incision lenticule extraction complications.

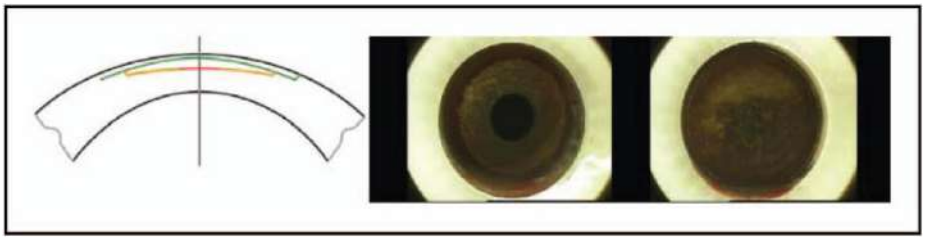
Intraoperative complications related to the laser

In this section, we will discuss the complications related to lenticule creation. During this step, the outcome depends on femtosecond laser delivery and precision placement in designing the lenticule.

Suction loss

The incidence of suction loss during SMILE ranges from 0.9 to 4.4%. However, in recent times, with the use of current software and experienced surgeons, this has reduced to 0.17 to 0.93%. The suction pressure during lenticule creation with the Visumax platform is lower than observed with other platforms and microkeratomes. Although the lower pressure reduces the risk of retinal detachment and intraocular pressure-related damage, it is a risk factor for suction loss.[14] Other known risk factors are: narrow eyelid fissure, forcible lid squeezing, Bell's phenomenon, smaller corneal diameter and conjunctival chemosis. [8,14] As the Visumax laser suction ring applies peripheral corneal suction, it is less impacted by conjuctival chalasis and chemosis. Osman *et al.*[8] also suggest other risk factors such as the surgeon inexperience, large cap diameter and higher amounts of cylinder, justified by the lower compatibility between the corneal and suction cone shape.

Liu *et al.* analyzed the incidence of suction loss in a series of 8490 eyes operated with SMILE. They observed 34 cases (0.4%) of suction loss. Among those, 51% occurred during the cap cut and 75% in the right eye. The authors suggested that the higher incidence of suction loss in the right eye is related to head and eye movements secondary to patient anxiety.[14] Faced with a case of suction loss, the surgeon must know that immediate re-treatment with the same parameters can be performed unless suction loss occurs during the posterior lenticular cut, when more than 10% of the posterior face of the lenticule is created (Fig.3). In this case, the procedure must be stopped and changed to a more traditional approach (i.e. LASIK or photorefractive keratectomy (PRK)] in order to avoid possible irregularities and intersecting lenticular cuts. A preferred option is to create an 8 mm diameter flap in the cap plane and complete the surgery as a FemtoLASIK. Despite being one of the main intraoperative complications, correct management of suction loss has good visual results. [12,14]



Prevention: Proper preoperative counseling of the patients is mandatory to prevent suction loss; further, the contact lens should be clear and the conjunctival surface should be dried with Merocel sponges before suction application.

Opaque bubble layer

The femtosecond laser separates tissue through a mechanism called photodisruption. Each laser pulse generates a plasma, followed by a cavitation bubble, which rapidly expands to assist in tissue separation, and then collapses. When the remaining gas bubbles created during this process cannot dissipate and coalesce at the stromal interface, the transient opacity remaining is called opaque bubble layer (OBL). [3,15]

The main risk factors for OBL are thick corneas and thin lenticules (low correction). [3,12] It is believed that the more compact arrangement of collagen fibers in the anterior third of the corneal stroma generates a greater resistance to dispersion of the bubbles.[15] Li *et al.* suggest that increasing cap thickness may reduce the risk of OBL in cases of low correction, which emphasizes the importance of knowing the biomechanical stiffness of each cornea before deepening the interface of laser scanning. As corneas stiffen as one gets older, age may contribute to the incidence of OBL and this may make the dissection process more difficult. Ma *et al*. classified OBL as phase 1 (OBL in the posterior lenticule interface) and phase 2 (OBL in the anterior lenticule interface).

Although OBL acts as a barrier to the visualization of deeper structures and often hinders the lenticule dissection, studies show that it does not affect the final visual outcomes. [3,12]

Prevention: Irrigation of ocular surface with a sterile solution to remove debris, followed by instillation of preservative-free artificial tears and removal of excess fluid using Merocel sponge could be used along with a soft docking technique, low laser energy, and deeper lenticule separation to reduce the incidence of OBL.

Black spots

Like OBL, the surgeon is able to visualize this complication during femtosecond laser scanning process. It occurs because of adherence of water droplets, meibomian secretions or conjunctival mucus onto the interface between the suction cone and cornea, acting as a barrier to block the photodisruption of laser pulses (Fig. 4). [9,12] When black spots present during the creation of a posterior and/or anterior laser interface, they indicate a regional absence in tissue cleavage, which in turn leads to great difficulties during the lenticule dissection. Wang *et al.* suggest that one should abort the procedure in cases of large black spots or when they reach the pupillary axis.

Prevention: Preoperatively, meibomian gland disease should be treated and intraoperatively it should be ensured that there is no debris on the corneal surface

Incisional bleeding and subconjunctival hemorrhage

Although the suction ring fixes on the peripheral cornea rather than the conjunctiva, incisional bleeding may still occur as the laser pulses transect the vessels of a peripheral corneal pannus, especially in patients with previous chronic conjunctivitis. Subconjunctival hemorrhage may also occur and is related to device suction pressure.

Treatment includes the application of pressure with sterilized cotton swabs and intraoperative use of vasoconstrictive eye drops along with balanced salt wash under the corneal cap to reduce visual blurring after surgery.

Intraoperative complications related to lenticule dissection

Complications related to surgeon difficulty in separating and dissecting the lenticule interfaces and edges will be discussed in this section.

Incisional complications

Excessive manipulation during the SMILE procedure can lead to incisional abrasion and sloughing of the adjacent corneal epithelium. Its incidence varies greatly in the literature because it is inversely related to surgeon's experience [1,2,12] Irregular tears with excessive dissection can disrupt the epithelial cells at the site of the tear and maybe a source of epithelial ingrowth. Artificial tears and a bandage contact lens are suggested for a speedy recovery. [9,12] and it does not affect the final visual outcome.[9]

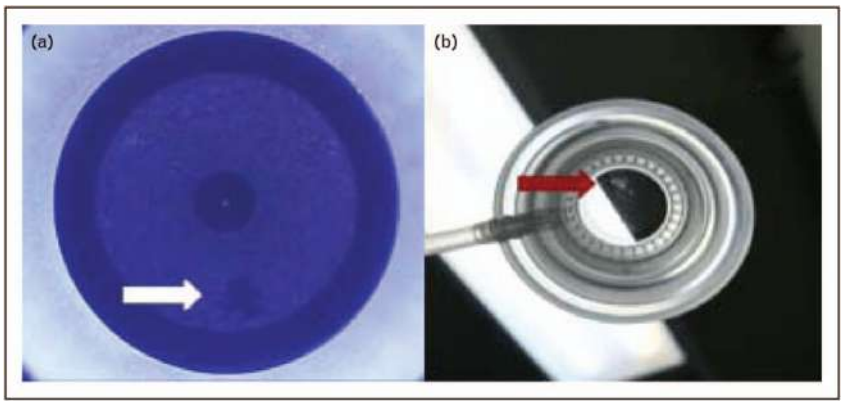


Figure 4. Black spot. (b) Surgeon view during laser scanning. (c) Adherence of conjunctival mucus onto the contact glass

Lenticule dissection difficulties

During the SMILE surgery, lenticule dissection should be performed carefully, respecting the sequence of anterior plane followed by the posterior plane in order to reduce risk of complications. One might anticipate difficulties in lenticule separation and dissection when problems are identified during the lenticule creation, such as OBL and black spots. In cases where tissue cleavage is defective, greater precaution should be adopted to avoid complications.

Epithelial defect

Epithelial defects in SMILE may occur at the incision site or in the center. The incidence of incision site epithelial defect varies from 0.17 to 11.25%. An epithelial defect may occur in the beginners' hands due to excessive surgical manipulation at the incision site. However, the presence of an epithelial defect at the incision site has no impact on visual outcome. In patients who had a central epithelial defect, interface inflammation was noted postoperatively. Treatment includes the application of a bandage contact lens and the use of copious lubricants.

Cap perforation and incisional tear

Inadvertent handling of the instrument when facing tissue resistance during anterior plane dissection may lead to cap perforation or incisional tear [1,9,12] In the case series published by Ivarsen *et al.*1 four patients presented cap perforation and were handled with bandage contact lens. At 3-month follow-up, only small scars were observed, with no visual outcomes impact. Incisional tear risk is greater when the incision is smaller than 2.0 mm.[12]

Inadvertent posterior dissection and cap-lenticule adhesion

The incidence of unintended posterior plane dissection varies between 0.33 to 7%. Difficulty in locating the correct plane of lenticule dissection may yield inadvertent entry into the posterior plane, leading to cap-lenticule adhesion and a more challenging and sometimes impossible extraction.[16] Urkude *et al.* reported several risk factors and different mechanisms related to this process. Surgeon inexperience and ocular movement by the patient may lead to inadvertent dissection of the posterior plane first, pushing the lenticule against the cap and causing adhesion. The occurrence of OBL or black spots may generate incomplete cleavage between cap and lenticule also causing local adherence. Finally, small corrections are made through creation of thin lenticules, which may cause difficulty in locating the desired dissection plane.

The surgeon's inability to initially perceive this complication, and repeated attempts to find the second dissection plane, can lead to creation of a false plane and even corneal perforation.[12] In addition, excessive manipulation and diminished resistance against the less firmly anchored cap leads to anterior stromal edema, making this approach even more difficult.

Recent studies suggest there are clinical signs and complementary tests capable that enable early detection of cap adhesion that might prevent extraction difficulties. [16,17] Various signs such as white ring sign, meniscus sign, shimmer sign, and stop sign have been described which help in the identification of the correct plane of dissection.Jacob *et al.* described the white ring sign, which is a reflection of light from the side cut on top of the dissecting instrument (Fig.5). When in doubt about the correct cleavage plane, the surgeon should reference the instrument position with an absence of the white ring before proceeding with dissection. [17] Another way to detect lenticule adhesion, even in swollen corneas, is through intraoperative OCT, which can reduce total surgery time and avoid excessive manipulation [16]

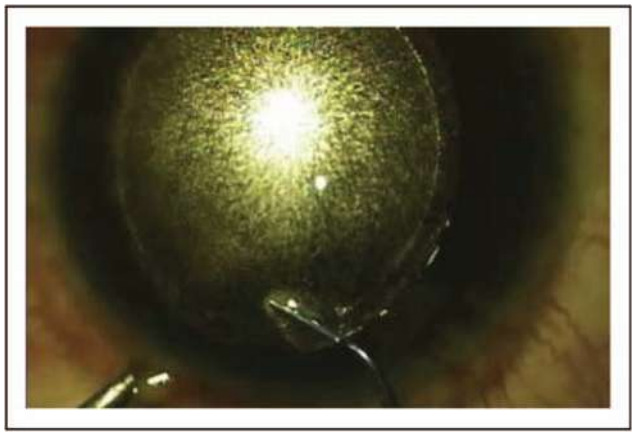


Figure 5. White ring sign

Different signs described for identification of the plane of the lenticule during SMILE surgery

Sign	Described by	Time of visualization	Details	Description	Implication
White Ring Sign	Jacob *et al.* 2016	During dissection of both posterior and anterior planes, the position of the white ring changes	Light reflex from the lenticule side cut is seen in darker iris under oblique illumination	Seen as a white ring posterior to the dissecting instrument during anterior plane dissection and anterior to the instrument during posterior plane dissection	Prevention and detection of unintentional initial posterior plane dissection, thereby preventing lenticule cap adhesions
Shimmer Sign	Shetty *et al.* 2017	Visible during dissection of the posterior plane	A distinct shining reflection is seen around the instrument as it enters the posterior plane and extends through the length of the instrument as it advances further	Seen as a bright reflex around the dissecting instrument. Not visible during dissection of the anterior plane	Helps in identifying the correct plane of dissection
Meniscus Sign	Titiyal *et al.* 2018	During delineation of the posterior lamellar plane.	Pushing the lenticule edge away from the surgeon creates a gap between the inner diameter of the cut and the lenticule edge.	Seen as a meniscus shaped gap between the inner cut and the lenticular edge	Provides for easy identification of lenticule edge. Prevents cap lenticular adhesion.
Stop Sign	Sachdev *et al.* 2020	After delineation of the anterior plane in the right half and posterior plane in the left half	Point of resistance noted at the junction between dissected and undissected halves of both anterior and posterior planes	Subsequent lateral movement of the instrument is difficult (left to right in the posterior plane and right to left in the anterior plane).	Confirms ideal delineation of both planes

Intraoperative complications related to lenticule extraction

The last step of the SMILE procedure, lenticule extraction, demands surgeon attention and inspection to avoid the possible complications discussed in this section. Most often related to surgeon inexperience. Complications occur during Lenticule creation, Lenticule dissection or Lenticule extraction

Lenticule tear and lenticule remnant

The incidence of problems during lenticule extraction varies from 2.16 to 9%. A torn lenticule during extraction can arise from situations prone to difficulty during lenticule dissection, especially those related to inadvertent dissection or thin lenticules. The surgeon must inspect and certify the integrity of the extracted lenticule and stromal pocket, because small segments (lenticule remnants) can remain attached (Fig. 6). When missed, these remnants can generate postoperative surprises, such as topographic irregularities, irregular astigmatism and visual loss.[18]

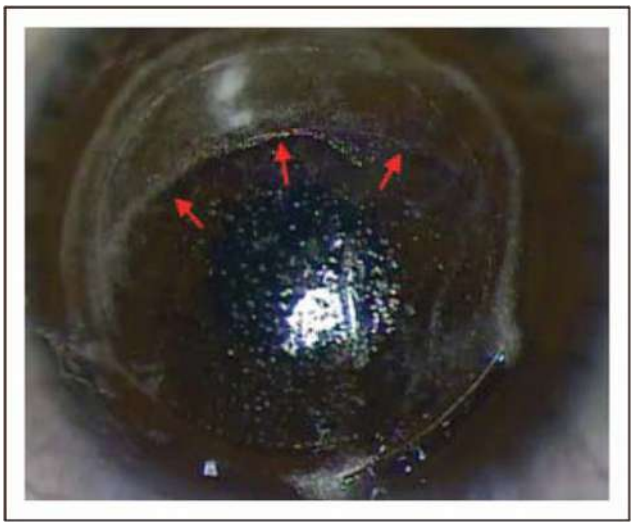


Figure 6. Lenticule remnant after extraction.

Alex *et al.* presented four case reports of apparently uneventful SMILE procedures that evolved with unexpected visual outcomes because of lenticule remnant. The authors emphasize that careful analysis of topographic maps and surgery video may help in early diagnosis.

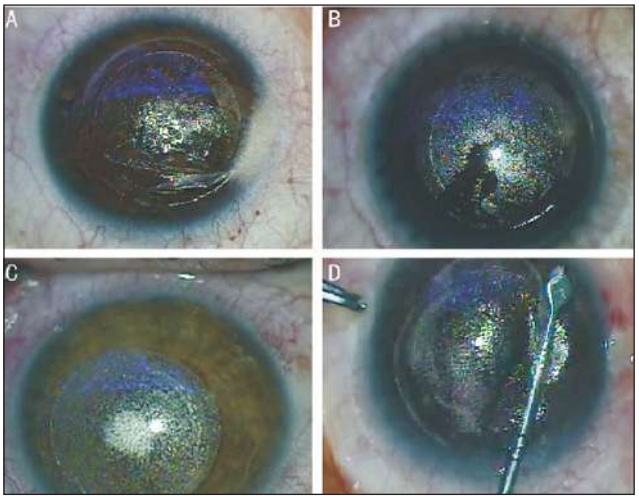
The retained lenticule may be identified by various methods which include the following: use of retro illumination with fully dilated pupil, intraoperative triamcinolone acetonide which highlights the edge of the lenticule, inadvertent entry of air which also delineates the edge of the lenticule, and the application of anterior segment OCT and intraoperative OCT which will identify the edge of the lenticule.

Treatment of lenticule remnant may be done in the same sitting using microscope-integrated OCT-guided lenticule extraction or as a secondary procedure. This depends on the amount of retained lenticule for partially retained lenticule, topography custom surface ablation, or remnant removal may be done; however, for the complete retained lenticule, PRK, or LASIK may be done. The CIRCLE software has also been used which converts the cap into the flap and helps in the removal of the retained lenticule. Once diagnosed, removing the lenticule remnant can bring immediate improvement in visual results.

Cap perforation

Excessive manipulation of the anterior lenticule during dissection leads to cap tear or cap perforation. The incidence ranges from 0.25 to 4.38%. The reasons are rough maneuvers by the beginners and the use of sharp instruments or thick blunt dissectors. Treatment is usually conservative as it heals by minimal scarring with little impact on visual outcomes.

Prevention: Gentle dissection and the use of thin blunt dissectors decreases the incidence of this complication.



A: Incision tear during lenticular extraction;
B: Black islands during SMILE operation;
C: Treatment decentration; D: Cap perforation.

Ablation decentration

Decentered treatment zone may result in unwanted aberrations and a decrease in visual acuity which may be attributed to the surgeon's inexperience, intraoperative involuntary ocular drift, and astigmatism of >2.5D Many studies attribute the presence of postoperative coma and spherical aberration to decentration. A prospective study by Huang *et al.* reported that 12.5% of eyes with high astigmatism had visual acuity between 20/20 to 20/40. Out of all the centration zones which have seen described, the coaxial sighted corneal light reflex or tear film method is the closest to the visual axis and has better outcomes. Decentration of more than 0.3 mm may cause visual problems. Despite the lack of eye-tracking in the SMILE system, centration of treatment zone improved with surgical experience and this has been found to have a good correlation when compared with the eye-tracking system in LASIK. Decentration can also be checked immediately after docking, by turning on the infrared mode after the suction is turned on. This helps to have a properly centered ablation.

Prevention: Preoperative marking on slit lamp, in cases of astigmatism more than -1 dioptre can aid in better centration. Besides, some authors have reported the use of triple marking in astigmatic cases. The incidence of ablation decentration can also be reduced by checking the preoperative angle kappa of the eye and ensuring that the patient is looking into the fixation light. In cases with large angle kappa, the fixation light may appear to be decentered in relation to the pupil center, and it is not necessary to undock and recenter. In cases with high astigmatism, accurate marking of the limbus at 0–180 degrees may prevent cyclotorsion error.

Postoperative complications

Theoretically, laser vision correction with a cap, rather than a flap, is associated with less corneal denervation and better biomechanical stability, which reduces, but not eliminates, the occurrence of postoperative complications.

Dry eyes

Among the postoperative complications related to SMILE, dry eyes have the highest number of publications, as it is considered a determining factor for patient satisfaction after surgery.[7]

Qiu *et al.* demonstrated that 56% of patients after SMILE present with symptoms of dry eye or alteration of tear film stability. However, these symptoms resolved rapidly, returning to preoperative parameters within 3 months follow-up. Xu *et al.* compared dry eye findings between patients undergoing LASIK and SMILE. Both had transient findings, but those who were treated with SMILE were less symptomatic and had better postoperative parameters.

Zhang *et al.* suggest that surface irregularity created after SMILE directly affects the tear distribution over the cornea, contributing to tear film instability and justifying the fact that these patients had reduced TBUT (tear break up time) while preserving tear secretion (Schirmer Test).

Prevention: It is important to do a thorough preoperative examination to look for signs and symptoms of dry eyes. SMILE could be advised over LASIK, especially in patients with mild dry eye symptoms if required. Postoperatively preservative-free drops should be prescribed. In patients with severe symptoms, one may consider punctal plugs or low concentration of topical cyclosporine.

Infectious keratitis

As with any other refractive surgery, SMILE carries the risk of developing postoperative infectious conditions. Chehaibou *et al.* published a case report of severe bilateral infectious keratitis after SMILE. Authors emphasize the importance of respecting antisepsis care to avoid cross-contamination during the surgery. Once diagnosed, it is recommended that treatment is started with the same protocol as for postoperative LASIK infections. Prompt interface irrigation with bactericidal povidone-iodine and antibiotic solution are recommended in order to improve the visual prognosis.[10]

Prevention: Preoperative screening and treatment of any ocular surface disorders, using a sterile gown, mask, cap and gloves by surgeon and assistant, proper sterilization of surgical instruments, betadine preparation of lid and eye as performed for cataract surgery, and use of separate instruments for both eyes could decrease the risk of infection.

Diffuse lamellar keratitis

This condition, also known as Sands of Sahara Syndrome, is an early and sight-threatening complication associated with the aggregation of sterile, inflammatory cell in the interface beneath a LASIK flap or SMILE cap.[4] Zhao *et al.* were the first to report the incidence of diffuse lamellar keratitis (DLK) after SMILE. They evaluated a cohort of 1112 eyes and encountered a DLK incidence of 1.6%. A statistically significant increase in DLK was observed in cases with both thin and wide diameter lenticules.

A lower incidence of DLK following SMILE in comparison with LASIK can be understood and justified by several factors. Less epithelial disruption generated by the small external incision provides a lower postoperative inflammatory response. Less exposure of the stromal bed during surgery and sufficient anti-inflammatory therapy during immediate postoperative period also seem to contribute.[4]

Severity of the inflammatory pattern varies greatly, and a detailed slit-lamp examination on the first day after surgery is essential for an early diagnosis and therapy. Topical steroids are recommended for mild or moderate cases, whereas irrigation of the interface followed by topical steroid are recommended for severe cases. Early diagnosis and appropriate treatment usually leads to a good prognosis.

Prevention: Preoperatively, a scrupulous wash with a suction cannula attached to special aspiration speculum can aid in a thorough clean-up of meibomian secretions and tear film debris thus decreasing the incidence of DLK. Intraoperative use of powder-free gloves, drape to cover lid margin to avoid lash contact is also a useful measure in prevention of DLK. During the procedure, tear film debris is avoided from reaching interface. Topical steroids should be judiciously used postoperatively.

Transient light sensitivity syndrome

A rare complication associated with LASIK, and recently also with SMILE 19 is transient light sensitivity syndrome (TLSS), which is characterized by severe photophobia manifested 2-8 weeks after surgery, and without change in visual acuity and slit-lamp examination findings. Desautels *et al.* emphasize the importance of surgeon awareness of this complication, and the good response to topical steroids.

Prevention: Reducing the laser parameters and increasing the postoperative steroid treatment has shown to reduce the occurrence of TLSS.

Ectasia

Despite the reduced biomechanical impact of SMILE, in comparison to LASIK, four cases (seven eyes) of SMILE-induced ectasia have been reported in Asia [20] In three of the four cases, a detailed topographic analysis showed preoperative corneal abnormalities as a risk factor for the disease. One case, however, showed no preoperative topographic abnormality, which suggests other risk factors need to be studied [20] On average, the diagnosis of postoperative ectasia was made 6.4 months after surgery.

Although the risk of ectasia with SMILE appears to be less than that with LASIK, there are still no specific predictors of ectasia risk with SMILE, and so it is recommended to be cautious with suspect topographic patterns. Collagen cross-linking of the cornea is performed in cases with progressive ectasia. Visual rehabilitation can be achieved by refractive correction using spectacles, rigid gas permeable contact lens, or intracorneal ring segments. Large diameter contact lenses/scleral lenses are particularly useful as they do not rest on the corneal surface, thus being more comfortable to the patient with good visual outcomes. Advanced cases may require anterior lamellar keratoplasty.

Prevention: All patients should be screened preoperatively as done for LASIK or PRK. Risk factors such as age, eye rubbing, hormonal influences, thyroid profile etc., must be considered. Stringent screening criteria for corneal topography also reduces the risk of corneal ectasia.

Pressure-induced stromal keratitis

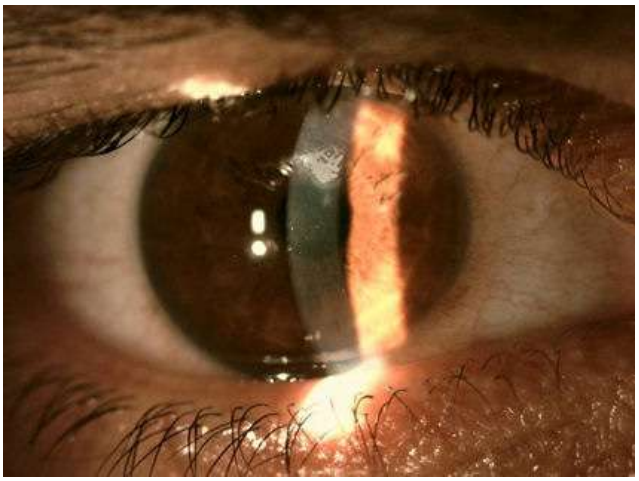
Pressure-induced stroma keratitis (PISK) or interface fluid syndrome or pressure-induced stromal keratopathy has been reported due to elevation in intraocular pressure (IOP) leading to visible fluid clefts in the interface. It is difficult to diagnose considering its variable presentation. It is often misdiagnosed as DLK, but unlike DLK, it presents usually in the 1st week post-operatively.[21,22,23] Patients usually present with worsening vision, pain along with elevated IOP. Interface haze is noted in mild cases while severe cases have fluid clefts in the interface. Elevated IOP secondary to steroid response is the presumed cause for fluid accumulation in the interface. This fluid accumulation could lead to falsely low IOP reading when recorded from the central cornea; therefore, IOP should be measured from the corneal periphery.[24] Dynamic contour tonometry and tonopen (reading from the peripheral cornea) are superior to Goldman applanation tonometry for these cases. Also, *in-vivo* confocal microscopy (IVCM) shows an absence of mononuclear cells and granulocytes in the interface, unlike DLK. Only two cases of PISK have been reported after SMILE in the literature,[25,26] both of them have Asian descent with myopia and darkly pigmented iris, which placed them as high risk for developing ocular hypertension and PISK. [27]

Management includes the lowering of IOP with topical beta-blockers and cessation of steroid therapy. Certain antiglaucoma medications like dorzolamide could affect the endothelial pump function and could exacerbate PISK theoretically. Early diagnosis and appropriate management with antiglaucoma medication is essential to avoid glaucomatous optic neuropathy in these cases.

Epithelial ingrowth

Epithelial ingrowth occurs when the epithelial cells get implanted in the interface accidentally during surgery or migration of these cells through the incision site in the postoperative period. Since SMILE does not involve corneal flap creation, unlike LASIK, this complication is rare. The patient could present with glare, foreign body sensation or diminution of vision in later stages. Incision/side cut tears, cap rupture, and diabetes could be a potential risk factor for epithelial ingrowth post SMILE.[28] Few cases of epithelial ingrowth after SMILE have been reported in the literature.[28,29]

They are usually treated with irrigation of the interface and removal of the epithelial ingrowth using a blunt spatula and micro vitreoretinal forceps followed by suturing of the incision.[29] A case of recalcitrant epithelial ingrowth which did not respond to the routine management was treated with hydrogel ocular sealant after epithelial scraping.[28] This hydrogel sealant, to avoid epithelial ingrowth post-LASIK had been described earlier. Postoperatively, topical steroids and antibiotics should be prescribed.



Epithelial ingrowth Post SMILE

Miscellaneous

Interface fluid syndrome/shifting ectasia: This is a rare complication post SMILE. Bansal *et al.*, [30] reported a case of interface fluid collection after SMILE. There was shifting ectasia (steepening) which was the diagnostic sign for fluid collection. Topical hypertonic saline could be used to treat this condition.

Interface debris/foreign body: Variable incidence of interface debris has been reported in the literature. In a large retrospective study by Wang *et al*.[31] the incidence was found to be 0.30% among 6373 eyes. It is usually identified postoperatively on slit-lamp examination and should be carefully differentiated from an inflammatory or infectious reaction. The debris could be talc from gloves, fibers from sponges used to dry the ocular surface, metallic particles from instruments, meibomian gland secretion, and eyelash. Most debris are biodegradable and do not induce any inflammation; hence, can be observed. However, in case it involves the central visual axis or is suspected to cause inflammation, it is managed by irrigation of interface. DLK and irregular astigmatism are complications reported following interface debris.

Prevention: Proper draping of the eyes to keep the eyelashes away. Meibomian gland secretions should be washed away from the surgical site. Using powder-free gloves, non-fragmenting sponges, proper instruments, and fibrocellulose ring (Chayet ring) could also help prevent any debris during the procedure.

Punctate epithelial erosions: In a retrospective study by Wang *et al*.[31] the incidence was found to be 0.39% among 6373 eyes. This could be due to the associated dry eye. This could be treated with lubricating eye drops prophylactic antibiotics and mild potent steroids if required.

Bowman's Membrane microdistortions: Bowman's membrane (BM) microdistortions were observed by OCT after SMILE. These microdistortions were common with SMILE rather than FS-LASIK.[32] They were more common in the inferior quadrant on the 1st day but there was no difference in the long-term follow-up. These distortions were related to increase in lenticule thickness or refractive error correction, however, they had no significant impact on long-term visual outcomes.[33] Luo *et al*.[34] found that eyes with >-6D had more microdistortions than those with -3 to -6D (65% vs 30.8%). In a study by Shetty *et al*.[35] intraoperative cap repositioning was found to reduce the extent of BM microdistortions.

Endothelial effects: Dissection plane of SMILE in the cornea is closer to the corneal endothelium than LASIK and the suction duration during SMILE is twice compared to that of LASIK. Because of the above reasons, there could be a possible endothelial damage post SMILE, but a study by Zhang *et al*.[36] found no difference in short- and long-term effects on endothelial cells.

Altered corneal biomechanics: Biomechanical property of cornea is majorly important to be considered to reduce the risk of postoperative ectasia. This could lead to underestimation of intraocular pressure in the postoperative period.[37] Many studies in the literature compared the biomechanical property of LASIK versus SMILE using Ocular Response Analyzer (ORA) and Corvis ST. Using ORA, few studies have found that there was a larger reduction in corneal hysteresis (CH) and corneal resistance factor (CRF) post LASIK than SMILE,[30] especially in the early postoperative period. Various studies concluded CRF was significantly affected after LASIK compared to SMILE[38,39,40] whereas few reported no differences. [41,42]

Few studies reported a comparable biomechanical response after LASIK and SMILE using Corvis ST, however, Osman *et al*.[43] found significantly less reduction in A1 (first applanation), A2 (second applanation), highest concavity time (HC), time after SMILE compared to LASIK. Pederson *et al*.[41] concluded that after adjustment for postoperative intraocular pressure, central corneal thickness and age, only HC time was significantly shorter in LASIK than SMILE which suggests LASIK corneas reached the highest concavity earlier (more compliant).

In a study by Kanellopoulos *et al*.[44] the tensile strength reduction measured using extensiometry was found to be comparable between LASIK and SMILE in higher myopic corrections but less strength reduction in LASIK than SMILE for the low myopic group. This could be explained as SMILE requires removal of more tissue than ablated in LASIK to reach the same correction.

Vision-Related changes

Various vision-related changes are part of the outcome of any refractive procedure. These includes residual refractive error or induction of residual error due to regression, change in contrast sensitivity (CS), and induction of HOA. These complications would affect the final visual quality of the patient.

Refractive error

In previous studies, LASIK was found superior to SMILE in terms of all visual parameters. Recent studies show comparable outcomes between the two procedures in terms of safety, efficacy, and predictability but the recovery in SMILE is prolonged compared to LASIK.

In a meta-analysis by Zhang *et al*.[45] both SMILE and FS-LASIK were comparable in terms of safety and efficacy. In a study by Ganesh *et al*. 3-month refractive accuracy was found to be better following SMILE compared to LASIK. Qin *et al*.[46] reported that the visual outcomes showed similar results following SMILE for myopic correction despite the magnitude of refractive error (>-10 D and ≤-10 D). Refractive outcomes showed slightly under-correction in higher myopic eyes. Shetty *et al*.[47] concluded that the eyes which underwent SMILE tend to be under-corrected compared to LASIK, and this under-correction was greater when the magnitude of preoperative cylinder exceeded 0.75D. Any cyclotorsion during the treatment could result in a shift in the treatment axis, resulting in refractive error and HOA. A simple technique for cyclotorsion compensation in SMILE surgery using an image-guided system has been described by Kose *et al*.[48]

Induction of higher-order aberrations

HOA in the postoperative period could compromise the visual quality leading to symptoms like glare, haloes, monocular diplopia, and reduced CS.

There are various studies which showed an increase in the HOA post SMILE. Coma and spherical aberration were found to be consistently affected. Induction of coma is associated with the magnitude of decentration and spherical aberration was associated with the magnitude of the dioptric correction. Large pupil diameter and small Optic zone (OZ) could result in blur circles which, in turn, could result in a poor quality of vision.

Chan *et al*.[49] found out that the anterior corneal astigmatism affected the treatment centration in SMILE but not in LASIK which lead to induction of coma and total HOA without affecting the lower order aberrations. Xia *et al*.[50] compared HOA between pre and post SMILE and concluded that the total HOA and vertical coma increased significantly, whereas, no significant differences were found in trefoil and spherical aberration. Jin *et al*.[51] found there was an increase in total HOA, horizontal coma, spherical aberration, oblique quadrafoil, and vertical secondary astigmatism post SMILE. Spherical aberration increase was higher in the high myopic group compared to those with mild-moderate myopia. In a study by Ji *et al*.[52] SMILE using femtosecond energy of less than 115 nJ facilitates better visual acuity with less induction of corneal aberrations in the early postoperative period.

Alteration in contrast sensitivity

CS helps in better assessment of patient satisfaction in terms of quality of vision subjectively rather than just a purely objective measurement of HOA. CS may be transiently affected in the initial postoperative period without any significant changes in the long-term follow-ups. Studies have shown that neither the mesopic nor the photopic CS showed any significant changes at 1-year follow-up.[53]

Regression

Blum *et al*.[54] evaluated the 10-year results of SMILE for myopia and myopic astigmatism. At 10 years postoperatively, there was no significant change from the 6-month results. Mean spherical equivalent was -0.35 ± 0.66 D which was close to the target refraction. Sixteen of the 56 eyes (29%) had gained one to two Snellen lines. There was no loss of two or more lines in the long term. Regression was -0.35 ± 0.66 D over the 10 years.

Management of residual refractive error

Retreatment after SMILE is required if there is any overcorrection, under correction, or optical regression. The incidence of retreatment following SMILE ranges from 1 to 4%. Major risk factors include high refractive error (>6.0 D), high astigmatism (>3D), suction loss, and older age (>35 years). There are various ways of correcting the residual error which includes surface ablation (PRK), LASIK, cap-flap conversion procedure (CIRCLE), and secondary SMILE procedure. PRK, though a simpler procedure, would result in postoperative haze. If the initial cap is thick, then a thin flap LASIK could be considered. However, this could result in flap buttonholes if ultrathin flaps are created. CIRCLE uses Visumax femtosecond laser to make a side cut which converts SMILE cap into LASIK flap. Riau *et al*.[55] found that flap created using pattern A and D resulted in a smooth and undisrupted stromal bed. CIRCLE resulted in more inflammatory and apoptotic changes than secondary SMILE; however, this procedure has been found to be safe and effective with better visual outcome than PRK. Secondary SMILE could be performed by creation of another pocket anterior or posterior to the original plane. Theoretically, of all the retreatment options, this procedure maintains the biomechanical stability of the cornea.

CONCLUSION

After 7-10 years of clinical practice with SMILE and more than one million procedures performed worldwide, the incidence and impact of SMILE complications have been reported in a number of publications in order to better understand and anticipate what might go wrong.

Due to the greater technical skill set required, special care should be taken during the learning curve period when most complications tend to occur. It is important to emphasize that if well managed, most complications do not affect the final visual outcome.

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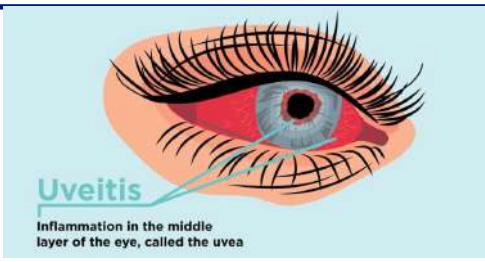
Review Article

Janus Kinase (Jak) Inhibitors in Uveitis



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Abstract

Cytokines are signalling proteins that have major roles in the pathogenesis of immunological and inflammatory systemic disorders and can be targeted therapeutically. Janus Kinase (JAK) inhibitors are targeted small-molecule that inhibit JAK proteins which are essential for signalling mediators that act downstream of pro-inflammatory cytokines. These molecules have gained popularity as effective treatments for autoimmune diseases, particularly in resistant and refractory cases. This group of drugs has been approved by Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. Topical JAK inhibitors has also been introduced that provide an attractive treatment option for patients with certain dermatological conditions. There are numerous case reports on these drugs being used to treat refractory autoimmune uveitis and scleritis.

Introduction

Autoimmune or non-infectious uveitis can occur in isolation or as a result of underlying systemic autoimmune diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis (JIA), ankylosing spondylitis, systemic lupus erythematosus, Behçet's syndrome, and relapsing polychondritis. The treatment of non-infectious uveitis involves a step-wise approach using topical or systemic corticosteroids and immunosuppressive agents, tailored to the underlying cause and response to treatment. Corticosteroids have long been the mainstay for uveitis treatment, but in some cases, they may not achieve complete remission of inflammation or have long-term use limitations due to ocular and systemic side effects. In such scenarios, immunosuppressive agents are often considered. However, there are instances where neither corticosteroids nor immunosuppressive agents provide adequate response. Therefore, the search for an ideal immunomodulatory agent for effective and long-term control of uveitis continues. The utilization of immunomodulatory agents in ophthalmology, specifically for uveitis, has historically been influenced by the progress made in rheumatology, transplant medicine, and oncology. Since Philip S. Hench and colleagues first employed corticosteroids for the treatment of rheumatoid arthritis in 1949, clinicians have looked to these related fields for insights. Medications like methotrexate, cytotoxic agents and azathioprine, originally developed and used by the rheumatologists and experts in transplant medicine and oncology, have been adapted for use in uveitis based on their experiences.

Recent advances in our understanding of immune receptors and signalling pathways have led to the development of small molecules targeting key nodes in these pathways. The Janus kinase (JAK) pathway plays a crucial role in regulating inflammatory cells, cytokine production, and proinflammatory signal transmission. Dysregulation of the JAK pathway is associated with various inflammatory and autoimmune disorders, making JAK inhibitors a potential avenue for reducing inflammation. However, the use of JAK inhibitors in clinical therapy is relatively recent, particularly for autoimmune diseases involving ocular inflammation. There are limited reports on the use of Tofacitinib, one such JAK inhibitor, in refractory uveitis and scleritis. This write-up focuses on the use of JAK inhibitors in patients with non-infectious uveitis, summarizing their therapeutic efficacy and tolerability.

Mechanism of action:

JAK inhibitors are orally available small molecules that enter cell cytoplasm and directly regulate intracellular signalling pathways by inhibition of kinases or phosphodiesterases. JAKs belong to the group of tyrosine-kinase family. Binding of cytokines and growth factors to their receptors results in the phosphorylation of JAK-associated receptors which in turn, phosphorylates intracellular components of the receptors, enabling the recruitment of transcription factors of the signal transducer and activator of transcription (STAT) family. Activated STAT proteins translocate to the nucleus and induce transcription. There are four JAK isoforms (JAK1, JAK2, JAK3, and

tyrosine kinase 2 (TYK2)) and seven STAT family members were identified. Individual JAKs are used based on their selective interactions with specific cytokine receptors.

The impact on specific inflammatory responses depends on each JAK inhibitor's selectivity. Five JAK inhibitors namely tofacitinib, baricitinib, peficitinib, upadacitinib and filgotinib are currently approved for the treatment of RA. The pharmacokinetics of these drugs has been studied in different populations that influence the safety profile of a particular drug. Tofacitinib is rapidly absorbed, with peak plasma concentrations reached within 0.5–1 h after administration. The oral bioavailability of tofacitinib is 74% and approximately 40% of tofacitinib is bound to plasma proteins (largely albumin). Clearance of tofacitinib is via hepatic metabolism (70%) and renal excretion (30%). Tofacitinib is rapidly eliminated with a half-life of approximately 3 hours. The other well-known drug Baricitinib was rapidly absorbed attaining maximum plasma concentration within 1.5 hours with a half-life ($t_{1/2}$) of about 8 hours. Baricitinib is mainly excreted in the urine (~75%) in an unchanged form.

Application in uveitis:

JIA-associated uveitis:

JIA-associated uveitis is the most common rheumatological disorder with ocular involvement in paediatric populations.[6] The most common form of presentation is chronic low-grade anterior uveitis resulting in significant ocular morbidity secondary to complications including band keratopathy, maculopathy, glaucoma, and cataract. Conventional treatment in JIA-associated uveitis includes primary treatment with oral steroids and methotrexate followed by biologics in case of failure to primary treatment. Adalimumab in combination with methotrexate is found to be an effective medication for the treatment of JIA-associated uveitis, as demonstrated by the SYCAMORE and ADJUVITE randomized controlled trials. [7,8] However, for the pediatric population in developing countries, it is challenging, because of its costs and injectable formulations. There are few reports of JAK inhibitors in the treatment of JIA-associated uveitis proving its efficacy in complete resolution of uveitis which was refractory to conventional immunomodulatory therapy with no unwanted side effects. [9,10,11] Baricitinib as a potential novel therapy for the management of JIA-associated uveitis was demonstrated in the JUVE BRIGHT trial.[12] The cost-effectiveness, oral formulation, and efficacy in polyarticular JIA have prompted increased usage of this drug in developing countries in recent times.

Rheumatoid arthritis (RA) associated uveitis:

RA represents a major cause of non-infectious autoimmune scleritis and keratitis but it is a rare cause of uveitis. The anterior segment is more commonly affected than the posterior segment in RA-related ocular complications. The Th1 and Th17 cell subsets require STAT pathways and may be the etiological agents responsible for uveitis and scleritis in these disorders.[13] Several case reports indicated the anti-inflammatory effects of JAK inhibitors on the ocular and systemic inflammation caused by rheumatoid arthritis.

Other autoimmune-related ocular inflammation:

Ankylosing spondylitis presents with acute anterior uveitis in 20 to 30 % of patients and may be the most common extra-articular manifestation. Ophthalmic manifestations occur in 10% of patients with psoriasis and 31% of patients with psoriatic arthritis (PsA). Iritis is found to be seen in 7.1% of patients with psoriatic arthritis. HLA-B27 status analyses revealed a significant association between JAK2 and AAU.[14] JAK inhibitors have emerged as a new therapeutic class of drug for HLA b 27-associated diseases. Tofacitinib and baricitinib are commonly used first-generation JAK inhibitors. Upadacitinib (Rinvoq) is a specific, newer Janus kinase inhibitor recently approved for the treatment of inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, atopic dermatitis, and psoriatic arthritis have been found efficacious in HLA b 27 associated refractory intermediate uveitis.[15]

The role of T helper cells producing Th1 cytokines including interleukin 2 (IL-2) and interferon-gamma has been implicated in chronic granulomatous choroid inflammation as in the acute phase of VKH.[16] JAK kinase inhibitors which can reduce the production of IL 2 have been proven as a useful alternative in treatment-resistant intraocular inflammation in VKH. [17]

Use of JAK inhibitors for remission of severe and refractory early-onset sarcoidosis or sporadic Blau Syndrome has also been reported.[18]

Safety profile:

As a potent immunosuppressive agent, the incidence rates of infections, including opportunistic infections, are comparable with those for biologics, with the exception of the rate of herpes zoster infections, which is slightly higher for JAK inhibitors.[19] The inhibition of JAKs may also affect the function of T and B lymphocytes and natural killer (NK) cells, resulting in decreased neutrophils and thrombocyte levels. This may result in a reduced defence mechanism, particularly against viral infections causing reactivation of the varicella-zoster virus. Therefore, chronic infectious diseases should be excluded before the start of therapy. Apart from viral hepatitis and HIV infections, latent or active tuberculosis should also be excluded. Potentially serious effects, including malignancy, major adverse cardiovascular events (MACEs), and venous thromboembolic events were also reported with JAK inhibitors. [20] Studies comparing the safety of tofacitinib and TNF inhibitors showed an association with the risk of venous thromboembolism and death in patients taking tofacitinib 10mg

twice-daily dosage, but not with 5mg twice-daily dosage. Further results also showed a higher incidence of MACEs and malignancies in patients with RA treated with either 5mg or 10mg twice-daily dosage of tofacitinib than in patients treated with a TNF inhibitor. FDA released a black box warning in September 2021 regarding the increased risk of death, MACEs, malignancies, and thrombosis with JAK inhibitors compared with TNF inhibitors. Although tofacitinib and adalimumab were compared in studies, the FDA was concerned about a JAK-inhibitor class effect and expanded the warning to include the other two JAK inhibitors, baricitinib and upadacitinib. Thus, regular monitoring during treatment should be performed for known risks including infection, cardiovascular disorders, thrombosis, and malignancy.

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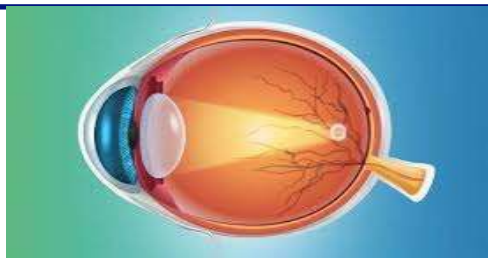
Review Article

Artificial and bio-mimetic cornea



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Corneal transplantation is highly successful in low-risk patients with corneal blindness but often fails those with high-risk indications such as recurrent or chronic inflammatory disorders, history of glaucoma and herpetic infections, and those with neovascularisation of the host bed. Moreover, the need for donor corneas greatly exceeds the supply, especially in disadvantaged countries. Therefore, artificial and bio-mimetic corneas have been investigated for patients with indications that result in keratoplasty failure. Two long-lasting keratoprostheses with different indications, the Boston type-1 keratoprostheses and osteo-odonto-keratoprostheses have been adapted to minimise complications that have arisen over time. However, both utilise either autologous tissue or an allograft cornea to increase biointegration. To step away from the need for donor material, synthetic keratoprostheses with soft skirts have been introduced to increase biointegration between the device and native tissue. The AlphaCor™, a synthetic polymer (PHEMA) hydrogel, addressed certain complications of the previous versions of keratoprostheses but resulted in stromal melting and optic deposition. Efforts are being made towards creating synthetic keratoprostheses that emulate native corneas by the inclusion of biomolecules that support enhanced biointegration of the implant while reducing stromal melting and optic deposition. The field continues to shift towards more advanced bioengineering approaches to form replacement corneas. Certain biomolecules such as collagen are being investigated to create corneal substitutes, which can be used as the basis for bio-inks in 3D corneal bioprinting. Alternatively, decellularised corneas from mammalian sources have shown potential in replicating both the corneal composition and fibril architecture

Artificial corneas can be defined as laboratory-made constructs, with or without the help of biological material but typically consisting of manmade materials, designed principally to replace the function of the native human cornea. Typically, keratoprostheses fall into this category. The benefits of artificial corneas tend to outweigh the disadvantages (Table 1), especially in difficult and high-risk cases where traditional donor cornea transplantation would have a poor outcome. Production of keratoprostheses (or KPros) is stringent in order to guarantee non-toxic, sterile products with high stability. Moreover, KPros overcome socio-cultural and policy difficulties while preventing viral invasion and immune rejection. These KPros are specialised constructs with limited swelling which results in limited water accumulation and less light scattering from the cornea. Improvement in KPro design is possible due to the continually evolving biomaterial technologies that enable functionalisation using synthetic materials or surface coating techniques. In addition, reservoir systems such as micro- or nanoparticles can be incorporated into these systems to facilitate biointegration and modulate inflammation. Furthermore, 3D fabrication methods can build a fully functionalised biosynthetic cornea with programmed spatial, optical properties and biomechanical properties which cannot be provided by a human corneal transplant.[1]

Table 1- Advantages and disadvantages of keratoprosthesis

Advantages	Disadvantages
Can restore meaningful vision in the most severe cases of corneal blindness where donor corneas fail	Uncomfortable to wear
Avoids religion, culture and policy problems	Transplantation process is complex; multiple surgeries and long-term topical medications often required
Overcomes immune rejection, immune graft risk and ocular surface disease	Limited field of view
Continuously evolving technologies	Unsatisfactory aesthetic appearance
Limited swellability therefore limited water accumulation and less light scattering	Potential for post-operative complications such as extrusion and glaucoma.

History and Development of Keratoprostheses

Transplantation, including that of corneas, was first referenced around 2000 BC by the Egyptians.[2] In 1760, the grandfather of Charles Darwin, Erasmus Darwin, first suggested the removal (trephination) of an opaque cornea and the addition of a KPro to restore vision.[3] This was followed by the first full description of a KPro by Guillaume Pellier de Quengsy in 1789 in his monograph on ophthalmology: he suggested a thin silver-rimmed convex glass disc can be used in place of an opaque cornea with the surgical instruments required for such a procedure.[4]

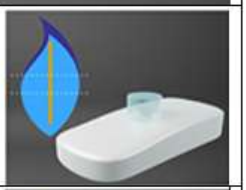
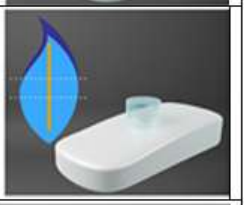
Nonetheless, there was little interest in KPros at that time. In 1853, Nussbaum manufactured a quartz crystal and implanted it into the cornea of rabbits. The first prototype was too large and was rapidly extruded. However, a smaller oblong-shaped prototype was successful in animals and was tried in human patients. These initial KPros had a high failure rate due to infection, leakage, and extrusion of the device.[5] Six years later, Heusser successfully implanted a quartz KPro into a blind girl's cornea in Switzerland, who experienced a significant improvement in vision and retained the implant for at least 6 months without complications.[6]

In 1862, Abbate made a KPro out of a glass disc surrounded by two rings assembled from natural polymers; gutta-percha and casein. The former was isolated from the exudate of trees and the latter from the precipitation of milk or cheese. The KPro implanted in cats and dogs were only retained for about a week. Although this KPro was quickly extruded, Abbate did emphasise the need for the KPros to be different from glass to allow for incorporation into the host tissue.[7,8] In the early twentieth century, Salzer implanted a quartz disc bounded by a platinum ring with prongs into four humans, with one almost lasting 3 years.[9] Much like Abbate, Salzer suggested later that the rim of the KPro should be based on materials that can be incorporated into the host cornea. He also noted that KPros could be made out of materials lighter than glass.[7]

Investigation into KPros stalled after Eduard Zirm performed the first successful bilateral keratoplasty in 1905.[10] However, the discovery of poly (methyl methacrylate) (PMMA) in WWII by Harold Ridley refocused attention on artificial corneas. PMMA splinters from crashed Perspex® canopies were found embedded in the cornea of pilots› eyes and were observed to be well-tolerated, thus providing a potential material for subsequent KPros.[5,11] To date PMMA has proven to be the material of choice, providing a stable and minimally toxic optic. Over time, a two-part "core–skirt" structure was devised for the KPro. Stone took advantage of PMMA to make perforated discs and implant them in corneal lamellae, which were retained for 3 years on average.[12,13] Using a PMMA skirt positioned retrocorneally forming the "nut," and the threaded optic making up the bolt, Cardona developed the first two-piece nut-and-bolt KPro in 1969.[14] Five years later, Dohlman introduced the collar-button model which had a front and backplate made out of PMMA.[15] Aquavella et al. performed a retrospective analysis of implanted Cardona and Dohlman devices, concluding that, although improved device design and surgical procedures reduce the severity of complications, further refinements aimed at KPro biointegration will enhance the long-term clinical outcome for patients.[16]

Several scientists took inspiration from Cardona's nut-and-bolt device but used several different materials as skirts to support biointegration into the host tissue, e.g., Proplast, Teflon, hydrogels, poly-2-hydroxyethyl methacrylate and silicone-carbon.[17-19] In this review, various soft and hard KPros and their design, outcomes and recent advances will be reviewed.

Table 2. Description of commercial Hard-Keratoprostheses with skirts based on resilient materials, and transparent optic cylinders composed of polymethyl methacrylate (PMMA).

Keratoprosthesis	KPro material	Schematic
Cardona Keratoprosthesis	Teflon(Skirt) PMMA(Optic)	
Boston keratoprosthesis (Type 1 and Type 2)	Titanium(Skirt) PMMA(Optic)	
The Osteo-odonto keratoprosthesis(OOKP)	Autologous tooth root and alveolar bone PMMA(Optic)	
The Modified Osteo-odonto keratoprosthesis(MOOKP)	Osteodental lamina surface PMMA(optic)	
Fyodorov-Zuev Keratoprosthesis	Titanium (skirt) PMMA(optic)	

Hard Keratoprostheses

Hard keratoprostheses include those made from PMMA as it is a rigid polymer that needs a resilient skirt material to function as a successful implant (Table 2). Moreover, the bonding between PMMA and its skirt must withstand intraocular pressure, and deformations caused by movement of the eye and blinking. Therefore, skirts made from softer materials like Dacron, Teflon and Proplast were extruded.[17-19] KPro models like the Boston KPro and osteo-odonto-keratoprosthesis (OOKP), based on harder skirts have been successful in wet blinking eyes and dry or non-blinking eyes, respectively. Although other hard KPros exist, such as the Fyodorov-Zuev KPro,[20,21] this review will focus on the Boston KPro and OOKP as there is an abundance of literature to demonstrate their efficacy in restoring sight, as well as a multitude of studies documenting improvements to their design and/or surgical procedure for enhancing clinical outcomes.

Boston Keratoprosthesis

As mentioned previously, the collar-button model called Dohlman–Doane KPro was a predecessor to the Boston KPro.[15] In 1992, the type-I Boston KPro was approved by FDA. Since then it has become the most implanted KPro with over 15,000 devices implanted worldwide. The type II Boston KPro is less popular than its counterpart and is indicated for patients with severe ocular diseases, for example, Stevens-Johnson syndrome (SJS) and mucous membrane pemphigoid (MMP).[22] The main difference consists in the anterior extension which allows implantation through surgically closed eyelids.[23]

Design

The Boston KPro consists of a PMMA front plate with a central diameter between 3.5 and 3.7 mm and a backplate made of PMMA or titanium. A titanium locking ring was also added to secure the backplate.[24] Donor corneal tissue acts as a carrier and is placed between the front and backplate. It was found that both frozen and fresh donor corneas could be used for Boston KPro Type 1.[25] It is thus important to consider that these KPros do not eliminate the need for donor human corneas but work in tandem with donor corneas.

Outcomes

The majority of short-term outcomes of the Boston KPro type-I are favourable. Retention rates are around 90% with post-operative visual acuity (VA) of 20/100 or better in 67% of patients at 6 months and 75% at 1 year.[26] However, there is inadequate medium and long-term follow-up data following Boston KPro surgery. This is particularly true for long-term (>5 years) outcomes; both retention rates and complication data are scarce.[27] It is important to know the medium- and long-term outcomes as it gives a realistic perspective on the real performance of KPros.

The majority of patients improve their VA following implantation. A meta-analysis of 406 articles found that 60% of patients had 6/60 vision or better at 2 years and 51% at 5 years.[27] Kanu et al. found 75 and 66.7% of patients had improved VA at 5 and 10 years, respectively.[28] Often, VA improves the longer the KPro has been implanted. Aravena et al.[29] found at 5 years 57% of patients had a corrected distance visual acuity (CDVA) ≥20/200 while at 8 years 82% of patients had a CDVA ≥20/200, while 5% of patients had a CDVA ≥20/200 pre-operatively. In contrast, Szigiato et al.[30] found only 36.5% of patients had a VA ≥20/200 post-operatively with 2.4% having a VA ≥20/200 pre-operatively. Szigaiato's study had more patients than Aravena's however (58 vs. 85). Interestingly, Driver et al. investigated 231 eyes: 67 primary KPro procedures and 164 after a failed keratoplasty. They found 78–87% of primary KPro procedures had a CDVA of ≥20/200 after 6 years. In comparison, 56–67% of those given the Boston KPro after failed keratoplasty had a CDVA of ≥20/200 at 6 years.[31]

Those with inflammatory diseases like SJS have a high probability of gaining a CDVA of ≥20/200. One study found that 100% of patients with SJS had a CDVA of ≥20/200 after a year.[32] Similarly, Brown et al. found 100% of patients with the herpes simplex virus (HSV) had a best-corrected visual acuity (BCVA) ≥20/200. However, only one patient out of four with herpes zoster virus (HZV) had a BCVA ≥20/200.[33] Interestingly, a study investigating patients with chemical or thermal injuries found that after a follow-up of 40.7 months on average, the median best-corrected visual acuity was 20/60.[34]

In general, retention rates for the Boston KPro have been quite high (between 74 and 100%) at the last follow-up.[31] The aforementioned meta-analysis review found accumulated retention rates of 88 and 74% at 2 and 5 years, respectively.[25] However, conditions that cause cicatrisation like SJS or MMP can significantly decrease retention rates.[32,33] Alexander et al.[32] found an increase in post-operative complications for those with SJS which resulted in decreased retention rates. Brown et al. found a similar disparity between the HSV and HZV groups in retention rates as seen with the BCVA. The HSV group had a retention rate of 100% whereas the HZV had a retention rate of 25% after around 50 months.[33] Phillips et al.[34] found that patients with chemical or thermal injuries, had an initial retention rate of 77.7% and the remaining KPros were successfully replaced. They did find that for those with severely damaged eyes, the rate of success can be increased by preparing the ocular surface before implantation with limbal stem cell transplants to reduce sterile ulceration.

Post-operative Complications and Advances

Adjustments in the design of the KPro were introduced to decrease post-operative complications such as the addition of holes to the backplate of the device. The backplate was originally a solid 8 mm PMMA plate which led to high keratolysis and decreased nutritional flow. Keratolysis is defined as the "thinning of peripheral corneal

stroma with an overlying epithelial defect due to autoimmune-induced inflammation".[35] Currently, the backplate is 8.5 mm with 16 holes for nutritional support. This led to a decrease in keratolysis from 50 to 10% following transplantation.[24] Wearing a large diameter soft or contour contact lens and long-term use of topical antibiotics also decreased sterile keratolysis.[8] In 2014, a titanium backplate was introduced as an alternative to PMMA which clicks into the stem without the need for a locking ring, thus easier to assemble. Titanium is well-tolerated by the surrounding tissue and is highly resistant to corrosion and is both light and strong. As it is not magnetic, patients can undergo magnetic resonance imaging.[24] Moreover, the titanium backplate can be coloured blue or brown by electrochemical anodisation to help with the cosmetic appeal of the device.[36]

There are conflicting reports about whether titanium can cause a reduction in retroprosthetic membrane (RPM) formation, which occurs when fibrovascular tissue grows behind the device. Up to 65% of patients with a Boston KPro form an RPM.[37] A study by Todani et al.[38] investigated the potential for RPM formation in 55 eyes with PMMA backplates and 23 with titanium backplates: 41.8% of patients with PMMA backplates developed RPM compared to only 13% for patients with titanium backplates at 6 months post-implantation. However, in the group of patients with PMMA backplates, 39 had threaded PMMA backplates which may, in itself, increase RPM formation (discussed below).[38] In contrast, a study by Talati et al.[39] compared 20 patients with a titanium backplate and 20 with a PMMA backplate with an average follow-up duration of 28.1 or 53.7 months, respectively: 45% of patients with a PMMA backplate developed RPM and 55% of those with a titanium backplate developed RPM. It was concluded that neither material was superior in reducing RPM formation.

In 2007, a newer PMMA stem was produced without screw threads. It was aimed at avoiding damage to the corneal graft associated with the screwing action during surgery and thus possibly reduce RPM formation.[40] This newer stem was both easier to use and less expensive to produce as the device was produced by moulding as opposed to machine-made.[24] Al Arfaj and Hantera investigated four eyes that underwent Boston type 1 threadless KPro implantation and found no RPM developed at the time of follow-up (i.e., up to 11 months).[41] This is consistent with the observations made by Todani et al. at 6 months post-surgery: 46.1% of eyes implanted with threaded PMMA backplates resulted in RPM, while RPM occurred only in 31.2% of cases implanted with threadless PMMA backplates.[38] Thus, combining a PMMA backplate with a threadless design may reduce the risk for RPM formation.[38]

One of the difficulties encountered by many hard KPros is the failure of the corneal graft to adhere to the surface of the PMMA stem. Although PMMA is minimally toxic to corneal stromal cells, poor biointegration between the PMMA and the corneal stroma can lead to corneal melting and graft detachment. Weak interfacial adhesion can create spaces into which bacteria or inflammatory cells can infiltrate.[42] In recent years it has been demonstrated that contact between cells and titanium results in increased growth of corneal limbus epithelial cells, alongside a decrease in cell death, thereby providing a superior surface for adhesion.[43,44] Titanium with smooth surface topography was found to enhance cell adhesion and proliferation while roughened titanium can reduce vision-impairing light reflectivity.[43]

Several novel techniques have been introduced recently to increase PMMA and corneal tissue adhesion. Sharifi et al.[45] used magnetron sputtering of titanium onto the Boston KPro PMMA stem to show that titanium sputtering can cause an increase in cell adhesion, with an increase in cell growth and collagen deposition, resulting in a more normal corneal stromal cell phenotype. For these reasons, titanium sputtering may improve PMMA-corneal tissue adherence, therefore improving long-term outcomes. Coating the titanium of the KPro with hydroxyapatite (HAp), a constituent from bone and teeth has also resulted in enhanced tissue adherence in rabbit corneas. HAp nanoparticles can also be trapped and immobilised on the PMMA surface which results in human corneal fibroblasts adhering and proliferating onto the coated PMMA.[42] Similarly, calcium phosphate (CaP) was used to coat PMMA sheets that had dopamine present to induce CaP deposition.[42] This resulted in better adhesion, but delamination occurred rather easily. Furthermore, L-3,4-Dihydroxyphenylalanine (L-DOPA) can be covalently bonded to the PMMA surface to support enhanced cellular adhesion, proliferation, and migration, thus improving the compatibility of PMMA.[48]

Another post-operative complication that may lead to possible changes in the Boston KPro design is glaucoma. Nonpassopon et al. gathered information from several Boston KPro clinical trials and found 20.2–40% of eyes had an increase in intraocular pressure (IOP), 14–36% developed *de-novo* glaucoma, and 13–33% had progression of previously present glaucoma.[24] These results are primarily due to the device being unable to detect elevated IOP early with standard tonometry techniques due to the rigidity of the KPro device.[49] Therefore, a potential solution has been introduced by integrating a micro-optomechanical pressure sensor into the Boston KPro device. Hui et al. investigated a fibre-optic Fabry-Perot pressure sensor for its cost-effectiveness and industrial quality control.[49] The sensor integrated onto the KPro was stable over long periods and successfully measured IOP. However, pressure sensors implanted in rabbit eyes showed an increase of IOP following RPM formation. It was concluded that RPM formation shortened the optical cavity and caused an artificial IOP increase.[50] Another alternative is to use three-dimensional (3D) spectral-domain optical coherence tomography (OCT)

to enhance the evaluation of KPro patients with glaucoma.[49]

Cost

In developing countries, the cost of the Boston KPro device can be prohibitive. In 2011, the Aurolab in Madurai, India designed a low-cost version of the Boston KPro, the auroKPro. Basu et al.[51] compared both KPros and found them to be similar in retention rates (70.5 vs. 62.5% for Boston Kpro and auroKPro, respectively) and post-operative complications, but more extrusions were observed with the auroKPro. In 2012, the Boston KPro team also produced a less expensive KPro, the Lucia KPro, which was approved by the FDA in 2019.[52,53] This device had a titanium backplate which was 7.5 mm in diameter with radial petaloid-shaped holes. It was anodised to a brown colour giving a more acceptable appearance to patients. Although efforts are being made towards reducing device manufacturing cost while maintaining ease of implantation, it is important to note that there are many additional costs associated with any corneal procedure, including access to additional clinical resources, and continued post-operative care, and it is ultimately these factors that create a cost-prohibitive option for many patients requiring corneal replacement .[51,54,56]

Osteo-Odonto-Keratoprosthesis

First introduced by Strampelli in 1963, OOKP is one of the longest-lasting KPros available.[57] Strampelli used a donor root tooth and alveolar bone to support the PMMA optical cylinder.[58] This was further improved upon by Falcinelli in 1998 by adding certain modifications such as using a larger biconvex optic and performing cryo-extraction of the lens. This led to the model which is now known as the modified osteo-odonto-keratoprosthesis (MOOKP).[59] The MOOKP is a device that uses the alveo-dental lamina of a single tooth (usually canine) to support the optical cylinder in its centre. This is covered with a resistant membrane called the buccal mucosa (BM) to give protection and nourishment. It is indicated for patients with bilateral corneal blindness with severe visual loss (<6/60) and dry eye or lid damage, as well as poor keratoplasty prognosis. Those with SJS, MMP, chemical or thermal injury view the OOKP as a life-changing surgery,[57] and over the last 40 years, centre-based studies across Europe and India have demonstrated excellent anatomical retention of the MOOKP and improvements in visual acuity for the almost 500 patients studied.[54]

MOOKP Device Preparation and Implantation

Creating the MOOKP device requires a complex surgical technique and patient counselling, and can only be performed by experienced surgeons. The technique can be separated into two stages: first preparing the bulbar anterior surface and the osteo-odonto-acrylic lamina, and secondly implanting the lamina OOKP into the eye.[59,60]

For those with normal conjunctiva, a 360-degree limbal peritomy is performed, followed by a superficial keratectomy to remove the epithelium and any scar tissue present . Oral mucosa is harvested from below the parotid duct and sutured in place, covering the cornea and sclera.[59,60] To prepare the osteo-odonto-acrylic lamina, a monoradicular tooth and surrounding alveolar bone are removed. Through constant irrigation with a balanced salt solution and with the aid of a dental flywheel, the tooth and alveolar bone are shaped into a 3 mm thick rectangular lamella. A hole is then drilled perpendicularly into the lamina to accommodate an optical cylinder. The PMMA optical cylinder is made up of an anterior stem that ranges in diameter from 3.5 to 4 mm and a posterior section ranging from 4.5 to 5.25 mm in width. The anterior stem protrudes 2–3 mm beyond the alveolar side while the posterior projects through the anterior chamber.[60] The completed osteo-odonto-acrylic lamina is then inserted below the lower orbital rim under the skin for ~3 months.[59]

In stage 2 the lamina is retrieved from the lower orbital rim and excess soft tissue is removed leaving new vascularisation intact. The mucosal graft is partially detached from top to bottom and the Flieringa ring is placed on the sclera to facilitate attachment of the lamina. A full-thickness disc is made in the cornea to facilitate the optical cylinder of the KPro. A 360-degree iridectomy is performed to remove the iris. This is followed by cryo-extraction of the lens. The lamina is sutured to the sclera and remaining cornea and is covered by the flap of the oral mucosa. Generally, a cosmetic prosthesis is applied which covers the ocular surface, 1 month after surgery.[59] Topical broad-spectrum antibiotics must be applied every night for the patient's lifetime.60

For those with no suitable teeth, a tooth allograft from a related or non-related donor can be used or tibial bone can be used. However, functional survival rates of KPros using tibial bone can be as low as 19% after 10 years.[61] Retention of bone strength is reliant on physical stress and so inactivity leads to resorption of the laminae.[62] Furthermore, a KPro has been developed for patients with unsuitable teeth for OOKP and no healthy eyelid skin for the Boston KPro type II called the "Lux" KPro.[63] It is made up of a PMMA optic, titanium backplate, and a titanium sleeve but it requires a corneal graft. Like the MOOKP, the "Lux" KPro is implanted through, and protected by, a mucous membrane graft.[63]

Outcomes

The VA of patients following OOKP surgery can be as good as 6/14. In a systematic review of eight different case studies, Tan et al. found VAs of ≥6/18 in 52% of patients after OOKP.[64] Similarly, Liu et al. recorded a VA of ≥6/12 in 53% of all OOKP patients.[65] In the same study, 78% of patients achieved a VA of ≥6/60. Iyer et al. recorded 66% of all patients had a VA ≥20/60.[66] However, complications involving the mucosa, retina, lamina and IOP can occur which affect visual outcomes.

Long- and medium-term anatomical retention rates for OOKP devices are high throughout several studies. Iyer et al. found 96% retention in 50 eyes, with a mean follow-up of 15.4 months. Liu et al. reported 72% of patients retained their OOKP after a mean follow-up of 3.9 years.[65] De la Paz et al. found 86% of patients with a chemical injury retained their OOKP while only 65% was retained when the Boston KPro type-I was used.[67]

Post-operative Complications

A common cause of OOKP retention failure is resorption. Although there must be a balance between resorption and reformation to preserve the lamina, the osteo-odonto-acrylic lamina is prone to excessive resorption. In a study undertaken by Liu et al., 19% of patients had laminar resorption, resulting in retention failure.[65] However, laminar resorption rates are most likely underreported as it tends to progress slowly and is difficult to detect as the lamella resides underneath the oral mucosal membrane graft. Laminar resorption can result in thinning of the lamina which may cause tilting of the optical cylinder, altered refraction, leaking, and endophthalmitis.[60]

Advances in imaging have resulted in earlier detection of laminar resorption. Avadhanam et al.[68] found that 40% of all cases of laminar resorption were detected in the first year of follow-up and 66% of cases were found within 3 years of OOKP surgery. They also discovered that laminar thickness did not affect the onset or progression of resorption.[68] Multi-detector computerised tomography (MDCT or CT) is widely employed when investigating laminar resorption. Along with imaging, clinical palpation can be carried out by an experienced surgeon to detect resorption early. It seems the best way forward is to implement both methods in the long-term. However, frequent CT scanning is not indicated for the detection of laminar resorption.[69]

An autoclavable μ-milling device has been introduced to contour and drill the lamina to increase its stability.[70] Iyer et al. introduced a new technique that augments the canine tooth using a mandibular bone graft to boost the labial side of the lamina and therefore decrease laminar resorption.[71] In a separate study, Iyer et al. administered a bone morphogenetic protein to 11 eyes with laminar resorption and yet to undergo additional intervention.[72] Bone morphogenetic proteins were administered to inhibit further resorption and promote bone generation. However, three eyes had further resorption after protein administration.[72] There is uncertainty around the ability of bisphosphonate drugs such as alendronate to decelerate laminar resorption. Several remedies are available that maintain mucosal health and in addition, smoking cessation can have an increased benefit.[69]

To decrease laminar resorption, and simplify the surgical procedure, decrease costs, and avoid oral trauma, skirts made of synthetic materials similar to the osteo-odonto-acrylic lamina have been introduced. Avadhanam et al. incorporated nano-crystalline hydroxyapatite (nHAp) coated poly (lactic-co-glycolic acid) PLGA microspheres with a high strength interpenetrating network (IPN) hydrogel to mimic the odonto-acrylic lamina microenvironment.[73] They also added poly(ethylene glycol) diacrylate (PEGDA) polymers and agarose to improve the mechanical strength of the hydrogels. This study suggested the PEGDA-agarose based IPN can be used in the future to replace the OOKP lamina.[73]

There is a strong correlation between laminar resorption and endophthalmitis, a condition that is caused by a bacterial or fungal infection of the vitreous and/or aqueous humour.[73] A recent study found a 9% incidence rate of endophthalmitis in eyes that had undergone OOKP surgery.[74] Falcinelli et al. identified endophthalmitis in 4 out of 181 eyes (2%) following OOKP at a mean 12 years follow-up. Poor pre-operative dental hygiene was reported in these cases.[59]

Two common causes of the slowdown in the rate of VA recovery are the presence of air bubbles in the vitreous humour or vitreous haemorrhage. Vitreous haemorrhage was the most common post-operative complication in the systematic review reported by Tan et al., with up to 52% experiencing haemorrhage.[64] However, vitreous haemorrhage, and also the problem of choroidal detachment, tend to resolve themselves soon after surgery.

Glaucoma is the main cause of a decrease in VA for those with an OOKP. Tan et al. stated glaucoma rates ranged from 7 to 47% between different studies.[64] However, pre-existing glaucoma can be hard to detect pre-operatively.[60] Generally, those with glaucoma undergo a trabeculectomy to relieve IOP; however, those with an OOKP will not benefit from this procedure. Kumar et al. found visual field testing and optic disc assessment with optic disc photographs may be used for the monitoring of eyes for glaucoma; but currently, drainage devices are the best method for glaucoma management in those with OOKPs.[75,76] Interestingly, a device called the Ahmed glaucoma drainage device was found to stabilise IOP in three-quarters of OOKP eyes with glaucoma if placed before the mucosal graft.[76]

Soft Keratoprostheses

Soft skirt materials have been adopted in recent years to increase biointegration based on a variety of synthetic polymers with or without biofunctionalisation with macromolecules (Table 3). Several skirt and optic type KPros have been brought to clinical trials over the decades, including the Keraklear,[77] the MIRO® Cornea,[78] the Legeais BioKpro III [79] and the Korea Seoul-type Kpro.[80,81] However, for the purpose of this review, we will focus on the AlphaCor™ keratoprosthesis, the first soft KPro to obtain FDA approval almost 20 years ago, while mentioning the two newest soft synthetic KPros that have begun clinical trials in the last year (CorNeat, and EndoArt).

Table 3. Description of commercial Soft-Keratoprostheses with skirts based on soft materials.

Keratoprosthesis	Material	schematic
Keraklear artificial cornea	PMMA+(Polyethylene Glycol) PEG	
MIRO® CORNEA UR keratoprosthesis	Hydrophobic acrylic polymer + Genetically engineered fibronectin	
Legeais BioKpro III	Fluorocarbon poly(tetrafluoroethylene)(PTFE)	
Alphacor keratoprosthesis	Polyhydroxyethyl metha acrylate) PHEMA	
Korea Seoul-type keratoprosthesis	PMMA+PEG	

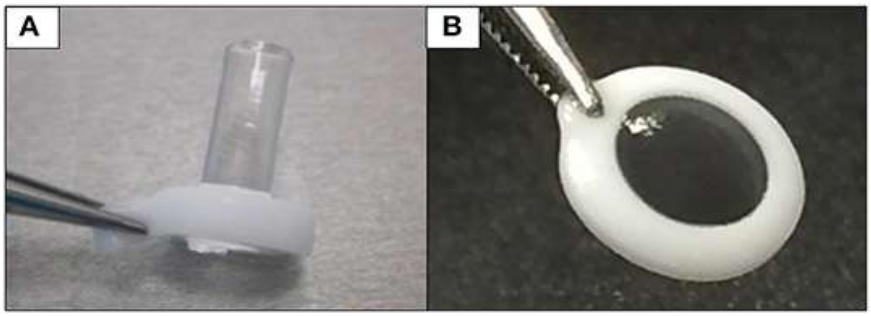
AlphaCor™ Keratoprosthesis

Chirila et al. at the Lions Eye Institute and the University of Western Australia in Perth aimed to produce an "ideal" KPro. They used cross-linked poly (2-hydroxyethyl methacrylate) (PHEMA), to form both the optical and skirt components.[82] The hydrophilic PHEMA forms a hydrogel by polymerisation. The skirt and optic are chemically identical with the exception that the skirt has higher water content, meaning it has larger pores to allow for biointegration. The optic and skirt are fused by an IPN to prevent leakage or down growth.[83,84] Formerly known as the Chirila KPro, the AlphaCor™ KPro (Figure 1) was approved by the FDA in 2003. In 1998, the original Chirila Type-I KPro was first implanted in three people who had failed keratoplasty and had vascularised and/or scarred corneas. This device required full-thickness removal of the host cornea, and the placement of a conjunctival flap to protect the KPro-corneal interface during post-operative healing; this flap is then removed in a second surgical stage. Unfortunately, two devices were quickly extruded due to retraction of the conjunctival flap. Full-thickness insertion increased the risk of exposing the porous skirt after conjunctival flap failure. In response to these observations, a thinner KPro (the Type II, AlphaCor™ KPro) was developed, allowing for lamellar pocket implantation instead of full-thickness insertion, followed by a subsequent second surgical step several weeks later to trephine the anterior host cornea. A pilot human trial in four patients implanted with the type II KPro observed no post-operative complications, and improved outcomes at seven months follow-up in all individuals.[85] This thinner design was subsequently utilised in the larger clinical trials that supported the FDA approval of the AlphaCor™ device.[84]

Outcomes

Retention rates reported for the AlphaCor™ have been relatively high. In a phase I trial, 93% of the 14 devices were retained for up to 2.5 years.[86] Some years thereafter, Hicks et al. undertook a retrospective study of 322 AlphaCor™ KPros and found at 6 months, 1, and 2 years, 92, 80, and 62% of devices were retained, respectively.[87] Of 322 AlphaCor™ KPros implanted, 65.8% were *in situ*, 26.7% had undergone a PK, 6.2% had been replaced with a second AlphaCor™, and 1.2% of patients had lost the eye. Stromal melts occurred in 27% of the cases, from which 65% had resulted in device expulsion.[87] Similarly, Jiraskova et al. recorded survival rates of 87, 58, and 42% after 1, 2, and 3 years, respectively.[88] Conversely, they found stromal melts occurred in 60% of patients and device removal was necessary in more than half of these patients.[88] Topical administration of medroxyprogesterone appeared to protect against melts. On the other hand, protection such as bandage contact lenses could have contributed to this decrease in corneal melts.[84]

Figure 1-Digital pictures of the AlphaCor™ produced by polymerisation of PHEMA to produce a transparent (optical) and white (skirt) PHEMA before **(A)** and after **(B)** lathing.



The high water content and therefore large pores of the AlphaCor™ can lead to inadequate suturing performance and overall poor mechanical strength which causes stromal melts and therefore extrusion. A T-style KPro based on a PHEMA hydrogel was introduced by Xiang et al. to address this problem. They found that adding hyaluronic acid and cationised gelatin to the skirt promoted cell adhesion and bound the device and native tissue firmly.[89] They also added poly(ethylene glycol) (PEG) to the bottom of the optical column and this caused resistance to RPM formation by decreasing cellular attachment and proliferation.[89]

Often patients will have pre-existing conditions such as macular disease or glaucomatous cupping which will limit VA improvement. This was the case for many patients in the study carried out by Hicks et al. The average VA was 20/200 and the lowest was light perception. Surprisingly, one patient did achieve a VA of 20/20.[87] Jiraskova et al. found BCVAs ranging from hand movements to 20/25.[88] Although there are promising visual acuity results, regain of sight was often impeded by the occurrence of deposits on the optic and surface spoliation of the device. Hicks et al. found that 11% of all patients implanted with an AlphaCor™ had intraoptic calcium or pigment deposition, four cases having white deposition and the other four brown.[90] The white deposits had been associated with topical steroid and beta-blocker administration and the brown deposits were correlated with cigarette smoking and topical administration of the beta-blocker levobunolol.[91] Interestingly, one study excluded stage 2 of the surgical process, in which corneal tissue is removed from the anterior flap, to find if this could decrease the rate of stromal melts, deposits, and aqueous leakage. All six patients had no stromal melting, infection, aqueous leakage, or extrusion.[91]

The AlphaCor™ was developed to address the problems observed in older generations of KPros; namely glaucoma, endophthalmitis, RPM formation, and extrusion. The AlphaCor™ is associated with reduced complications, but corneal stromal melts and optic deposition have been a major setback. Current efforts to improve the clinical outcome include enhancing the stiffness of the skirt material to allow for better suturing of the device into the host eye. Furthermore, the incorporation of gelatin to improve cell attachment and proliferation are also under consideration to enhance device skirt biointegration. In addition, efforts are being made to improve the optics of the AlphaCor™, such as the addition of a UV philtre co-monomer to avoid any UV-associated damage to the retina, as well as the use of an anti-calcification comonomer to reduce the risk of optic depositions that impair visual improvements. It is hoped that these modifications will target the majority of complications previously identified with AlphaCor™, and that future patients will benefit from these improved clinical outcomes.

Synthetic Cornea Alternatives

An interesting alternative to the AlphaCor™ is the CorNeat KPro, a completely synthetic, sterile cornea made using inert materials. Whereas, the AlphaCor™ attempts to somewhat biointegrate with native tissue (stroma), the tissue itself is avascular and is slow to heal. The CorNeat KPro takes advantage of the highly vascularised, fibroblast rich, regenerative environment of the conjunctiva and biointegrates with the tissue.

In contrast to the lengthy MOOKP surgical technique, CorNeat implantation requires just 45 min of surgery using a surgical kit with a marker and snapper. The PMMA lens is designed to effortlessly snap on into a trephined cornea. If successful, the device should withstand IOP and uphold the eye's integrity. The degradable skirt is implanted subconjunctivally.

The CorNeat KPro is indicated for those who have had keratoplasty failure or an indication that would result in keratoplasty failure.[92] The CorNeat has just entered its first-in-human clinical trial in Israel as of January 2021 (ClinicalTrials.gov Identifier: NCT04485858). Several other clinical trials are planned and have a predicted release date of 2023. Moreover, a synthetic endothelial layer has been produced by an Israeli company, EyeYon Medical, known as EndoArt.[93] It is a polymer film that acts as a barrier, preventing excess fluid from entering the cornea from the anterior chamber, thereby avoiding corneal oedema and vision loss. The EndoArt is implanted by a minimally-invasive procedure and can reduce pre-existing edoema, as evident in pre-clinical studies and in an early clinical trial (ClinicalTrials.gov Identifier: NCT03069521).

Future Trends for Corneal Implants

In contrast to KPros, a growing area of research and development relates to corneal substitutes aimed at reducing reliance on human donor tissue, in particular for the low-risk cases comprising the majority of corneal transplantations performed worldwide. Various biomaterials have been employed to form full- or partial-thickness corneal substitutes to replicate the structure and function of the cornea. Both natural and synthetic polymers have been used as scaffolds and substitutes for corneal stroma.[94] Natural polymers have the advantage of biocompatibility, but synthetic polymers allow for manipulation of chemical and mechanical properties to meet individual needs.[95]

Biopolymers of extracellular matrix (ECM) components are being investigated to mimic the corneal microenvironment. In theory, ECM components should be ideal for promoting and supporting regeneration as it is the ECM that supports the growth and embryonic development of an organ. The ideal biomaterial should be biocompatible, transparent, strong (to allow suturing and IOP), non-immunogenic, refractive, permeable to nutrients and oxygen, and resistant to neo-angiogenesis.[96]

Collagen and Derivatives

The corneal stroma, which makes up the bulk of the cornea, consists mainly of collagen. Collagen type-I is abundant in several areas of the body, and it is commercially available.[95] In the cornea, collagen type-I, III and V form a complex lattice-like structure that provides considerable strength, but this is difficult to replicate in a laboratory setting using purified collagen from different species and tissues. Several treatments have been applied to collagen hydrogels to increase their tensile strength.[96] Collagen hydrogels have been plastically compressed to increase density,[97] cross-linked chemically (glutaraldehyde, genipin), physically (UV or dehydrothermal treatment) or enzymatically (transglutaminase),[95] and added to other materials capable of forming an IPN or double network.[98]

One promising solution for patients with a high-risk of graft failure is a bioengineered corneal implant made from recombinant human collagen type III (RHCIII). In a phase I clinical study, Fagerholm et al. prepared a biosynthetic cornea composed of type III recombinand human collagen crosslinked with the non-toxic zero-length crosslinkers 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride and N-hydroxysuccinimide (EDC-NHS). It was found that the biomimetic cornea had good biointegration, regenerated the corneal epithelium, partially replaced the corneal stroma and facilitated nerve regeneration, that restored the corneal reflex better than corneal allografts in low-risk patients.[99] A 4-year follow-up showed all 10 implants maintained their transparency and no tissue rejection was reported.[100] However, these RHCIII implants were only suitable for low-risk patients as they led to neovascularisation in rabbit models with severe pathology.[101]

To identify whether the risk of implant-related neovascularisation in high-risk patients could be reduced, modified RHCIII implants were developed to include the synthetic phospholipid methacryloyloxyethyl phosphorylcholine (MPC). These RHCIII-MPC implants had previously been shown to prevent vascularisation in a high-risk alkali burn corneal injury model.[101] This device was implanted into three patients with ulceration, decreased corneal integrity, near blindness and associated pain and discomfort.[102] Although the implants improved vision in only two of the three patients, in all three cases, the implants remained free of neovascularisation at 1-year follow-up. Functional restoration of corneal integrity was observed, with stable regeneration of both the corneal epithelium and nerves, providing all three patients relief from pain and discomfort.[102]

In 2018, Islam et al. grafted cell-free corneal implants consisting of recombinant human collagen and MPC by anterior lamellar keratoplasty.[103] The patients were unilaterally blind and at high-risk of graft failure. Three out of six patients gained significant improvement in vision and the corneal stability of the remaining patients was sufficient to allow surgery to improve vision. Grafting outcomes in mini-pig corneas were superior to those in human subjects, indicating that animal models are only predictive for patients with non-severely pathological corneas.[103] Another method to combat neovascularisation is to integrate a sustained release nanosystem of bevacizumab (an anti-VEGF drug) into the cell-free biosynthetic scaffolds,[104] while ulceration and a neurotrophic deficit could be addressed by sustained release of nerve growth factor, demonstrated recently in a collagen-based scaffold releasing the drug in a controlled manner during a 60-day period.[105]

Limbal epithelial stem cells (LESCs) have been successfully cultivated on recombinant human collagen type-I (RHCI) hydrogels.[106] LESCs at the junction of the sclera and cornea are responsible for the regeneration of corneal epithelial cells and also prevent invasion by conjunctival epithelial cells.[107] Severe limbal stem cell deficiency requires keratolimbal and limbal stem cell allografts but these have poor survival rates and usually require immunosuppression post-surgery.[108,109] One study found that the LESC cultivated hydrogels were biocompatible, had promising optical characteristics, comparative microbial resistance and successful composite graft generation.[106] Additionally, human corneal stromal-derived mesenchymal stromal cells (MSCs) have been shown to culture successfully on a porcine collagen-based hydrogel scaffolds.[110]

In 2020, McTiernan et al. introduced the LiQD cornea. The LiQD cornea is made up of short collagen-like peptides conjugated with PEG which are functionally similar to RHCIII implants.[111] Fibrinogen was also added to act as a natural adhesive. The LiQD Cornea is liquid at temperatures above 37°C and solidifies to a gel at lower temperatures. It therefore can be used as either a sealant or an alternative to corneal transplants. A 12-month study carried out on pigs found the cornea capable of regeneration and a reduced risk of allergy or immune reaction was observed in traditional corneal transplants or xenogeneic materials, however, all implanted pigs had corneal haze and neovascularisation post-operatively.[111]

Alternatively, gelatin, a denatured form of collagen, can be used to construct membranes for corneal cells. It is more pre-disposed to biodegradation and absorption than collagen itself. Gelatin can be cross-linked dehydrothermally or chemically using EDC or glutaraldehyde (GA). Mimura et al. cross-linked a gelatin hydrogel with GA and found the hydrogel was capable of supporting the growth and maintenance of cultured rabbit fibroblasts for 4 weeks.[112]

Several other materials beyond collagen or gelatin, such as silk and chitosan are now being investigated to form corneal substitutes with some success.[113] This ever-growing area of research has the potential of forming full-thickness corneal biomimetic substitutes in the future.

Decellularised Corneas

Decellularised corneas are one of the most promising forms of replicating the complex structure and function of actual corneas.[94,114] Decellularisation is a process by which cells from mammalian organs or tissues are removed to form a cell-free scaffold with intact ECM integrity. Although hydrogels derived from ECM components such as collagen mimic the cornea's ECM, they may lack its fibril organisation[110] and thereby the tensile strength that the lamellar collagen structure imparts to the stroma.

Decellularised corneas mimic both the fibril architecture and corneal composition and therefore, are a very attractive option. It is the organised and complex architectural structure of the stromal collagen fibrils in the cornea that allow for the appropriate biomechanical properties of the cornea. Collagen fibrils in the anterior part of the cornea are more isotropic and thus allow the IOP to be better withstood and to sustain corneal curvature. Here, spring-like structures extend into deeper fibrils.[115] Peripherally the fibrils are circumferentially orientated, more compact and the fibril diameter increases with the merging sclera collagen to reinforce the limbus stabilising the corneal curvature and sustaining its refractive properties.[116] The larger and wider fibrils of the posterior cornea and their orthogonal arrangement, as well as the ones of the central cornea, strengthens against strain from extraocular muscles. Narrower bundles in the posterior stroma are directed to the four major rectus muscles. This complex collagen structure is maintained by proteoglycans and glycosaminoglycans. Decellularised corneas are a promising source for engineering corneal tissue as they retain this complex structure of corneal collagen.[115]

The process of decellularisation starts with the isolation of the donor tissue followed by the removal of the cells. New healthy cells can then be added to increase biointegration and finally, the cornea is implanted into the patient.[114] Decellularisation can be achieved using physical (freeze-thaw cycle, high hydrostatic pressure, electrophoresis, supercritical CO_2), chemical (Triton X-100, sodium dodecyl sulphate, formic acid, ethanol) and/or biological agents (trypsin, phospholipase A2, Dispase® II). Decellularisation aims to eliminate from the cornea all major histocompatibility complexes to prevent an immune response and therefore rejection once transplanted into the recipient.[114] It has been shown that ineffective decellularisation causes macrophages to change into their pro-inflammatory M1 phenotype *in vivo* and *in vitro*.[117] Moreover, decellularisation may expose new antigenic sites due to the deformation of the collagen fibrils, which may lead to graft rejection.[118] In addition, the process of decellularisation often significantly reduces proteoglycan content. This reduction in proteoglycan content reduces the water holding capacity of these constructs and compromises bioactivity.

Porcine corneas are commonly used for decellularisation studies as they are easily procured and have anatomical similarities with the human cornea. In the case of porcine cells, decellularisation is necessary to eliminate the epitopes Galactose-alpha-1,3-galactose (α-Gal) and N-glycolylneuraminic acid (Neu5Gc) which are extremely immunogenic to human hosts .[119] Suboptimal decellularisation procedures leading to immunogenic reactions are likely the source of inflammation, neovascularization and rejection observed in the first clinical reports of acellular porcine corneas implantation.[120]

To address potential issues of xenogeneic transplantation, a potential alternative is to first generate "humanised" pigs. To develop "humanised pigs" one must remove multiple xenoreactive cell surface molecules and porcine endogenous retroviruses (PERV). The revolutionary CRISPR-Cas9 gene-editing technique has been introduced to obtain pigs with GGTA1, CMAH and β4GalNT2 gene knockouts involved in immunogenic surface glycans .[121] PERVS were also inactivated using the same technique,[122] possibly making the corneas of transgenic pigs a non-immunogenic alternative. However, the process is very costly compared to using decellularised corneas from "normal" pigs.

Following decellularisation, these matrices may be populated with human cells to generate a viable corneal transplant. There are three parameters used to establish that decellularisation has taken place: staining to verify the absence of intact cell nuclei, quantification of double-stranded DNA (dsDNA), and determination of the maximum length of DNA remnants using agarose gel electrophoresis. The difficulty in choosing the optimal decellularisation technique lies in the fact that researchers have obtained different results using similar techniques. Also increasing decellularisation efficiency is associated with increased damage to the ECM.[114]

Recellularisation of the cornea can be achieved using cells from many different origins, all of which are associated with certain advantages and disadvantages. As the cornea is avascular, allogenic cells can be used with a decreased risk of rejection, provided the implanted tissue remains sequestered from the host immune system. Recellularisation of the three different cell types-epithelium, stroma and endothelium-has been carried out using different approaches.

Recellularisation of the stroma is possible using autologous stromal cells by obtaining a biopsy from the uncompromised eye. If both eyes are compromised, adipose-derived MSCs can be activated to produce keratocytes.[123] Induced pluripotent stem cells (iPSCs) cultured on cadaveric human corneas have produced cells with a similar phenotype to keratocytes.[123]

Different means of achieving cell penetration into the thick densely

packed fibril structure of the cornea have been investigated. Human keratocytes seeded directly onto the surface of the scaffold have resulted in distributions resembling human counterparts. In a phase I clinical trial, Ali del Barrio et al. successfully recellularised 120 µm thick laminas from donor corneas by seeding autologous adipose-derived MSCs which were implanted in four patients.[124] Each patient had an improvement in VA and CDVA. However, there was no significant difference between the recellularised and non-recellularised groups, questioning the need to add adipose-derived MSCs, which are obtained from an extra liposuction surgery .[124]

Injections of cells into the stroma can damage the stromal fibril structure.[114] Freeze-drying creates pores which allow for greater cell penetration.[125] Bioreactors have been used where the construct is kept in suspension using a magnetic stirrer and cells, prevented from attaching to other surfaces and promoting the colonisation of the structure. Ma et al. seeded thin sheets of decellularised porcine cornea with keratocytes during transplantation. Cells were added to each sheet, creating a 5-layer recellularised cornea which was then transplanted into rabbits by lamellar keratoplasty.[126] Surgery using these recellularised sheets was more successful and had greater transparency than surgeries involving acellular tissue in the model.[126]

Epithelial recellularisation was carried out using limbal stem cells isolated from a biopsy of the unaffected eye.[127] When both eyes are compromised, oral mucosal allogeneic cells can be used.[128] iPSCs could also be used as a non-autogenic cell source due to their ability to differentiate into limbal epithelial stem cell-like cells.[129] Xu et al. reported the production of an anterior hemi-cornea using acellular porcine corneal stromata injected with human corneal stromal and epithelial cells.[130] These constructs were transfected into dog eyes by lamellar keratoplasty and found to maintain corneal transparency, thickness, and composition.[130]

Native corneal endothelial cells are arrested in the G_1 phase, and therefore will not proliferate. However, *in vitro* endothelial cells can proliferate but procedures must be established to restrict the cells from transitioning into MSCs.[114] The use of these cells relies on donor corneas. iPSCs can form human corneal endothelial-like cells which can potentially be used for implantation.[131] Choi et al. reported the dissection and sectioning of donor corneal stroma to 120–200 mm thick.[132] Following decellularisation, these stromal sections were seeded with human donor-derived corneal endothelial cells which resulted in a neo-cornea with biomechanical properties comparable to a normal cornea after 14 days in culture.[132]

Some reports have questioned the merits of recellularisation as no significant difference had been observed between the acellular and recellularised corneas.[124] However, this is a developing field that requires more *in vivo* studies and clinical trials to assess the possible advantages of recellularisation. Nevertheless, decellularised corneas could provide a potential cornea alternative that mimics both its composition as well as its fibril architecture.

3D Bioprinting

3D printing has become an attractive method to manufacture a corneal equivalent. With the emergence of various biomaterials in corneal bioengineering, bio-inks and inks can be made to mimic the corneal microenvironment. Currently, much of the emphasis is on rebuilding a stromal equivalent using several methods which include inkjet printing, extrusion printing, and Laser-assisted printing. Duarte Campos et al.[133] bioprinted corneal stromal keratocytes (CSK) in collagen-based bioinks to form stromal equivalents. Theoretically, 3D bioprinting could produce a multi-layered cornea embedded with epithelial cells, keratocytes and endothelial cells.

Isaacson et al.[134] demonstrated the feasibility of engineering an artificial corneal structure using 3D bioprinting. Using an existing 3D digital human corneal model and a composite bio-ink comprising of collagen and alginate, which contained encapsulated corneal keratocytes, 3D constructs anatomically analogous to a human model were produced.[134] Keratocytes remained viable for 7 days post-printing. However, the metabolic activity and the protein expression of the keratocyte cells was low which might be linked to the high crosslinking density of the 3D bioprinted scaffold and the lack of a curved geometry.[134]

Ulag et al. have 3D printed a cornea suitable for transplantation using an aluminium mould, necessary to achieve the correct shape and a PVA-chitosan construct.[135] Scanning electron microscopy and UV spectrometry showed favourable optical properties. Tensile strength could support fluctuations in IOP and the structure remained biocompatible with stem cells after 30 days of degradation.[135]

Moreover, decellularised corneal ECM-based bio-inks can be used to mimic the corneal stroma structure. Kim et al. investigated the effects of changing the nozzle diameter and hence the shear stress when extrusion bioprinting was used to bio-print human keratocytes into a bio-ink made from decellularised corneal ECM.[136] Widening the nozzle to lower shear stress resulted in non-aligned collagen fibrils. While giving highly structured fibrils, the narrower nozzle and higher shear stress damaged the keratocytes, thereby activating fibroblasts. Finally, the optimal nozzle diameter produced a structure similar to the native human corneal stroma with viable keratocytes.[136]

Sorkio et al. produced a scaffold containing a stromal layer and an epithelial layer using laser-assisted bioprinting.[137] The epithelial layer was created using a bio-ink containing human recombinant laminin, hyaluronic acid, and human embryonic stem cells-derived LESCs. The stromal layer was printed with a bio-ink comprised of collagen type 1,

blood plasma, thrombin and human adipose tissue-derived stem cells. The structure mimicked the human corneal stroma and supported high cellular viability, but the scaffold lost its shape after a few days. In addition, the supporting membrane added to support the stromal layer led to opacity, rendering the structure non-functional.[137]

Finally, Kim et al. bioprinted a scaffold using a gelatin ink in which human corneal endothelial cells were embedded. These cells had been genetically modified to express ribonuclease 5 (R5) which increases endothelial cell proliferation.[138] The scaffolds showed transparency and cell viability, and 4 weeks after transplantation of the 3D structures to rabbit corneas, this group showed better transparency than the non-printed group.[138] Even though the majority of research focuses on manufacturing a stromal equivalent, 3D bioprinting does have to potential to form a full-thickness, multi-layered cornea model in the future.

Conclusions

Artificial corneas range from KPros with biological interfaces for treating intractable cases where donor corneas fail, to cell-free medical devices intended to be a primary replacement for donor corneas. The focus of this review was the evolution of KPros and recent developments in corneal substitutes. The Boston KPro and OOKP have stood the test of time by adapting to arising complications. In terms of the Boston KPro, many changes in its design have been implemented to address certain problems: (i) holes were added to the backplate for nutritional support which significantly reduced keratolysis, (ii) titanium sputtering has been introduced to increase PMMA and corneal tissue adhesion, (iii) pressure sensors were investigated to prevent *de-novo* glaucoma, (iv) titanium backplates and a threadless design have shown potential in decreasing RPM formation, and (v) electrochemical anodisation can colour the titanium backplates blue or brown to increase its aesthetic appeal.

In comparison to the Boston KPro, the OOKP has had limited modifications since its creation in 1963, but there have still been several advancements in the surgical procedure involved. Since alterations to the surgical procedure, introduced by Falcinelli, the OOKP has provided the best visual outcomes of any KPro. Some studies have attempted to address the frequent laminar resorption observed with the OOKP, by using an autoclavable µ-milling device, bone morphogenetic proteins, bisphosphonate drugs and/or remedies to maintain mucosal health. The OOKP serves patients with different indications to the Boston KPro. In general, the Boston KPro is for patients with wet, blinking eyes while the OOKP is for patients with dry, non-blinking eyes.

To address the problems of the previous generations of KPros (namely *de-novo* glaucoma, endophthalmitis, RPM formation and extrusion), the AlphaCor™ was developed. This PHEMA-hydrogel-based KPro significantly reduced these complications; however, other complications arose, such as the occurrence of corneal stromal melts and optic deposits, which have greatly curtailed its use. Some hope comes in the form of synthetic corneas such as the CorNeat which have the potential to completely integrate into the native tissue by joining the conjunctiva, improving both the aesthetic appeal and incidence rate of complications associated with artificial corneas. Nevertheless, the CorNeat has only begun clinical trials.

Although these approaches have focused mainly on artificial corneas made of synthetic materials, much of the interest now lies in using naturally occurring matrix macromolecules such as collagen to form scaffolds for tissue reconstruction and/or delivery of cell-based therapies. These technologies have the advantage of potentially addressing the much larger group of low- to medium-risk indications for corneal transplantation, in contrast to KPros. Decellularised corneas have a potential although a multi-layered corneal alternative and recellularisation using the three corneal cell types has yet to be accomplished. In contrast to biomaterials-based scaffolds, decellularised corneas mimic the complex corneal fibril architecture. However, the immune response to these decellularised constructs is not yet fully understood and initial clinical outcomes have been suboptimal.

First conceived in 1789, artificial corneas have come a long way- from a rudimentary quartz crystal implanted in rabbit eyes to a fully functional, full-thickness KPro implanted in thousands of eyes. Albeit only specified for those who have, or will fail, corneal transplantation, artificial corneas have restored sight to many blind patients. Furthermore, constant improvements in the design have greatly impacted the rate of complications such as RPM formation, glaucoma and endophthalmitis. Soft KPros have demonstrated enormous clinical potential; however, the use of certain biomaterials as components in polymer-based synthetic corneas or 3D printed structures, and the development of decellularised corneas have still presented with serious complications. Concentrated efforts towards improving the biointegration and reducing complications of biofunctionalised soft Kpros may hopefully lead to a successful artificial cornea in the near future.

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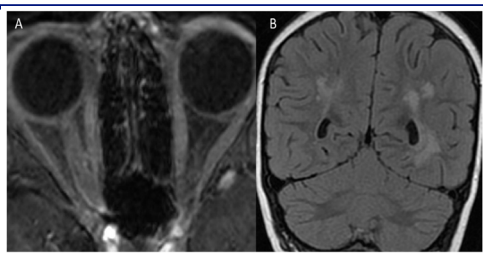
Review Article

Recent developments in the management of Pediatric optic neuritis



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Abstract

Purpose of this review is to summarize recent developments in the classification, investigation and management of pediatric optic neuritis (PON). A recent surge in interest surrounding antibodies to myelin oligodendrocyte glycoprotein antibody (MOG-Ab) has instigated a paradigm shift in our assessment of children with PON. This serological marker is associated with a broad spectrum of demyelinating syndromes that are clinically and radiologically distinct from multiple sclerosis (MS) and aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (AQP4+NMOSD). Optic neuritis is the most common presenting phenotype of MOG-Ab positive-associated disease (MOG+AD). MOG-Ab seropositivity is much more common in the pediatric population and it predicts a better prognosis than MS or AQP4+NMOSD, except in the subset that exhibit a recurrent phenotype.A better grasp of MOG+AD features and its natural history has facilitated more accurate risk stratification of children after a presenting episode of PON. Consequently, the initial investigation of PON has broadened to include serology, along with neuroimaging and cerebrospinal fluid analysis. Acute treatment of PON and chronic immunotherapy is also becoming better tailored to the suspected or confirmed diagnoses of MS, AQP4+NMOSD and MOG+AD.

Keywords: aquaporin-4 antibody; multiple sclerosis; myelin oligodendrocyte glycoprotein; neuromyelitis optica spectrum disease; pediatric optic neuritis

Introduction

Optic neuritis is an inflammatory condition of the optic nerve that causes visual impairment and may herald demyelinating disease. While our understanding of adult optic neuritis (AON) is considerable, we have a weaker grasp of pediatric optic neuritis (PON), owing to its relative rarity.

Recently, there has been a substantial increase in studies of PON that can be attributed to an expanding interest in myelin oligodendrocyte glycoprotein antibody (MOG-Ab). When this biomarker first emerged, it was most frequently associated with acute disseminated encephalomyelitis (ADEM) in young children; however, recent studies have found optic neuritis to be its predominant phenotype. Seropositivity for MOG-Ab (MOG+) was previously thought to designate a benign subset of multiple sclerosis (MS), but is now understood to prognosticate a non-MS disease course. It has also been identified in many patients with neuromyelitis optica (NMO) spectrum disorder (NMOSD) who lack serological evidence of aquaporin-4 antibodies (AQP4-Abs). Now that MOG-Ab positive-associated disease (MOG+AD) is recognized as a nosological entity, our categorization of optic neuritis and associated demyelinating syndromes is changing.

The current review article compares PON with AON and summarizes recent data regarding clinicoradiological features, natural history and management of PON due to MS, AQP4-Ab and MOG-Ab.signal transmission. Dysregulation of the JAK pathway is associated with various inflammatory and autoimmune disorders, making JAK inhibitors a potential avenue for reducing inflammation. However, the use of JAK inhibitors in clinical therapy is relatively recent, particularly for autoimmune diseases involving ocular inflammation. There are limited reports on the use of Tofacitinib, one such JAK inhibitor, in refractory uveitis and scleritis. This write-up focuses on the use of JAK inhibitors in patients with non-infectious uveitis, summarizing their therapeutic efficacy and tolerability.

Pediatric versus adult optic neuritis

PON is rare with an annual incidence rate of 0.15-0.57 per 100 000 person-years, [1-4] compared with 5.1 per 100 000 person-years in adults.[5] The incidence of PON is substantially higher among adolescents compared with younger children [1-4] Most studies observe a female predilection resembling that in adults, with a female-to-male ratio ranging from 1.42 : 1 to 2.7 : 1 [1-3,6,7]. A racial disparity may also exist, with higher incidence of optic neuritis seen in non-white children, than non-white adults. [2,4,8]

Considerable clinical differences exist between childhood and AON. Bilateral involvement is rare in adults, but reported in 32-50% of children in recent studies. [6,7,9,10,11] Optic disc edema is more commonly observed in PON (50-74%) (Fig. 1a) [6,7,9], compared with AON (35%) [12]; and orbital pain is less frequent in children (43-49%) [6,7,10], compared with adults (92%).[12] Vision loss is more pronounced in PON, with more than 50% of children presenting with visual acuity poorer than 20/200 [6,9,10], compared with 36% of adults.[12] However, better recovery is seen in children, with 71-81% regaining visual acuity of 20/20, in comparison with 50% of adults, a year after optic neuritis [6,10,13].

Many of the commonplace PON signs and symptoms are unusual in AON and mimic the 'atypical features' that trigger exhaustive investigations in adults. It is important to consider alternative diagnoses such as sarcoidosis, infectious neuroretinitis, papilledema, leukemia, systemic lupus erythematosus and viral or vaccination-induced PON. However, this review will concentrate primarily on isolated PON or that associated with demyelinating disease.

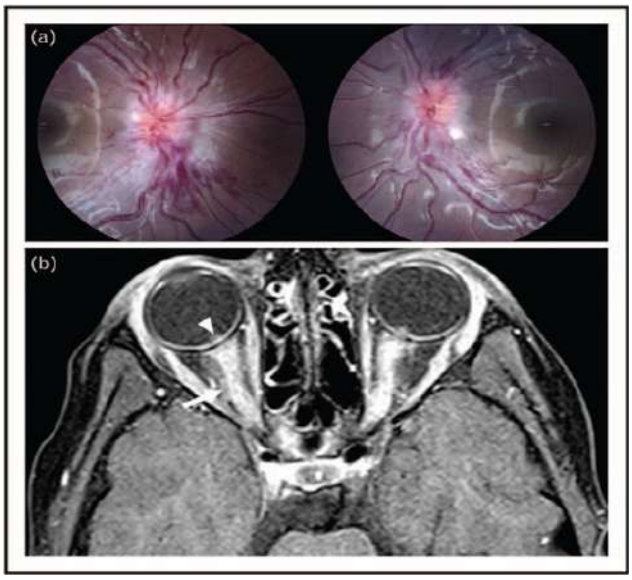

Figure 1. Images of a 7-year-old girl presenting with bilateral myelin oligodendrocyte glycoprotein-optic neuritis: (a) fundus photographs showing bilateral disc edema with multiple disc hemorrhages, (b) gadolinium enhanced MRI demonstrating bilateral, longitudinally extensive optic nerve enhancement with nerve sheath enhancement (arrow) and optic disc edema (arrowhead).

Categorization of pediatric optic neuritis

Optic neuritis can occur as an isolated, monophasic condition or may be recurrent without any other manifestations. Alternatively, it may represent a sentinel attack or relapse of a chronic demyelinating disorder such as MS, NMOSD or MOG+AD.

Multiple sclerosis

MS is an inflammatory demyelinating disease of the central nervous system (CNS), for which the precise immune-mediated pathophysiology remains uncertain. Predicting progression from PON to pediatric-onset MS (POMS) remains challenging. A quarter of children presenting with PON are subsequently diagnosed with MS, and this risk increases with age [10,11]. Overall, the likelihood of conversion to MS is lower in children than adults, with 22-29% over varied follow-up periods [10,11] compared with 50% over 15 years, respectively [14].

Clinical features and investigations

Certain presenting features of PON raise suspicion for MS. The absence of optic disc swelling is more commonly seen in MS-related optic neuritis (MS-ON) [10], as is the presence of cerebrospinal fluid (CSF) oligoclonal bands (OCB) [10,15-18], and characteristic periventricular white matter lesions on initial brain MRI [10,11,17-19]. A study of 357 children with isolated PON found a 27-fold higher hazard ratio of developing MS when OCB and MRI lesions were present, compared with absence of both markers [17].

Diagnostic criteria

The updated 2017 McDonald diagnostic criteria for MS [20] has been found to perform well in children [21,22]. It differs from the 2010 version by reintroducing OCB as evidence of dissemination in time, and eliminates the requirement for MRI lesions to be clinically silent [23]. These changes facilitate earlier diagnosis of MS and hence earlier treatment. However, optic nerve lesions are still excluded as evidence of dissemination in space, as their common occurrence in other demyelinating syndromes reduces specificity [23,24].

Visual prognosis and clinical course of multiple sclerosis-optic neuritis

The diagnosis of MS-ON imparts a poorer visual prognosis in children. A recent multicenter study of 102 children found that only 27% of children with MS-ON experience complete visual recovery after a year, compared with 90% of isolated PON [10]. Furthermore, 68% of children with MS-ON had persistent visual field deficits, compared with 22% of isolated PON cases [10].

POMS is associated with higher relapse rates [25,26] and greater accrual of MRI lesions [27] when compared with adults; in addition to failure of age-expected brain growth [28] and prominent cognitive impairment [29]. Younger children exhibit a slower pace of MS progression [30];

however, irreversible disability occurs approximately 10 years earlier than in adult MS, due to earlier onset of disease [31]. After the initial demyelinating episode, the risk of relapse is highest within the first 2 years [26,29], and remains elevated for 5 years [25]. Early exposure to disease modifying drugs (DMDs) is a protective factor against relapses and worsening of disability [30].

Acute treatment

In the absence of controlled studies assessing treatment of PON, a widely accepted protocol has been derived from the optic neuritis treatment trial (ONTT) [12], that also concurs with the international consensus for treatment of other demyelinating attacks seen in POMS [32]. It consists of intravenous methylprednisolone (IVMP) 20-30 mg/kg/day (maximum 1 g daily) for 3-5 days. If there is incomplete symptom resolution, oral prednisolone can be used at a starting dose of 1 mg/kg/day, tapered over 1-4 weeks [32].

Although there is evidence that superdoses of oral prednisolone are equivalent to IVMP in adults [33], dosing is uncertain in children; hence it is rarely used [32]. The ONTT reported that steroid therapy hastened visual recovery, but did not affect final visual or neurological outcomes [12,14,34]. It is unknown whether these findings are applicable to the pediatric population.

If steroids are contraindicated, or there is little improvement with IVMP, then treatment options include plasma exchange (PLEX), five to seven exchanges over 10-14 days, or intravenous immunoglobulin (IVIG), 2 g/kg divided over 2-5 days [32].

Chronic immunomodulation

Historically, a second demyelinating episode would transpire before the diagnosis of MS was made. However, the current trend is toward earlier diagnosis so that DMDs can be promptly initiated, with the aim of minimizing long-term disability.

In 2018, the first randomized controlled trial (RCT) investigating DMDs in POMS reported superiority of fingolimod over intramuscular IFN[beta]-1a in reducing annualized relapse rates [35]. Ongoing RCTs are assessing the efficacy of peginterferon [beta]-1a [36,37], dimethyl fumarate [36,38,39], teriflunomide [40] and alemtuzumab in children [41]. Observational studies have also shown promising results for natalizumab [42,43] and rituximab [44,45].

Neuromyelitis optica spectrum disease

NMO is typified by acute, severe episodes of optic neuritis and transverse myelitis. It is most often associated with antibodies against AQP4, a water channel protein that is highly concentrated on astrocyte endfeet [46]. There is growing evidence that AQP4-Ab causes direct astrocytopathy and neuronal necrosis with secondary oligodendrocyte loss and demyelination [47,48]. This mechanism is thought to explain the severity of NMOSD attacks in comparison with those seen in MS and MOG+AD.

Clinical features and investigations

Roughly 60% of children with NMOSD initially present with PON [49,50]. Poor visual recovery despite high-dose steroids should raise suspicion of NMOSD. Other red flags include bilateral optic nerve involvement, MRI enhancement of the posterior optic nerve, optic chiasm or optic tract and lesion extension beyond half the optic nerve length; especially in the absence of brain lesions [19,51]. MRI brain and full spine with contrast is recommended in all patients presenting with suspected NMOSD [52].

Recent optical coherence tomography (OCT) studies have observed that thinning of the peripapillary retinal nerve fiber layer (pRNFL) is more pronounced and diffuse in NMOSD-related optic neuritis, compared with MS-ON [53,54]. The utility of ganglion cell layer (GCL) OCT when disc edema precludes reliable pRNFL measurements has yet to be assessed. OCT can be a useful objective measure of severity in younger children who cannot reliably perform visual acuity, visual field or color vision testing.

In clinically suspicious cases of PON, obtaining AQP4-Ab serology is critical as seropositivity portends a poorer prognosis and is predictive of a relapsing course. Newer cell-based assays for AQP4-Ab have specificities approaching 100%, but sensitivities range from 70 to 100% [55,56]. Hence, retesting should be considered in typical cases that are initially seronegative. Circulating AQP4-Ab increases just before an attack and can decrease during remission or after treatment with steroids or PLEX, but AQP4-Ab titers do not currently appear to be a reliable indicator of disease activity or prognosis [57].

Diagnostic criteria

In 2007, the term NMO was broadened to NMOSD, which is inclusive of patients with limited forms of the disease who are at risk of future relapses, for example recurrent or bilateral optic neuritis [58]. In 2015, the international criteria were stratified into NMOSD with AQP4-Ab (AQP4+NMOSD) and NMOSD without AQP4-Ab, permitting inclusion of newer biomarkers such as MOG-Ab, and seronegative patients who otherwise meet clinical diagnostic criteria [58]. As most clinical, radiological and laboratory characteristics of pediatric NMOSD are similar to adult disease, these diagnostic criteria are considered to be applicable in children [50,58].

Acute treatment

Acute treatment of PON with suspected NMOSD is similar to that outlined for MS-ON. The threat of profound disability with each attack is cause for swift escalation of therapy. Hence, there is a low threshold to commence PLEX and/or IVIG, which can be administered as described for MS-ON [59,60]. After IVMP, PLEX is the preferred second-line therapy, due to its mechanism of autoantibody

clearance; followed by IVIG if PLEX is unavailable [59,61]. PLEX must precede IVIG administration to avoid extracting IVIG from the circulation [51]. Only a few case reports describe successful treatment of PON with PLEX or IVIG [62-66], and this treatment algorithm is largely derived from adult studies.

In contrast to MS-ON, children with presumed NMOSD are usually subject to a slow taper of oral prednisolone over 2-6 months. Many clinicians choose to maintain doses above 20 mg daily until AQP4-Ab status is known [51]. Even a short course of glucocorticoids will cause hypothalamic-adrenal axis disruption and growth suppression, among other side effects; hence, early transition to steroid-sparing agents is vital.

Clinical course and chronic immunotherapy

More than 90% of children with NMOSD experience relapses [49] and due to the severity of attacks, cumulative disability often surpasses that seen in POMS [50]. Therefore, prevention of recurrences is paramount and immunotherapy is often continued despite long periods of clinical remission, as relapses are unpredictable and can even be life-threatening. Azathioprine [67], mycophenolate mofetil [68] and rituximab [69] have all shown favourable clinical results with reduced annualized relapse rates in children [70]. Certain DMDs used in MS have been reported to exacerbate NMOSD and should be avoided, including alemtuzumab [71] IFN[beta] [72], fingolimod [73] and natalizumab [74].

Children with AQP4-Ab-negative NMOSD should be tested for MOG-Ab as this has implications for long-term prognosis and treatment. Over 20% of AQP4-Ab-negative NMOSD patients are MOG+ [75,76], and future iterations of the NMOSD diagnostic criteria could exclude these patients, as they may be better categorized under the umbrella of MOG+AD.

Myelin oligodendrocyte glycoprotein antibody disease

Positive MOG-Ab-associated disease encompasses a broad spectrum of clinical phenotypes, including monophasic ADEM, multiphasic disseminated encephalitis, isolated optic neuritis, relapsing optic neuritis and ADEM followed by recurrent optic neuritis [77]. Optic neuritis is the predominant phenotype of all MOG+AD episodes, both in children and adults [78-80]. Pediatric optic neuritis can often occur in conjunction with ADEM or as relapses after an initial episode of ADEM; however, in depth discussion of encephalomyelitis is beyond the scope of this review article.

MOG is a transmembrane protein that forms a minor component of the CNS myelin sheath. Its functions include myelin adhesion, regulating oligodendrocyte microtubule stability and mediating the complement cascade [81]. Unlike AQP4-Ab-mediated astrocytopathy, MOG-Ab is thought to cause inflammation and myelin destruction without direct astrocyte injury [82]. This mechanism may explain the less severe course of MOG+AD, in comparison with AQP4+NMOSD.

Indeed, MOG+AD was initially considered to be benign and monophasic. This assumption was disputed by growing reports of a relapsing phenotype that exhibits milder attacks, but can accrue impairment matching that of AQP4+NMOSD [83,84].

Demographics

Among MOG+ children, PON is more common in teenagers (13-18 years), whereas encephalitis dominates in the younger age group (4-8 years), which suggests that regional expression of MOG is age-dependent [79,85,86,87]. The slight female preponderance of MOG-optic neuritis (MOG-ON) is in keeping with adult MOG+AD and is weaker than that seen in AQP4+NMOSD [78,80,87,88,89].

Positive MOG-Abs have been reported in 17-57% of recent PON cohort studies [16,90,91]. The proportion of MOG-ON surpasses that of AQP4-Ab-associated optic neuritis (AQP4-ON) in each cohort, with MOG+ children tending to be younger [16,90,91]. Although MOG-ON is purported to be more common in the white population [78,83], recent studies suggest that an ethnic bias may not exist [90-92]. In contrast to AQP4+NMOSD, there is no known association between MOG+AD and other autoimmune diseases [51].

Clinical features and investigations

Many patients with MOG-ON report a prodromal illness, but thus far, no specific viral link has been identified [51,78]. Bilateral optic nerve involvement is reported in more than 80% of patients [19,83,90]. While mixed adult and child studies report that optic disc edema is more prevalent in MOG-ON [19,83], no significant difference is noted in exclusively pediatric studies [90]; suggesting that disc edema may just be more prevalent in all subsets of PON (Fig. 1a). Despite equivalent presenting visual acuity, MOG-ON demonstrates better visual recovery compared with AQP4-ON, with 89-98 versus 33% achieving visual acuity of 20/25 or better after 6 months [90,91].

There are mixed reports regarding OCT findings after MOG-ON. Some describe significantly less thinning of pRNFL and GCL compared with AQP4-ON [91,93], whereas others report profound thinning that is comparable with AQP4-ON, but with relatively preserved vision [90,94,95]. A proposed explanation is that demyelination in the optic nerve is accompanied by relative sparing of ganglion cell axons, as MOG-Ab is not known to cause direct astrocytopathy [95].

In mixed adult and child studies, bilateral and longitudinally extensive lesions with perineural enhancement are commonly seen with MOG-ON (Fig. 1b) [19,88]. Although some overlap exists with AQP4-ON, MOG-ON tends to exhibit more involvement of the

anterior optic pathways, with relative sparing of the chiasm and optic tracts [19,96].

On MRI, the absence of Dawson's fingers, absence of well defined periventricular ovoid lesions and the presence of poorly demarcated brain or brainstem lesions is helpful in distinguishing POMS from MOG+AD [51,79,97]. However, MRI distinctions may not be useful in children with isolated MOG-ON, who tend to have small, nonspecific brain lesions, if any at all [78,79]. While CSF pleocytosis is common, presence of CSF OCB is unusual in MOG+AD [15,78,87].

For more reliable results, it is currently recommended that MOG-Ab testing is performed with cell-based assays, using full length human MOG as the target antigen [77,98,99]. To minimize false positives and overdiagnosis of MOG+AD, international recommendations released in 2018 outline indications for MOG-Ab serology in adults and adolescents. They advocate less scrupulous adherence to the guidelines in children due to the higher prevalence of MOG-Ab in this population [77]. When cell-based assays are used, double seropositivity for MOG-Ab and AQP4-Ab almost never occurs [82]. Therefore, testing for the more likely autoantibody with reflex testing to the other, is preferred to testing for both autoantibodies simultaneously.

Visual prognosis and clinical course

After the initial attack of MOG-ON, visual recovery in children is typically good, and significantly better than that seen in AQP4-ON [19,83,90,91], and adult MOG-ON [80,88]. A monophasic course is reported in approximately two thirds of MOG+ children [18,79]. The remaining third develop relapsing disease, with recurrent optic neuritis being the most frequent manifestation, especially in children older than 9 years [16,18,78,79]. In fact, reassessment of adults previously diagnosed with chronic relapsing inflammatory optic neuritis has found that the vast majority are MOG+ [83,100-102].

Currently, there are no reliable predictive factors at the outset of pediatric MOG+AD to forecast a relapsing course. There is no correlation between MOG-Ab titer at the first demyelinating episode, but persistence of raised MOG-Ab titers is associated with a recurrent disease course [16,18,51,103]. Hence, some clinicians elect to repeat MOG-Ab titers at regular intervals to help predict the risk of relapse. Seroconversion to MOG-Ab negativity is not uncommon in children, after which they tend to remain relapse free [80,104]. MOG+ at the initial PON episode has the added benefit of predicting a non-MS disease course [15,18,105].

Acute treatment

There are no guidelines for initial management of MOG-ON, but accepted acute therapy is akin to that described for MS-ON and AQP4-ON 51. The pace of oral steroid taper depends on the severity of the attack and clinical suspicion of seropositivity. Once MOG+ is confirmed, children typically remain on steroids for 4-6 weeks [51]. The majority of patients will experience rapid resolution with steroid therapy, but are more vulnerable to relapses on tapering or withdrawal. About 70% of patients relapse when oral prednisolone is weaned below 10 mg daily, or within 2 months of steroid cessation [78].

The decision to commence maintenance immunotherapy is challenging. The high proportion of monophasic MOG+AD argues against commencing immunotherapy after the first demyelinating episode [87]. However, this choice should also be influenced by the severity of the initial attack, response to first-line therapy and the perceived likelihood of relapse [51] that may be suggested by persistently raised MOG-Ab titers [98]. A relapse plan involving prompt recommencement of steroids at the earliest symptoms of recurrence, is a valuable management option [78].

If chronic immunotherapy is endorsed, there are few studies to help guide drug selection. A mixed adult and child study of 59 patients with MOG+AD found that annualized relapse rates were effectively reduced by maintenance prednisolone, IVIG, rituximab and mycophenolate mofetil. Treatment failure rates were lowest with maintenance steroids (5%) in comparison with the nonsteroidal immunotherapies (38%). Cyclophosphamide, azathioprine and methotrexate were poorly tolerated [78]. Another retrospective study of 102 children with MOG+AD found that IVIG was most effective in reducing annualized relapse rates, followed by rituximab, mycophenolate mofetil and finally azathioprine [87]. These findings largely concur with a recent multicenter retrospective study of 68 adults with relapsing MOG+AD [106], that suggested a prominent role of IVIG as maintenance therapy for MOG+AD. There is no current consensus on whether cessation of immunotherapy is advisable after a long period of remission.

Distinguishing MOG+AD from MS is imperative, as conventional MS DMDs including IFN[beta] and glatiramer are ineffective [87], and some agents such as alemtuzumab can cause disease worsening [107].

CONCLUSION

PON is a rare condition that in general entails good visual recovery. Although isolated, monophasic forms of PON impart a good prognosis, a substantial proportion of children will subsequently develop recurrent demyelinating disease with cumulative disability. Due to substantial phenotypic overlap, distinguishing PON patients with MS, AQP4+NMOSD and MOG+AD can often be difficult, but is critical. Thorough investigation from the outset, including OCT of pRNFL and GCL, gadolinium enhanced MRI of the brain and orbits, CSF analysis for OCB, and serology for AQP4-Ab and MOG-Ab, facilitates early risk stratification. This enables timely administration of PLEX, IVIG or a prolonged steroid taper to prevent early relapses and facilitates appropriate choice of chronic immunotherapy if indicated.

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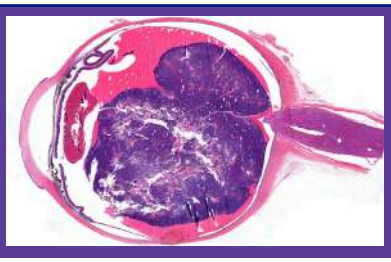
Review Article

What's new in Ocular pathology?



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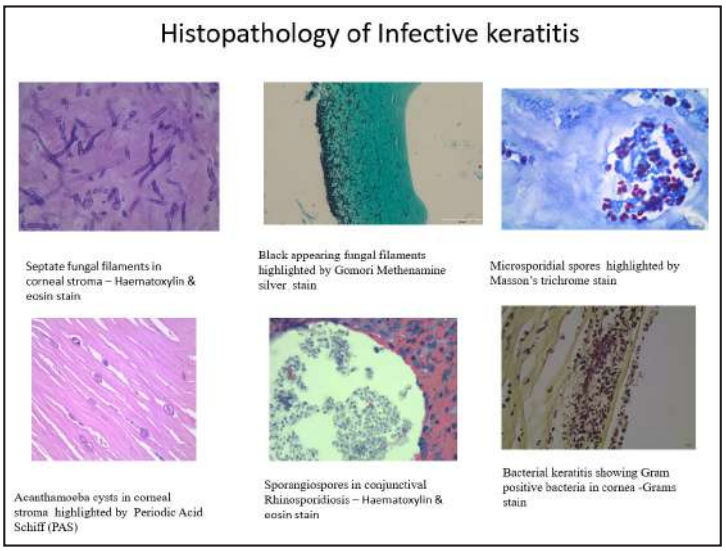
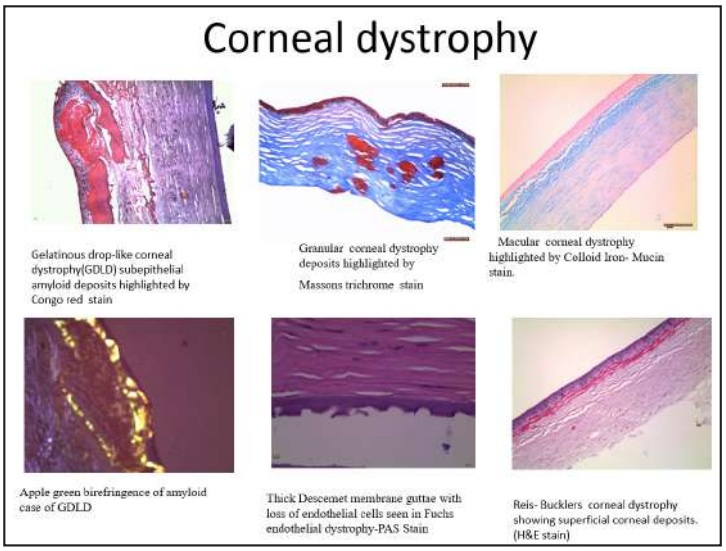
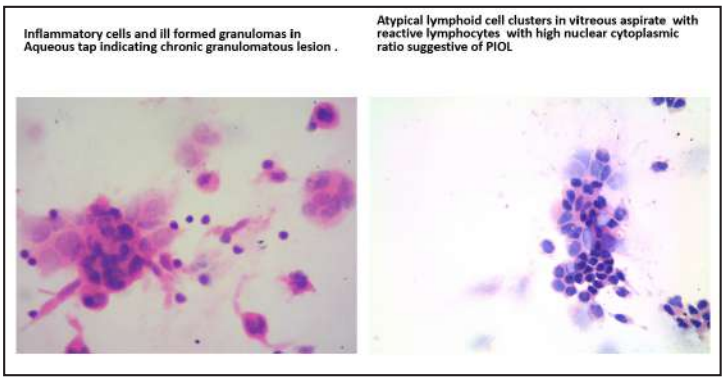
Ocular pathology, a subspeciality of ophthalmology and pathology gained importance mainly during the late 17th and early 18th century ,which is said to be the golden era for the rise of this subspeciality ,Ernst Fuchs of Vienna is considered the father of modern ophthalmic pathology , following his contributions many societies were formed and consensus meetings took place , leading to the formation of the Verhoeff-Zimmerman society to honour ,Dr Verhoeff and Dr Zimmerman who have contributed immensely to this branch. From then till date ocular pathology like any other branch in medicine is evolving and undergoing transformation ,at present in the 21st century as described by Dr Deepak Edward , this field has progressed from the routine practice of looking at glass slides to a broader speciality incorporating molecular biology and gene testing giving us novel insights leading to acurate diagnosis ,prognosis and ultimately targeted therapy[1] .Dr Hans E Grossniklaus points out that to the present day ophthalmic pathology continues to an area of expertise that is important in the basic understanding of eye disease ,fundamental in the training of future ophthalmologists and contributory to the overall advancements of ophthalmology[2] .As we progress in the era of personalized and precision based medicine, ophthalmic pathology, a subspecialty of pathology and & ophthalmology has evolved in a long way[3,4].





Ocular pathology is an integral part of ocular oncology, providing critical insights into the diagnosis, classification, prognostication, molecular analysis, and follow-up monitoring of ocular tumors. It contributes to improved patient care, treatment decision-making, and advancements in ocular oncology research. Apart from ocular oncology, it also plays a very crucial role in decoding the other pathologies in the orbit which is considered to be a Pandoras box. Histopathological study of infected corneal buttons, failed grafts ,corneal dystrophies with special stains is essential for diagnosis as well as helps in understanding the pathophysiology of the disease.

Ocular cytology which includes conjunctival impression cytology, cytological analysis of Aqueous humor ,cyst fluids, vitreous ,subretinal fluids are useful for the evaluation of inflammatory, neoplastic, degenerative, and autoimmune conditions of the ocular surface, anterior chamber, and posterior segment of the eye.



Some of the recent developments in this field include.

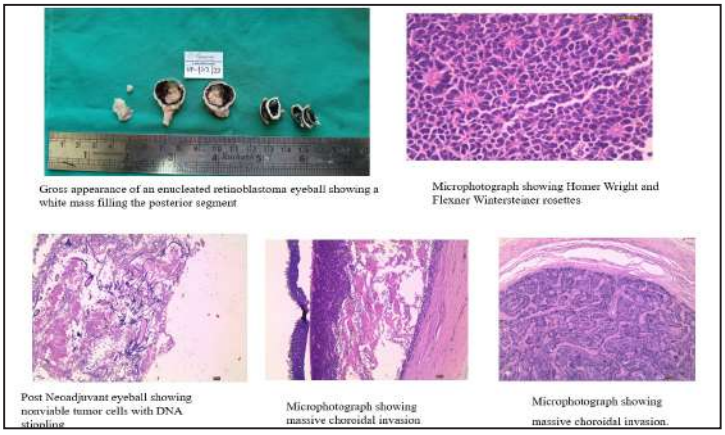
Updates in Retinoblastoma pathology

Retinoblastoma ,the most common paediatric intraocular malignancy continues to be one of the widely researched ocular tumor, till date histopathological examination of the eyeball in both upfront and secondary enucleations and identification of histological high risk features is the mainstay for further management , Rb gene mutation testing by molecular methods was previously the only known mutation in these patients ,however with recent advances it was shown that both copies of this gene was also lost in benign tumor retinocytoma , which led to the identification of many additional mutations which are required for the malignant transformation into retinoblastoma .Ophthalmic pathologist Dr Chevez Barrios and team were the first in the world to use intraocular gene therapy and to research on the feasibility of adenovirus mediated therapy as a treatment for the tumor seeds in RB patients.[5]

Some of the other new recent advances in retinoblastoma include Liquid biopsy in Retinoblastoma research, aqueous and tears being easily accessible are being extensively studied using Next generation sequencing (NGS) and other molecular methods to find newer wild mutations and potential biomarkers which would predict the outcome of treatment and guide the treatment.

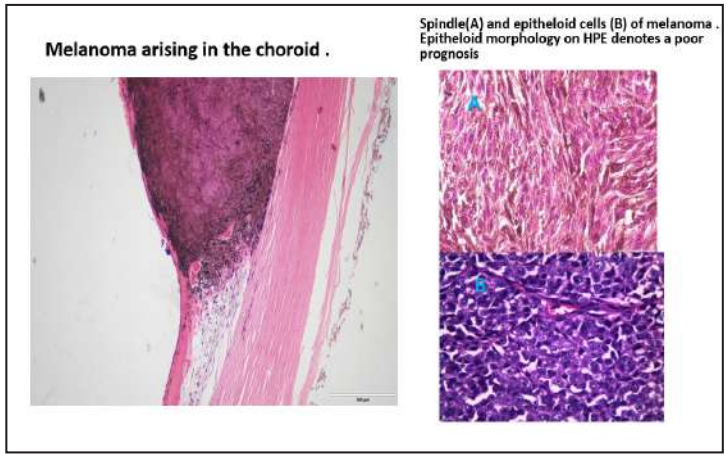
Recently Artificial intelligence (AI) model for intraocular RB is being studied[6]

AI tool is a promising screening tool for RB. It has shown high sensitivity and specificity for the detection of RB, though the sensitivity and specificity are variable for grouping of intraocular RB.



Advances in Uveal Melanoma pathology

With the publication of The Collaborative Ocular oncology group study(COOG)newer insights into translational research came up which helped in understanding the etiopathogenesis of this common adult intraocular tumor , the aspect of Vascular Mimicry in Melanomas is now being explored and the use of anti angiogenesis drugs in addition to the conventional treatment is being considered.



Also besides the histopathological high risk features identification, Loss of BRCA Associated Protein (BAP1) nuclear expressionby immunohistochemistry (IHC) in Uveal Melanoma is being used to predict metastatic risk.[7]

Primary Intraocular lymphoma (PIOL), a subset of Primary CNS lymphoma , often poses a diagnostic challenge especially in cases with atypical fundus findings and imaging , in such cases cytological examination forms the gold standard for diagnosis along with confirmation by ancillary techniques like Immunophenotyping by Flow cytometry and establishing the clonality of the atypical lymphoid cells by IHC . Recently discovery of MYD88L265P mutation analysis in Aqueous and Vitreous for detection of PIOL has shown promising results.[8]

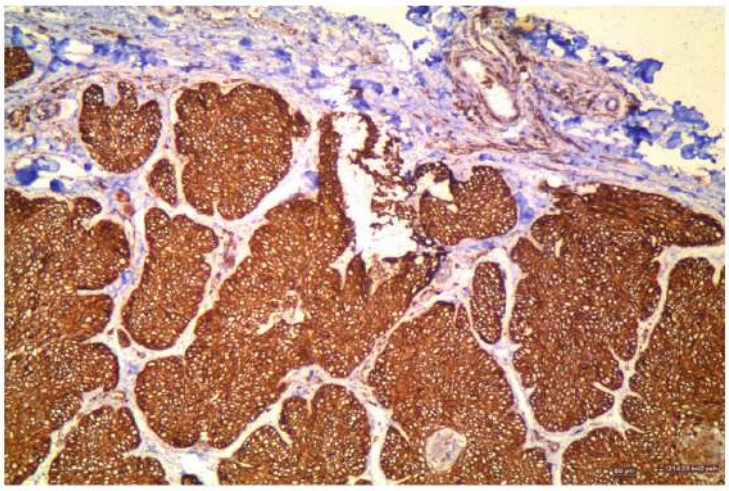
Orbital lymphomas : Cytogenetics and molecular assay are widely used in classification of lymphoproliferative disorders, recently identification of immunoglobulin chain rearrangements by PCR are useful in diagnosis of Bcell lymphomas when histology and immunophenotyping is equivocal.

Rabdomyosarcoma, the most common orbital malignancy in children has also been extensively studied , recently in cases which have challenging histomorphology , discovery of PAX3/FOX1 gene fusion transcripts helps to accurately differentiate alveolar and embryonal RMS in turn helping to predict prognosis.[9]

Solitary fibrous tumor(SFT) , a spindle cell tumor which occurs in orbit exibits low to highly aggressive behaviour and warrants early and accurate diagnosis , since the microscopic findings often always mimics other benign spindle cell tumors , NAB2/STAT6 fusion gene identification in Orbital SFT is a recent advance which helps in specific diagnosis and timely treatment like radiotherapy which inturn reduces the chances of recurrence. [10]

Molecular Analysis and Ancillary studies: Immunohistochemistry (IHC) is an ancillary tool which has revolutionized the field of pathology, helps in ruling out differentials which morphologically appear like similar lesions and to identify specific marker /protein expression to predict outcome.

Ocular pathology incorporates molecular techniques to analyze ocular tumor samples for genetic alterations and specific biomarkers. This molecular analysis can aid in identifying targetable mutations or gene expression patterns, which can guide the selection of personalized therapies, such as targeted molecular therapies or immunotherapies. Additionally, molecular profiling can contribute to research and advancements in ocular oncology.



Immunohistochemistry microphotograph showing BCL2 positive Basal cell carcinoma of the eyelid.

Digital pathology and whole slide scan imaging .

Digital pathology involves the scanning and digitization of histopathology slides, allowing for remote access, storage, and analysis of images. This technology facilitates collaboration, consultation, and research among pathologists, ultimately leading to improved diagnosis and patient care.[4] Whole slide imaging helps in Nuclear morphometric analysis which studies the grade of anaplasia in RB thus helping in predicting chemotherapy response.

Currently, only a handful of laboratories in our country provide exclusive ocular pathology services.It is indeed very important to send the ophthalmic specimens to pathologists or ophthalmologists who are specialized and experienced in ocular pathology, since in residency pathology postgraduates do not get exposed to a large number of ophthalmic samples, also most of the routine pathology laboratories are not experienced in handling and reporting tiny ophthalmic specimens and whole mounts of eyeballs.

In scenarios where there are cases which needs expertise ophthalmic pathologists review, patients ocular samples or slides and blocks from outside laboratories can be easily transported to these centers for an additional opinion for a better patient management. Also it is very important to communicate with the ocular pathologist the clinical details, imaging findings and other additional findings for an accurate report. A multidisciplinary approach is always the key for better treatment outcome.

To conclude, as ophthalmology moves towards personalized treatments it is very important for all the practicing practicing ophthalmologists and postgraduates to be aware of the importance and timely updates in ophthalmic pathology.

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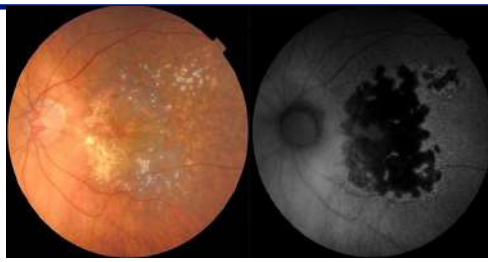
Review Article

Imaging in Age-Related Macular Degeneration



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Age-related macular degeneration (AMD) is a group of agerelated macular diseases induced by a variety of factors. The common characteristic of AMD is the pathological changes in the nutritional structure of macular like retinal pigment epithelium (RPE) and choroid, which might lead to visual impairment and progressive loss of central vision. [1–3] The disease can be divided into two basic subtypes: neovascular AMD (wet) and non-neovascular AMD (dry). The main characteristic of nAMD is the formation of abnormal neovascularization from choroid (CNV). Due to functional and structural abnormalities, these CNVs will lead to hemorrhage, edema, and fbrosis under and intra the retina, then resulting in rapid loss of central vision. Dry AMD is relatively common, manifested as progressive loss of photoreceptor cells and aggravative geographic atrophy. The vision loss of dry AMD patients is relatively slow, but there is no effective treatment at present, thus regular follow-up is usually adopted to prevent the transformation from dry AMD to nAMD.

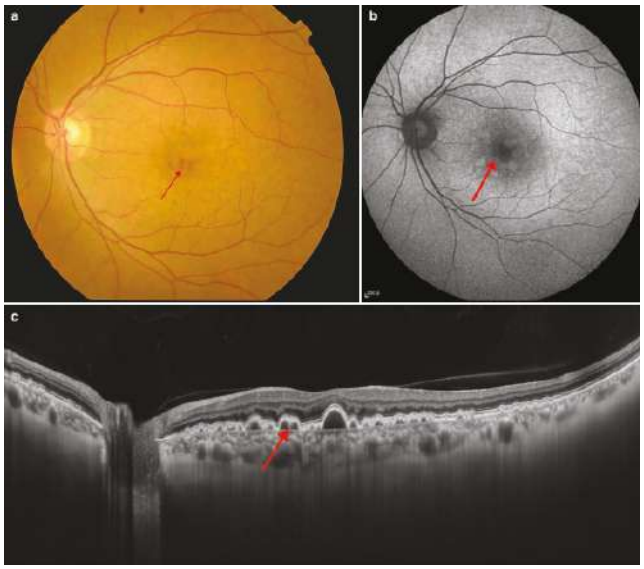


Figure 1- SS-OCT of drusen. (a, b) Color fundus photograph and fundus autofuorescence show drusen (red arrow); (c) OCT (Single-line HD 12 mm) shows medium-sized drusen through macula, located under RPE (red arrow)

Non-neovascular AMD

The Age-Related Eye Disease Study (AREDS) divides the AMD as follows [4]

- **Non-AMD (AREDS 1):** The control group in AREDS, with no or only very small drusen (<63 µm in diameter)
- **Early AMD (AREDS 2):** Multiple small drusen and some medium-sized drusen (diameter 63–125 µm), or with RPE abnormities;
- **Intermediate AMD (AREDS 3):** Widespread medium drusen, with at least one large drusen (diameter greater than 125 µm), or with geographic atrophy not involving macular fovea;
- **Late AMD (AREDS 4):** Geographic atrophy involving macular fovea

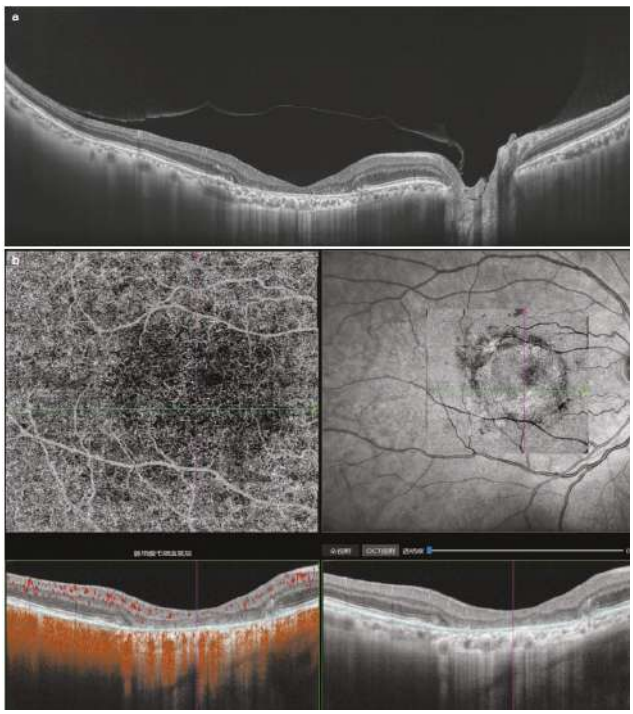


Figure 2- SS-OCT of geographic atrophy. Note the diffuse atrophy of retina and PRE in macular area (a, Single-line HD 12 mm), combined with decreased choroidal blood fow signal (b, Angio 6 × 6 mm, Choriocapillar layer)

Neovascular AMD

Specifc manifestations of neovascular age-related macular degeneration

1. Choroidal neovascularization (CNV): Type I CNV: occult CNV, which does not break through the RPE layer and only exists under RPE; Type II CNV: Typical CNV, which breaks through the RPE layer; Type III CNV: retinal angiomatous proliferation Mixed CNV.

2. Serous and/or hemorrhagic detachment of sensory retina or RPE layer[5]

3. Hard exudation in retina (secondary to long-term leakage from any origin)

4. Retinal edema, exudation, and hemorrhage combined with subretinal membrane

5. Fibrovascular disciform scar

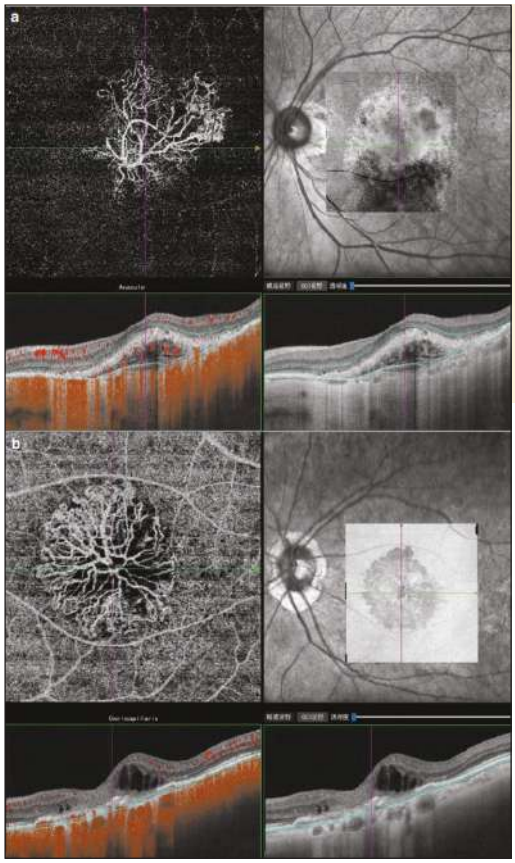


Figure 3- (a) Occult CNV, OCTA (Angio 6 × 6 mm, avascular layer) indicates that CNV is located under RPE; (b) typical CNV, the CNV breaks through RPE and lies between neuroretina and PRE (Angio 6 × 6 mm, Choriocapillar layer)

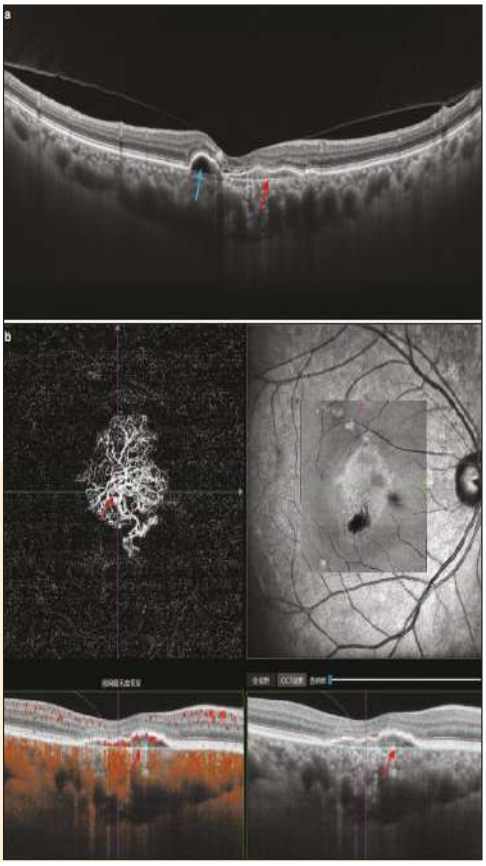


Figure 4-SS-OCT and OCTA images (scanning range 6 mm × 6 mm, avascular layer) note the Type 1 choroidal neovascularization located under RPE (a, b, red arrows), with serous pigment epithelial detachment (PED, blue arrow)

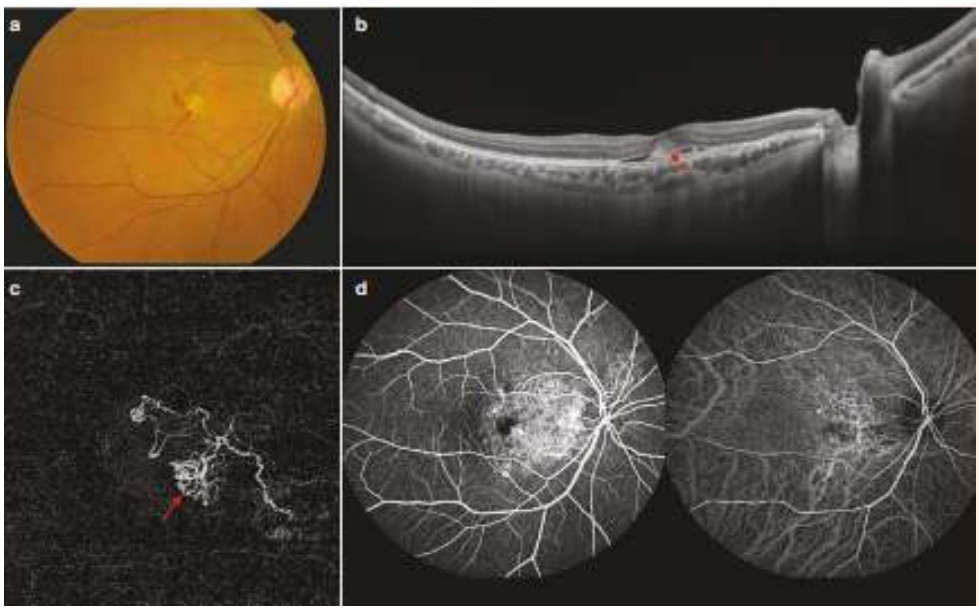


Figure 5-Note the hemorrhage in macular area (a, red arrow) in color fundus photograph, and SS-OCT indicates CNV (red arrow) with subretinal fuid, accompanied by high refection signal in the retina, corresponding to the hemorrhagic lesion (b), CNV shape can be clearly seen in SS-OCTA (c, Angio 6 × 6 mm, Avascular layer, red arrow) and FFA&ICGA (d, red arrow)

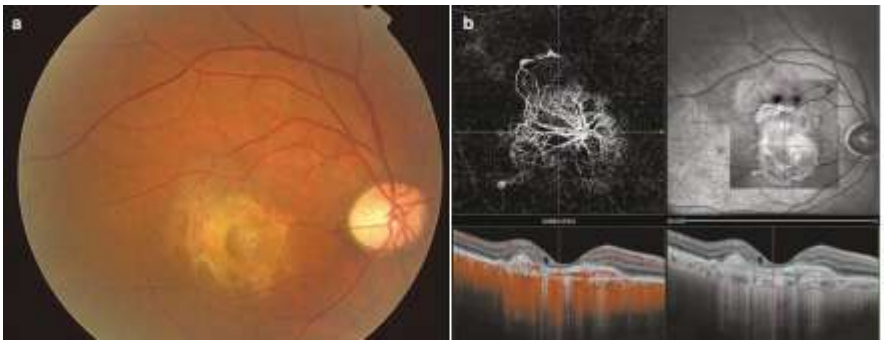


Figure 6-Fibrovascular disciform scar is clear in the fundus photograph (a), OCTA (Angio 6 × 6 mm, avascular layer) indicates the stable CNV without bleeding and exudation, combined with retinal and choroidal atrophy (b)

Serous Pigment Epithelial Detachment (With or Without Neovascularization)

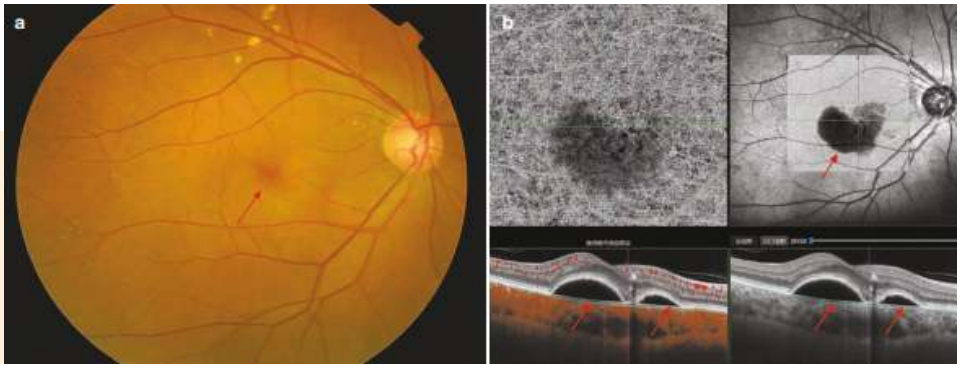


Figure 7-Color fundus photograph (a) and SS-OCTA (b, Angio 6 × 6 mm, Choriocapillar layer) shows serous PED (red arrow)

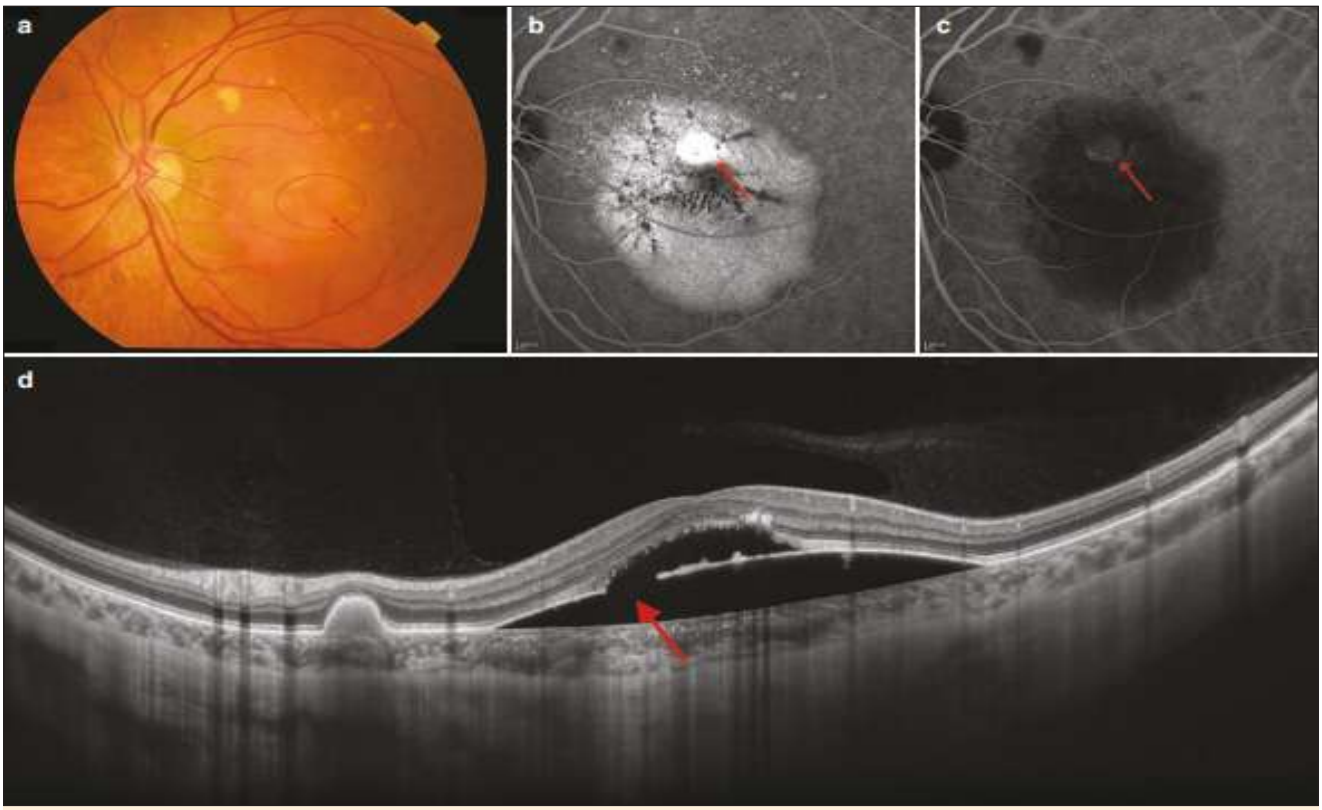


Figure 8-For this patient with nAMD, color fundus photograph shows pigment changes in the parafoveal area (a, inside the red circle); FFA indicates window defect (b, red arrow), and choroid vessels are seen in the window defect area of ICGA (c, red arrow); (d) SS-OCT shows serous PED with local RPE layer fracture (red arrow) in macula

Type 1 CNV No break through the RPE layer and only exists under RPE

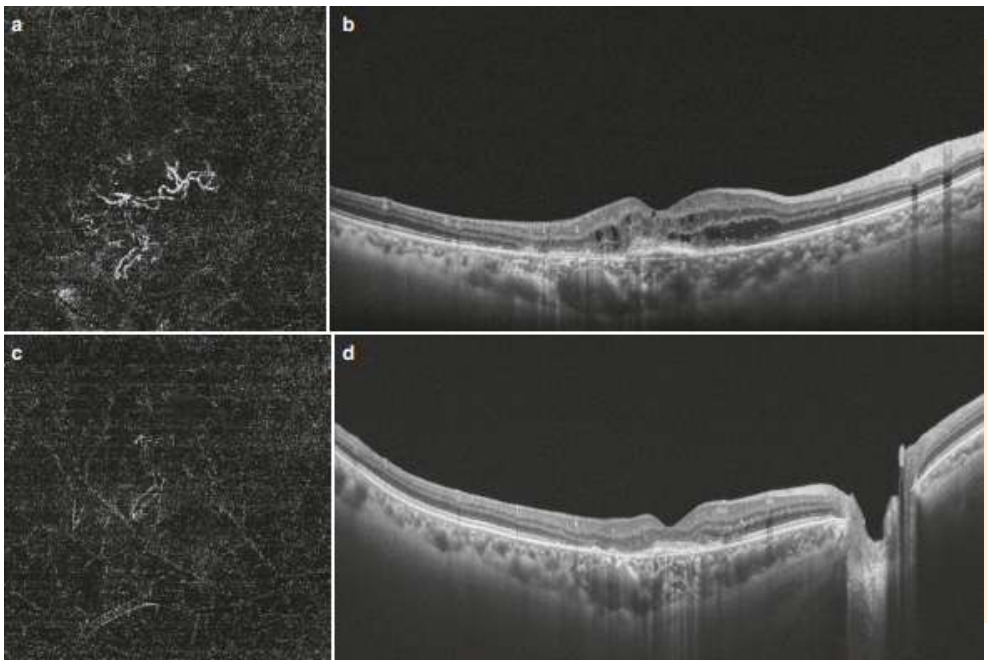


Figure 9-Type 1 CNV. (a, b) OCT and OCTA (Angio 6 × 6 mm, Avascular layer) shows type 1 CNV with intraretinal fuid and macular edema; (c, d) after anti-VEGF treatment, SS-OCT and OCTA (Angio 6 × 6 mm, Avascular layer) indicate that the CNV, intraretinal fuid, and macular edema subsided, while high refex tissue under RPE layer was left

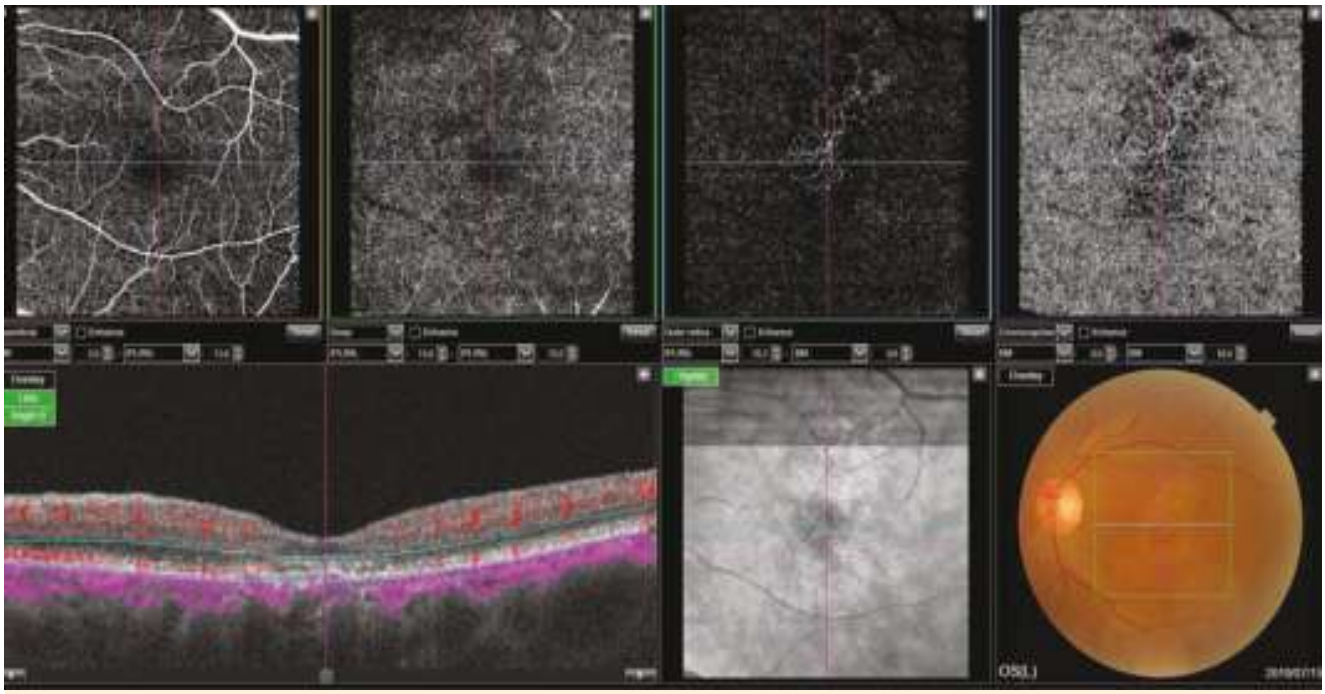


Figure 10-Type 1 CNV after anti-VEGF treatment. OCTA (Angio 6 × 6 mm) of different layers of type 1 CNV after several injections of anti-VEGF agents; Both the outer retina and choriocapillary layer show after anti-VEGF treatment, SS-OCT and OCTA (Angio 6 × 6 mm, Avascular layer) indicate that the CNV, intraretinal fuid, and macular edema subsided, while high refex tissue under RPE layer was left

Polypoidal Choroidal Vasculopathy (PCV)

First described by Yannuzzi et al. [6] in 1982, polypoidal choroidal vasculopathy (PCV) is a common choroidal vasculopathy in Asian populations manifesting as orange-red nodules and tremendous bleeding at the posterior pole. PCV is characterized with aneurysmal dilation, namely "polyp-like," of abnormal branching vascular network (BVN) of the choroid, appearing as specifc orange-red lesion on fundus examination. Patients with this disease most often present with recurrent hemorrhagic or serous retinal pigment epithelial detachments.

Typical OCT features of PCV include PED, PED notch, double layer sign (DLS), pachychoroid, and occasionally focal choroidal excavation. The presence of subretinal and intraretinal fuid indicates that PCV is active, usually corresponding to fuorescein angiography (FA) leakage. Optical coherence tomography angiography (OCTA) is a new noninvasive method of vascular imaging. The detection rate of BVN on OCTA is high. Polyps manifest as the tangled vessel at the end of BVN or type 2 choroidal neovascularization on OCTA, but the detection rate has been reported inconsistently in the literature. [8]

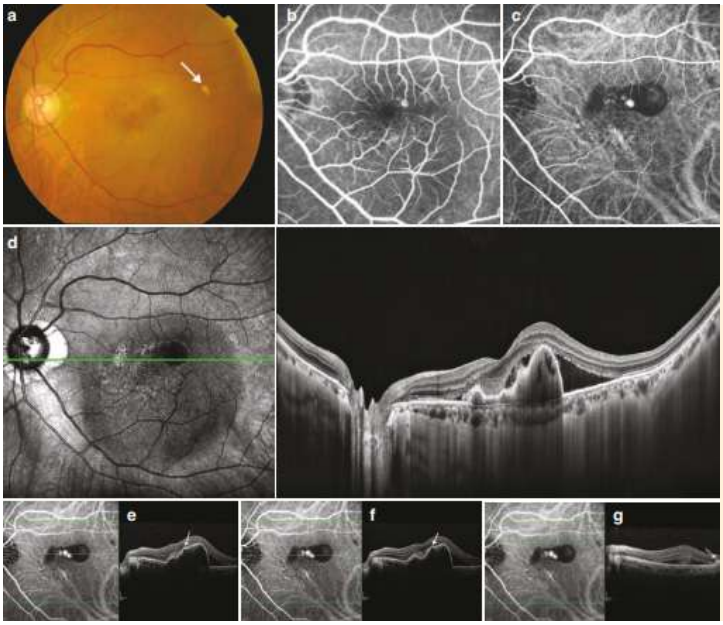
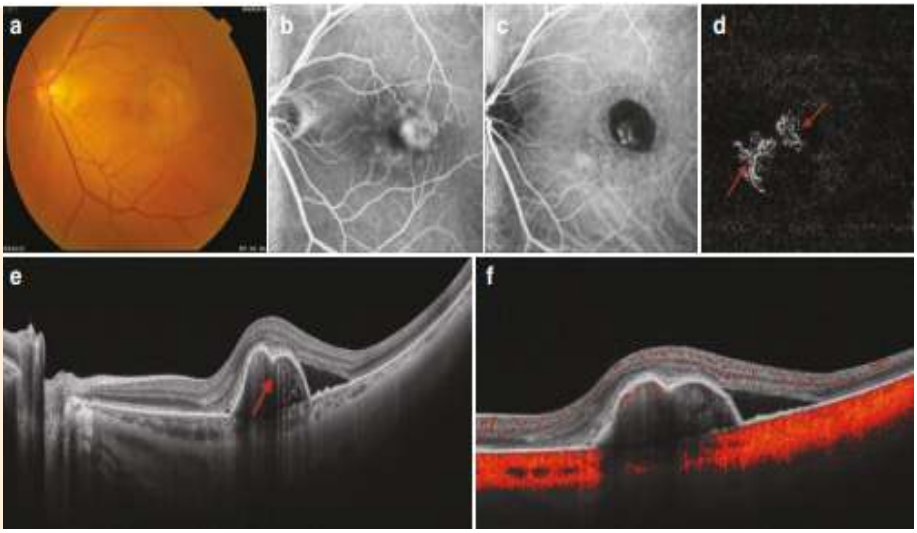


Figure 11-PCV in the left eye (69-year-old male). (a) Color fundus photography shows an orange-red lesion in the macula. Notice the presence of well-defned but irregular pachydrusen on the temporal side of the macula; (b) FFA shows fuorescein leakage in the macula; (c) ICGA shows a spot like hyperfuorescent lesion at the edge of the PED, i.e., a polypoidal lesion. Notice the signifcant dilatation of the inferior temporal vortex vein; (d) 12 mm SS-OCT single-line scan, showing subretinal fuid, PED, and PED notch. The signal underneath PED is heterogenous. The overall choroidal thickness did not increase signifcantly, but there is obvious dilatation of large choroidal vessels (e–g)

Figure 12-PCV in the left eye (67-year-old male). (a) color fundus photography, serous retinal pigment epithelial detachment and orange-red lesion in the macula. (b, c) FFA and ICGA showed fuorescein leakage and dotted hyperfuorescent signal (arrow); (d) en face OCTA shows abnormal sub-PED vessels; (e) wide angle SS-OCT 12 mm horizontal single-line scan shows subretinal fuid, PED, and PED notch (arrow). (f) Angio OCT shows abnormal signal of blood fow in the PED, with the polyp-like lesion beneath the RPE



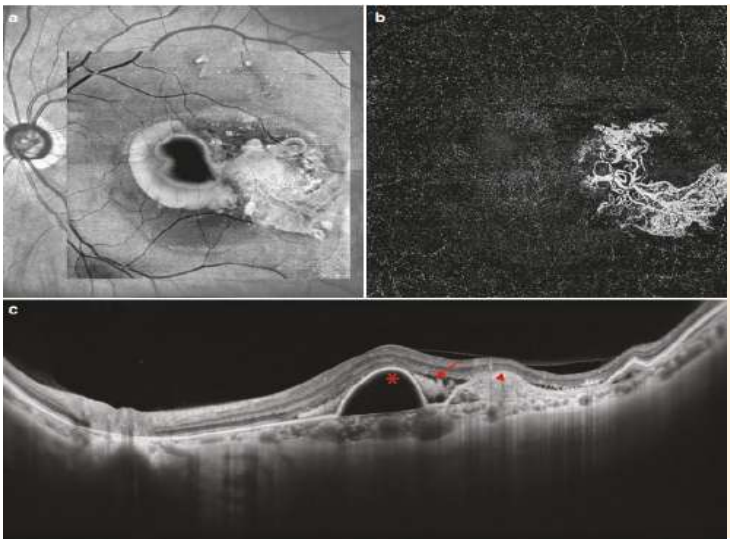


Figure 13-PCV in the left eye (elderly female). (a) En face OCT shows regular low signal for serous PED and heterogenous signal for fbrovascular PED, suggesting that PEDs in PCV patients can be of multiple types. (b) 9 mm × 9 mm SS-OCTA shows BVN and peripheral polyp-like lesion; (c) SS-OCT 16 mm wide-angle single-line scan shows serous retinal pigment epithelial detachment (*), fbrovascular PED (triangle), and subretinal hemorrhagic fuid (arrow). Note the marked dilatation of localized large vessels in the choroid in this patient

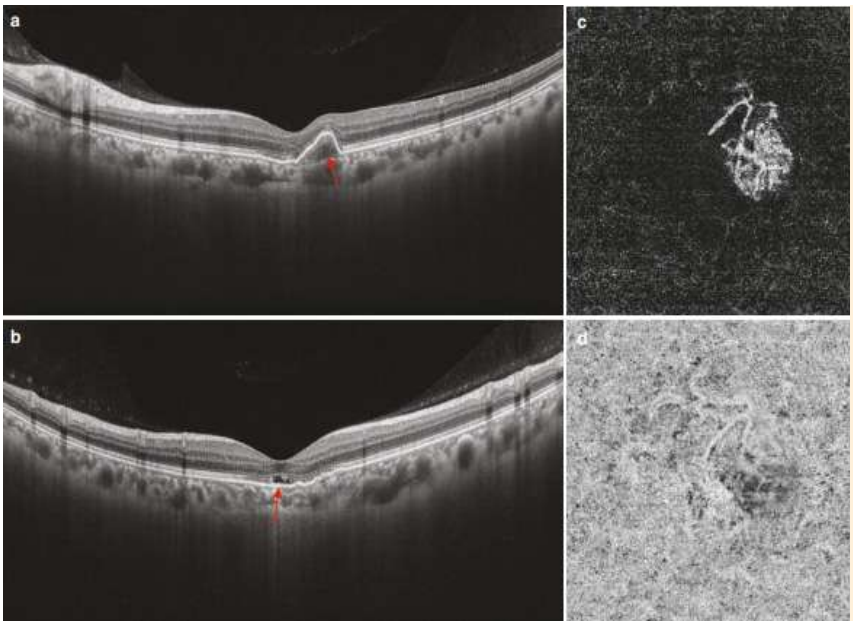
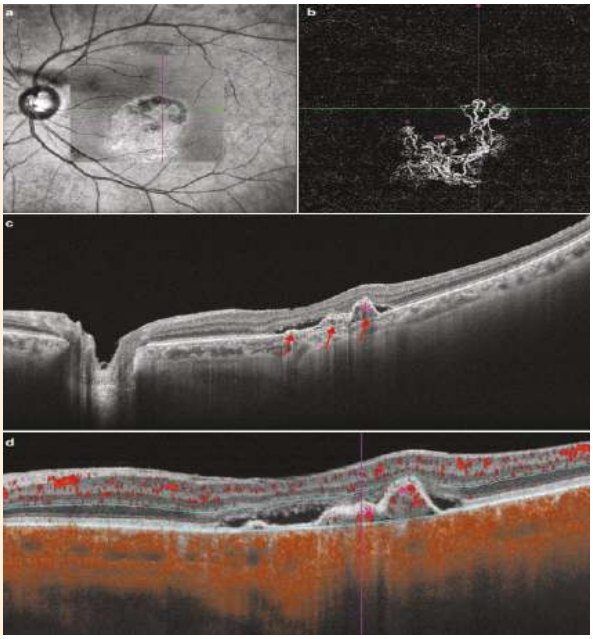


Figure 14-PCV in the left eye (45-year-old male). (a) Wide-feld SS-OCT 12 mm single-line scan. Notice the PED at fovea with bubble sign (arrow), and the clearly dilated choroidal large vessels; (b) Widefeld SS-OCT 12 mm single-line scan (non-major lesion). The PCV lesion originates from the inner layer of the choroid, and the arrow depicts the Bruch's membrane break, where new vessel appears to stem from and grow between the Bruch's membrane and RPE. (c) OCTA shows blood fow signal in the PED and abnormal tangled vessels after stratifcation; (d) OCTA shows large abnormal vessels in choriocapillaris layer

Figure 15 - PCV in the left eye (62-year-old female). (a) En face OCT; (b) 6 mm × 6 mm SS-OCTA shows reticulated abnormal branching vessels in the avascular layer. Notice the twisted and tangled vessels at the edge of the lesion, appearing as polyps (*); (c) 12 mm SS-OCT B-scan. The lesion is mainly located between the RPE and Bruch's membrane, and the polypoidal lesion manifests as an elevated PED with heterogeneous signal (*); (d) SS-OCTA B-scan shows multiple abnormal blood fow signal within the PED (*), suggesting that the lesion is a tangled vessel



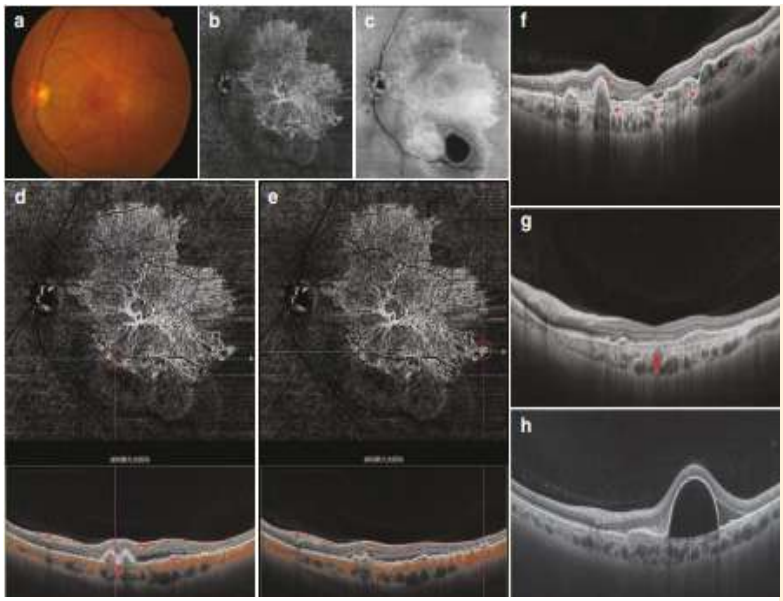


Figure 16-PCV in the left eye (56-year-old male). (a) Color fundus photography shows an orange-red lesion; (b) SS-OCTA (12 mm × 12 mm, 1024 × 1024 pixel) shows a large abnormal vascular network within avascular layer, which branches from the thick trunk of BVN, and the end of the lesion are small vascular tangles; (c) en face OCT shows large lesion in the posterior pole. (d, e) 12 mm × 12 mm SS- OCTA showing a typical polypoidal lesion. En-face OCTA shows tangled vessels (circle), corresponding to the PED (arrow) connected to the double layer sign in B-scan. Blood fow signal is visible beneath the RPE; (f) SS-OCT 12 mm wide-feld single-line scan of chronic PCV. There are many typical features of PCV, the most obvious of which is tremendous double layer sign (triangle), followed by thumblike polys (arrows) and choroidal vessel dilatation. (g) OCT B-scan of the vascular trunk in (b) shows local Bruch's membrane break, where large vessels appear to enter between the RPE and Bruch's membrane; (h) SS-OCT B-scan shows communication of DLS with serous PED

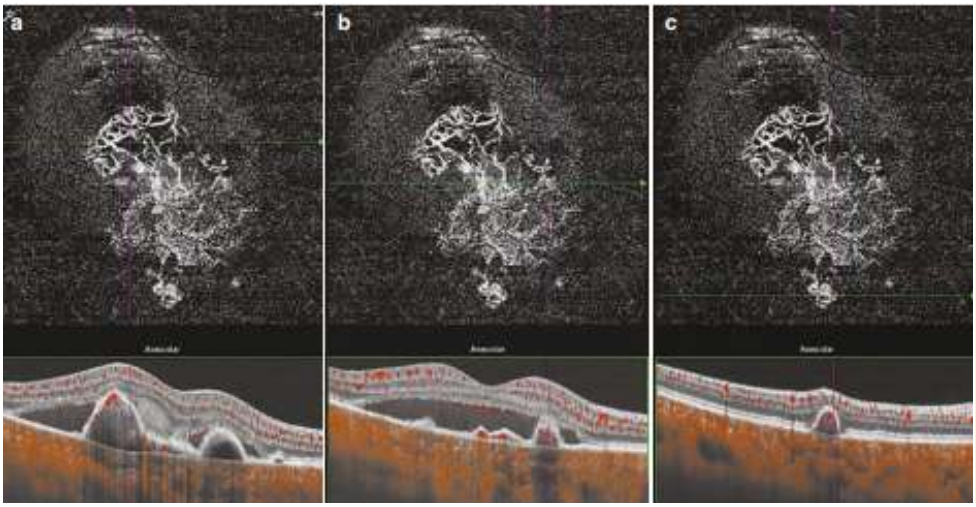
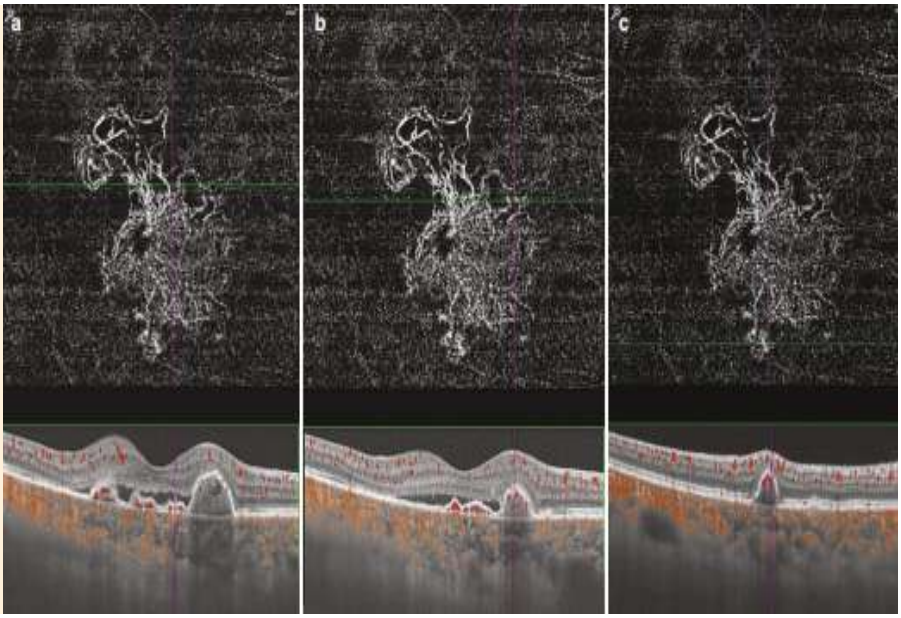


Figure 17-PCV in the right eye before treatment (59-year-old female). The upper part of the scans are 6 mm × 6 mm SS-OCTA, showing the entire lesion with an abnormal branching vascular network (BVN); the lower part are B-scan SS-OCTA in different layers. Before treatment, there were many fne tangled vessels at the end of the BVN, and substantial subretinal fuid in B-scan

Figure 18-Post-PCV treatment in the right eye (59-year-old female). Same patient as Fig. 17. After three injections of anti-vascular endothelial growth factor (VEGF) agents. The upper part of the scans are 6 mm × 6 mm SS-OCTA, showing the entire lesion with an abnormal branching vascular network (BVN); the lower part are B-scan SS-OCTA in different layers. After treatment, most of the disorganized fne tangled vessels at the end of BVN resolved, while the BVN trunk poorly responded to anti-VEGF injections. B-scan showed a signifcant absorption of subretinal fuid, while the sub-RPE polypoidal lesions did not regress significantly



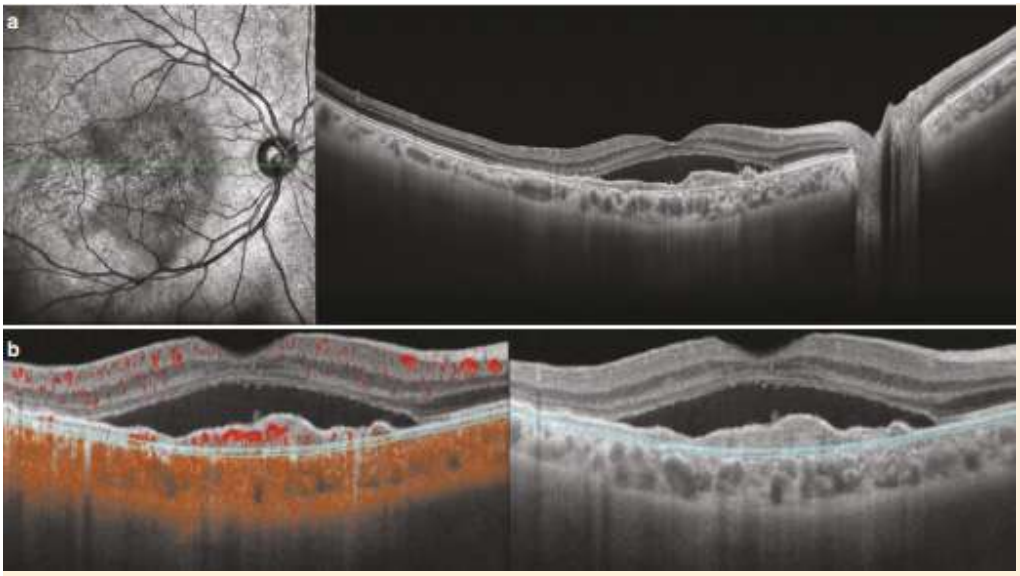


Figure 19-PCV in the right eye (63-year-old male). The patient had a history of visual distortion and vision loss in the right eye for more than 5 years and had been treated with anti-VEGF injections for more than ten times. (a) SS-OCT B-scan 16 mm wide-feld single-line scan showing extensive subretinal blood signal representing the vascular network. (b) OCTA B-scan showing substantial subretinal fuid, indicating despite multiple anti-VEGF injections, there is still leakage from the neovascularization at the end of BVN, and the lesion is still active

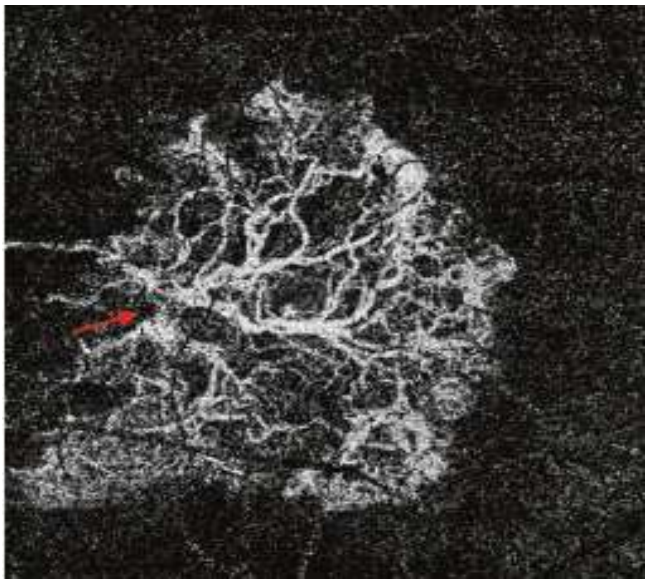


Figure 20 -PCV in the right eye (63-year-old male). Same patient as Fig. 19, 6 mm * 6 mm SS-OCTA of the avascular layer clearly shows the BVN. The arrow shows BVN trunk, where BVN initially breaks through Bruch's membrane, and grows in various directions. The mature abnormal vessel becomes thicker, decreasing in diameter level by level, and ends in tangled vessels

Type 2 CNV (Breaks through the RPE Layer)

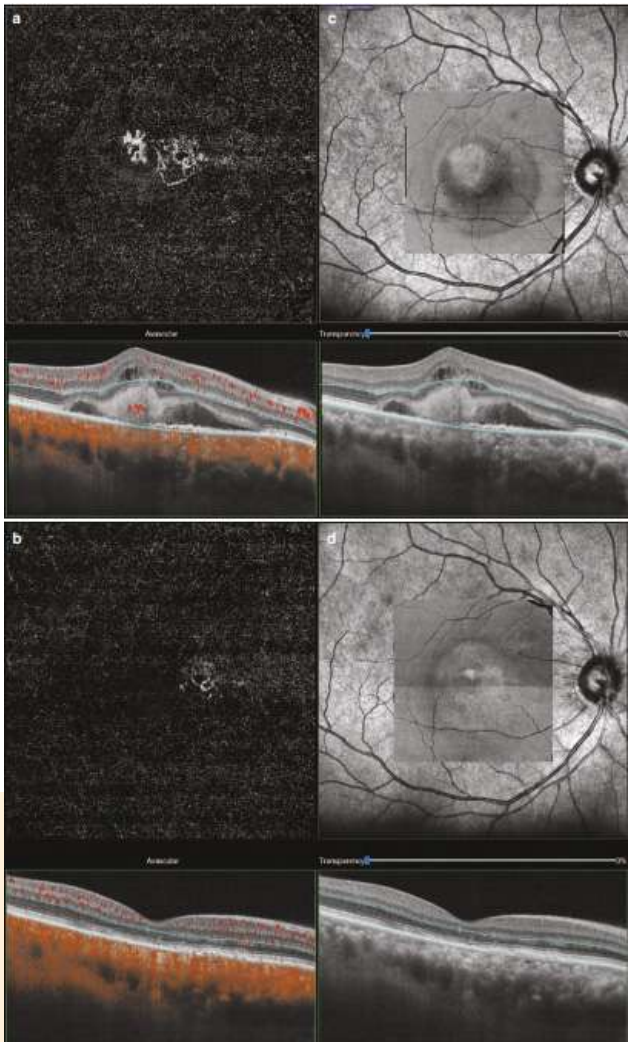


Figure 21-Type 2 CNV. (a, c) SS-OCTA (Angio 6 × 6 mm, Avascular layer) and OCT shows type 2 CNV with hemorrhage, subretinal fuid, and intraretinal fuid; (b, d) after anti-VEGF therapy, OCTA (Angio 6 × 6 mm, Avascular layer) and OCT show CNV regression, hemorrhage, and subretinal fuid absorption, leaving irregular changes in RPE

Type 3 CNV (Retinal Angiomatous Proliferation)

Retinal angiomatous proliferation (RAP) is a special type of AMD, which was frst reported in wet age-related macular degeneration (wAMD). Also known as type 3 CNV, it originates from the deep capillary layer of the paramacular retina and is characterized by multiple small focal retinal hemorrhage, PED, and retinal choroidal anastomosis (RCA), causing serious visual loss

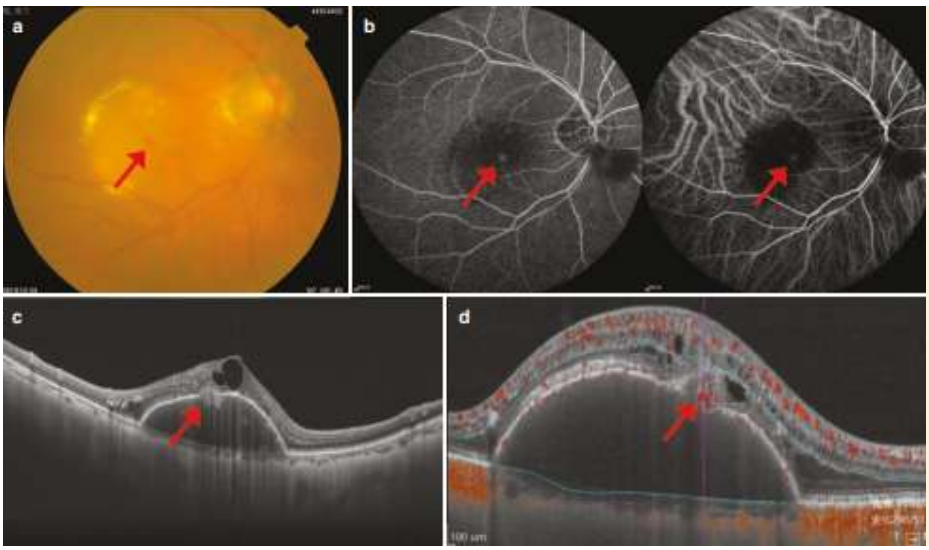


Figure 22-Type 3 CNV. (a) Red lesions (red arrow) can be seen in color fundus photograph; (b) Hyperfuorescent lesion (red arrow) can be seen in FA&ICGA; (c) OCT shows a high refective nodule (red arrow), penetrating from the neuroretina to the RPE layer below. (d) SS-OCTA displays the blood fow signal in the high refective mass (red arrow)

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Review Article

Neuroimaging in neuro-ophthalmic disorders

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Abstract

Advances in neuroimaging and interventional techniques have revolutionized the early diagnosis, prognosis, and treatment of neuro-ophthalmic disorders. These techniques include computed tomography (CT), magnetic resonance imaging (MRI), CT and MR angiographic techniques, catheter digital subtraction angiography, functional MRI, positron emission tomography, and single photon emission computed tomography. In this review, the value of current techniques in the diagnosis, localization, and treatment of various neuro-ophthalmic disorders is described.

Keywords: Neuro-ophthalmology, computed tomography, magnetic resonance imaging, angiography

Introduction

As a superficial organ, the eye is easily accessible to the ophthalmologist for assessment using clinical tests. The initial assessment of the globe, its optical properties, and the light conducting media is best done by direct ophthalmological examination. In case of opacity of the media, or other difficulties in evaluation of the globe directly, ultrasound provides excellent visualization of the orbital contents. However, the evaluation of neural pathways of vision is not possible using these resources. Although initial clinical assessment plays a vital role in assessment of the visual neural pathway, diagnostic imaging is required subsequently to assess the anatomy and pathology of the visual neural pathways. Before the advent of cross sectional imaging, radiological assessment was limited to relatively insensitive techniques such as conventional radiography or tomography. The investigations such as catheter angiography, cisternography, pneumoencephalography, and ventriculography offered limited visualization of intracranial structures. These investigations relied on secondary changes produced in the CSF spaces or vascular anatomy. In addition to being invasive, these investigations had poor sensitivity towards parenchymal pathology. With wider availability and utilization of computed tomography (CT) and magnetic resonance imaging (MRI), the imaging has an increasing role to play in neuro-ophthalmology. These two complementary techniques form the bedrock of imaging in neuro-ophthalmology. Catheter angiography maintains its position in modern imaging primarily limited to intervention and treatment rather than diagnosis. Functional MRI, positron emission tomography (PET), and single photon computed tomography (SPECT) are used mainly as problem solving tools and to provide a functional counterpart to the anatomical information provided by CT and MRI.[1]

Indications

Common indications for which radiological imaging is requested in neuro-ophthalomology are as follows.[2]

- Visual loss, unilateral or bilateral
- Field defects and scotomas
- Anisocoria or ptosis
- Proptosis
- Diplopia or ophthalmoplegia
- Oscillopsia (for example, nystagmus)
- Ophthalmoscopic abnormalities (papilloedema, drusen)
- Pupillary defects

Imaging modalities used

- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- CT and MR angiographic techniques
- Catheter DSA
- fMRI, PET, and SPECT

Computed Tomography (CT)

First results and descriptions of clinical CT were published in British journal of radiology in December 1973, by Hounsfield.[3] CT rapidly became an excellent modality for investigation of CNS, because of relatively static CNS structures and ability to immobilize the head. It depends on relative attenuation of the radiation beam by tissues with different density and atomic number. With rapid advances in computational technology and radiological hardware, it is now possible to image large volumes in very short time, effectively removing the deleterious effects of even physiological movements such as respiration and cardiac motion. Conventional CT was limited to scanning in one plane i.e., the axial plane and other planes had to be reconstructed using computer manipulation leading to loss of resolution in the Z axis. Multi slice helical CT allows acquisition of isometric volumes leading to spatial resolution in the sub mm range in all three planes, removing one of the big disadvantages of conventional CT [Figure 1].

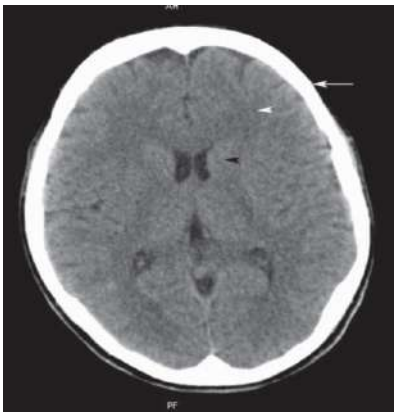

Figure 1-An image from CT of head showing gray matter (black arrowhead) denser than white matter (white arrowhead). Tissues with high calcium content like bone are very dense and appear white (arrow)

Magnetic Resonance Imaging (MRI)

The first principles of image formation by using nuclear magnetic resonance were published by Lauterbur in 1973.[4] Since those early days, there had been rapid development and great progress made in software and hardware capabilities of MRI to overcome many of its early limitations. Similar to CT, the initial work in MRI was predominantly in CNS. The reasons for this are also similar to CT that is the scanning time was very long extending in some cases up to 45 to 60 mins. However, rapid progress in computational capabilities has led to considerable reduction in imaging times. In current practice, MRI is the imaging modality of choice in all neuro-radiological imaging.[1,2,5] With dense bone surrounding the optic nerve at the apex of orbit, MRI provides unique possibilities of assessing the intrinsic lesions of the optic nerves and tracts. The study depends on interaction of protons (hydrogen nuclei) with a strong magnetic field in which they are placed. The CT was an extension of conventional imaging where it studied attenuation differences in tissues. The use of detectors and computers to enhance the difference in attenuation, changed the amount of information available, but did not change the kind of information available. The MRI has proven to be a paradigm shift in imaging as it involves fundamentally different principles and physics for assessment of anatomy and pathology. MRI offers the possibility of varying many factors thus opening up a large vista of different protocols and sequences and thus can have a long learning curve [Figures 2–5].

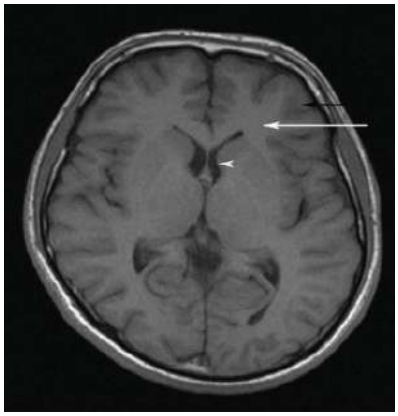

Figure 2- T1 weighted MR showing dark grey matter (black arrow), brighter white matter (white arrow) and dark CSF (White arrowhead)

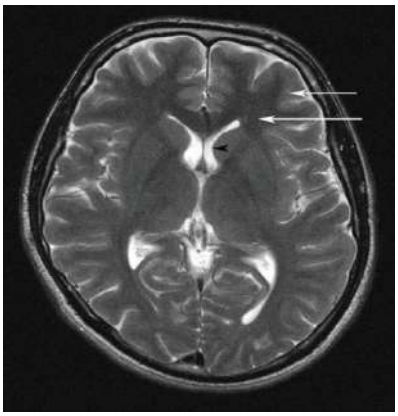

Figure 3- T2 weighted MR showing bright CSF (black arrowhead), dark white matter (long arrow) and brighter gray matter

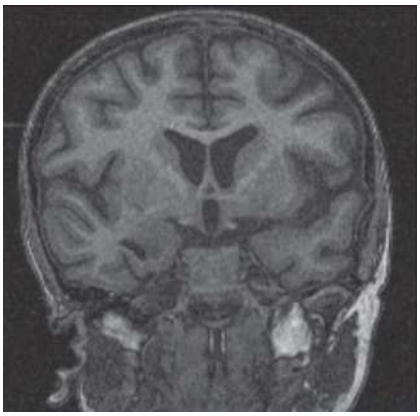

Figure 4- Thin section high resolution gradient echo MR image

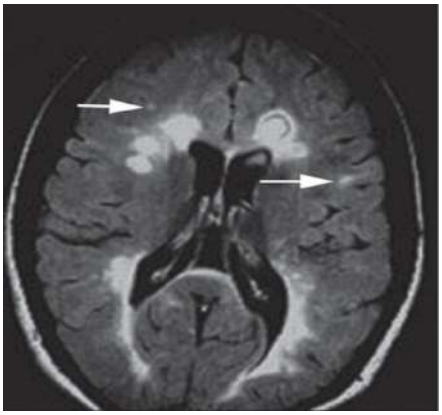

Figure 5- FLAIR MR Image showing bright signal from the plaques of MS (white arrows)

Although the advantages offered by MRI are many, there are certain areas where CT can be more useful such as, evaluation of bony trauma, evaluation of calcification, and in very sick patients who need rapid assessment [Table 1]. In spite of all attempts, there is a small number of patients who can not undergo MRI because of claustrophobia.[6]

Table 1- A brief comparison of CT and MRI imaging capabilities

Computed tomography	*Magnetic resonance imaging*
Ionizing radiation	No ionizing radiation
Excellent visualization of acute hemorrhage	Difficult visualization of acute hemorrhage
Very sensitive to calcifi cation and bony lesions	Difficult visualization of calcifi cation and bony lesions
Limited planes	Multi planar imaging
Limited visualization near dense bone	Dense bone does not impose any limitation
Limited contrast resolution in soft tissues	Superb soft tissue contrast resolution
Quick to obtain, easily available, inexpensive	Limited availability, time consuming, expensive

Note: In addition to the above, the patients who are on life support systems are difficult to assess with MRI as most life support systems are not compatible with MRI. Special life support equipment compatible with MRI is available but is very expensive.

CT and MR angiography

The patients with suspected vascular abnormalities may undergo assessment using MR or CT angiographic techniques. The CT angiography entails assessment of arteries after intravenous injection of iodinated contrast; it provides anatomical information. On the contrary, MR depends on flowing blood to provide contrast, and MRA can be done with or without intravenous contrast [Figures 6 and 7].

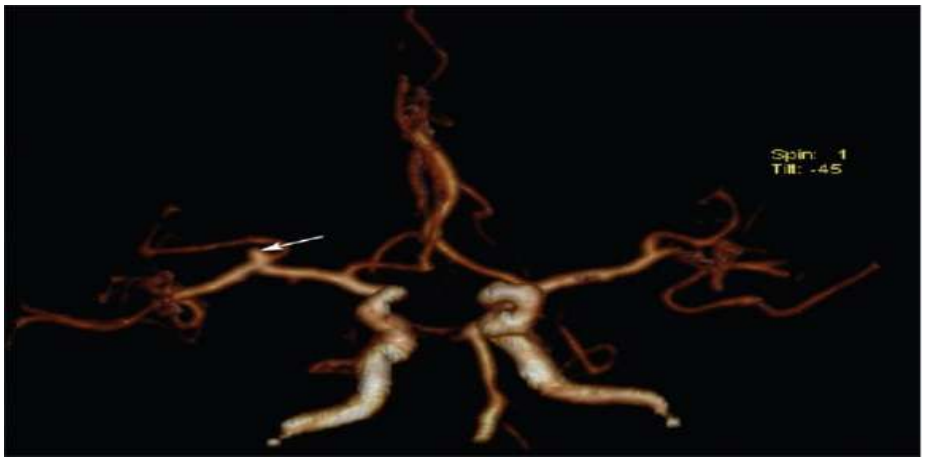

Figure 6- CT angiography showing a right middle cerebral artery aneurysm (white arrow)

Figure 7- MR angiography showing normal vasculature at the skull base

Diffusion weighted imaging and white matter tractography

The diffusion weighted uses the property of Brownian motion of free water molecules to assess the freedom with which the molecules can move in a particular tissue. Generally, the pathology is demonstrated by restriction of diffusion. An extension of this technique is used for white matter fiber tracking. In axons, the water is free to diffuse along the length of the white matter fiber tracks but diffusion is restricted at right angle to the length of the white matter tracts. This is called anisotropic diffusion. By acquiring diffusion weighted images in multiple planes it is possible to track the white matter fibers along their course. This technique has potential implications in assessment of the following: white matter tract connectivity in congenital anomalies; age related degenerative changes in white matter tracts; demyelinating conditions of white matter; neoplastic involvement and displacement of white matter tracts; and surgical treatment of CNS pathology while sparing the white matter tracts leading to reduced morbidity of the surgical procedure [Figure 8][6-8]

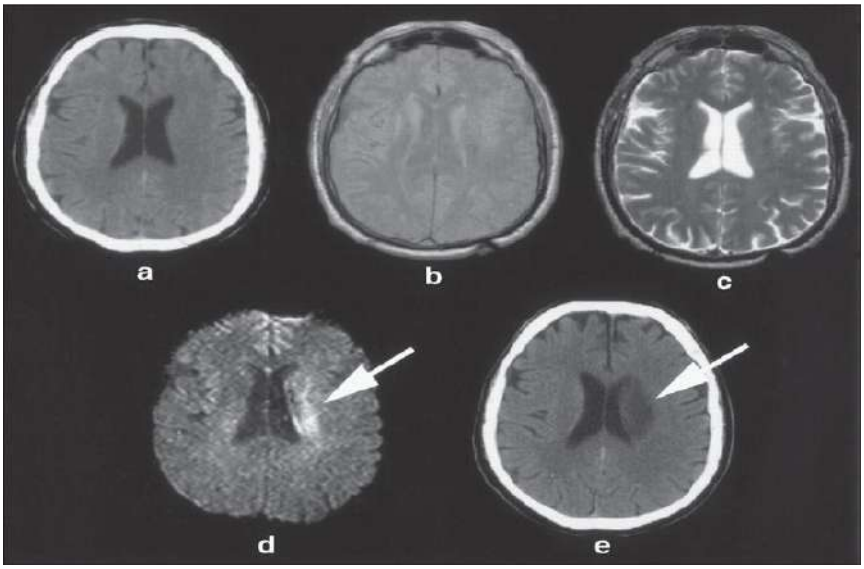

Figure 8- Composite image showing advantage of diffuse weighted MR in acute infarct.a,b and c show normal CT, and conventional MR images not showing the infarct. Diffusion weighted image (d) shows an area of restricted diffusion in left anterior cerebral artery distribution consistent with an infarct.A CT at 48 hours, and (e) shows the infarct

Catheter angiography and treatment

Prior to advent of the CT and MR angiography, catheter angiography formed the basis of all vascular assessment in the CNS. Besides being an invasive procedure, it has the potential to precipitate potentially devastating neurological sequelae. As a result, the CT and the MR angiographic techniques are supplanting catheter angiography for diagnostic purposes. However, with advances in catheter techniques and materials, catheter angiography has come to play a central role in endovascular management of many CNS vascular lesions with excellent results [Figure 9].[9]

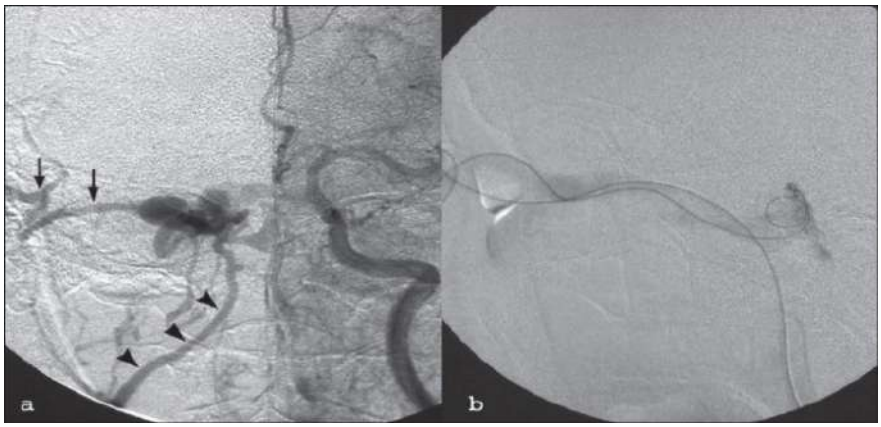

Figure 9- Catheter DSA in a patient with carotico cavernous fistula. The black arrows and arrowheads in (a) show orbital veins, and in (b) show catheterization of fistula prior to endovascular treatment

Guidelines

In general, MRI is the investigation of choice for most neuro-ophthalmological assessments. CT is better for evaluation of bony orbit in patients of trauma or suspected destructive osseous lesions. It is also superior for detection of presence of calcification such as in optic nerve drusen. The fact that MRI entails so many different variables leading to many sequences such as T1, T2 weighted, FLAIR, GRE, diffusion weighted imaging, spectroscopy, etc. means that the studies need to be tailored to the patients' needs and clinical requirement. As in CT, IV contrast improves visualization of the lesions. Typically, the clinician need not worry about different sequences, as the imaging radiologist will decide which sequences will provide maximum information, depending on the patients' clinical picture in the shortest time. This in turn places extra responsibility on the shoulder of the referring physician to provide complete and accurate information regarding the patients' clinical profile, as it will determine what imaging the patient should undergo. Typically, the clinical information must include the site of suspected lesion and if possible the nature of suspected lesion. The information on site is important to allow detailed study of the relevant area. As detailed study of multiple areas in one examination ends up adding the time required for each examination individually; which leads to a very long and time consuming examination which in turn reduces the patient cooperation. Another potential down side in trying to cover a large area is reduced resolution in an attempt to reduce time of examination. The information regarding the nature of the suspected pathology is important in deciding the protocol of examination and if intravenous contrast is required. In case of any doubt or confusion regarding which examination would best serve the interests of the patient, the best course of action would be to contact the radiologist. Direct interaction with the radiologist will reduce the potential for miscommunication and allow the radiologist to ask for supplementary information and give his suggestions regarding the best course of action.

Common errors

Wolintz *et al*., in 2004 reviewed their case material for assessing the errors in use of MRI for neuro-ophthalmic disorders.[10] According to them the errors could be divided into prescriptive and interpretive errors. Each of these categories could further be divided into four types.

The four prescriptive errors were:

- Failure to apply a dedicated study.
- Inappropriate application of a dedicated study.
- Omission of intravenous contrast.
- Omission of specialized sequences.

The interpretive errors were:

- Failure to detect a lesion because of misleading clinical information.
- Rejection of a clinical diagnosis because an expected imaging abnormality was absent.
- Assumption that a striking abnormality accounted for the clinical abnormality.
- Failure to consider lack of clinical specificity of the imaging abnormalities.

After reviewing the above points it is clear that most of the errors resulted directly from inadequate communication between the referring clinician and the performing and interpreting radiologist.

Suggestions for improving the results

The most common point of dispute is when either the imaging is normal in face of definite clinical signs or the imaging finding is not able to explain the clinical profile of the patient. In these cases the solution is to call the radiologist and discuss the case. Preferably, the neuro-ophthalmologist and the radiologist should together see the images and ensure the adequacy of the study. In such cases, the clinician brings his clinical acumen and possibly additional clinical data to the table and then the radiologist can make sure that the clinically relevant areas are imaged adequately without any artifacts. In case, the clinical symptomatology is progressive, it is also appropriate during this discussion to see if additional imaging with different imaging parameters such as different magnification or slice thickness will improve or add to the quality of imaging. Finally the referring clinician must realize that the images are representation of different processes in the patient and could be normal in face of definite clinical findings.[11]

Teaching points

An imaging study is only as good as the clinical information provided to the radiologist.

Communication between the referring clinician and the radiologist is the single most important problem solving mechanism in difficult or complicated cases.

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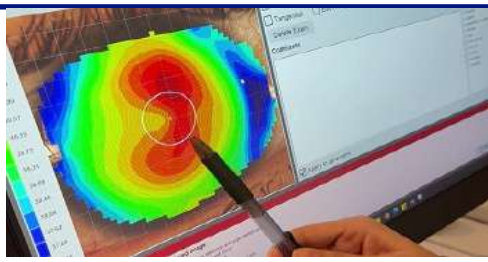
Review Article

Corneal Topography and Tomography



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Abstract

Introduction: Accurate assessment of the corneal shape is important in cataract and refractive surgery, both in screening of candidates as well as for analyzing postoperative outcomes. Although corneal topography and tomography are widely used, it is common that these technologies are confused. The aim of this study was to present the current developments of these technologies and particularly distinguish between corneal topography and tomography. Methods: The PubMed, Web of Science and Embase databases were the main resources used to investigate the medical literature. The following keywords were used in various combinations: cornea, corneal, topography, tomography, Scheimpflug, Pentacam, optical coherence tomography. Results: Topography is the study of the shape of the corneal surface, while tomography allows a three-dimensional section of the cornea to be presented. Corneal topographers can be divided into large- and small-cone Placido-based devices, as well as devices with color-LEDs. For corneal tomography, scanning slit or Scheimpflug imaging and optical coherence tomography may be employed. In several devices, corneal topography and tomography have been successfully combined with tear-film analysis, aberrometry, optical biometry and anterior/posterior segment optical coherence tomography. Conclusion: There is a wide variety of imaging techniques to obtain corneal power maps. As different technologies are used, it is imperative that doctors involved in corneal surgery understand the science and clinical application of devices for corneal evaluation in depth.

Keywords: cornea; topography; tomography; optical coherence tomography; keratograph; scheimpflug imaging; pentacam

Introduction

Accurate assessment of the corneal shape is important in cataract and refractive surgery, both in screening of candidates for surgery as well as for analyzing postoperative outcomes [1–3]. It is also critical for the diagnosis of corneal disorders, which include keratoconus, pellucid marginal degeneration, corneal scars, limbal dermoid or pterygium. It can also be used in contact lens fitting, for assessment of intrastromal ring placement and several other conditions.[4] primarily, corneal topography has only been used to describe the anterior surface of the cornea. Devices are now able to characterize both the anterior and posterior corneal surfaces, creating a three dimensional map of the cornea. Advances in digital photography and computer processing have immensely increased the utility of corneal imaging techniques. It is imperative that doctors involved in corneal surgery understand the science and clinical application of devices for corneal evaluation in depth.[4] The aim of this study was to present the current developments of these technologies and particularly distinguish between corneal topography and tomography.

Methods

The PubMed, Web of Science and Embase databases were the main sources used to investigate the medical literature. An extensive search was conducted to identify articles in the matter of "corneal topography" and "corneal tomography" up to 28 June 2021 (Supplementary Materials). The following keywords were used in various combinations: cornea, corneal, topography, tomography, imaging, Scheimpflug, Pentacam, optical coherence tomography, OCT. Of the studies retrieved by this method, we reviewed all papers in English and the abstracts of non-English publications. The reference lists of these articles were also considered as a potential source of information. We attempted to present all methods that allowed a precise evaluation of the corneal shape. Emphasis was placed on studies published after the reviews by Oliveira et al.[5]and Shih et al.[6] However, we aimed to present the current developments of these technologies and particularly distinguish corneal topography and tomography.

Results

The search identified 2633 unique articles. After removing duplicates and irrelevant studies, 91 articles were included in the review. Interestingly, a search of a combined phrase “topography” and “Pentacam”, which is obviously incorrect as Pentacam is a corneal tomographer, gave 687 results.

Corneal Topography

The expression topography is derived from the Greek words “place” (topos) and “to write” (graphein), which means to describe a place.[7] This was originally related to studying the shape of the Earth’s surface and features or those of planets, moons and asteroids.[8] Topography is the study of the shape of the corneal surface [9]. The beginnings of corneal topography date back to the 17th century.[10] A major advancement was achieved by António Plácido da Costa (1848–1915), a Portuguese ophthalmologist and microbiologist, who introduced a handheld device for precise evaluation of the corneal shape and published his report in 1880.[11–13] The tool had a diameter of 23 cm, with painted concentric black and white circles, and an opening in the center of the device. The patient was to be placed in a well-lit location (e.g., in front of a window), and the corneal reflex from the keratoscope was to be evaluated at a distance of 15 cm from the cornea. Currently, most of the corneal topographers employ a Placido disc (the examination is historically named keratoscopy) and a system for image registration (videokeratoscopy). The contemporary devices employed for corneal topography are presented in Table 1. Placido-disc devices can be classified as either large-cone (Figure 1) or small-cone systems. Small cones collect more data points and thus could be more accurate. However, they have a shorter working distance, which might make it more difficult to collect data in patients with deep orbits. Several Placido topographers acquire data based on 22 white Placido rings, with an angular resolution of 2 degrees.[14] Although corneal topographers allow instant image acquisition, their disadvantages include skew ray error [15,16], data interpolation at the corneal apex [17] and potential inaccuracy in areas of abrupt corneal elevation changes.[18,19]

Figure 1. Corneal topography in the Oculus Keratograph 5 M

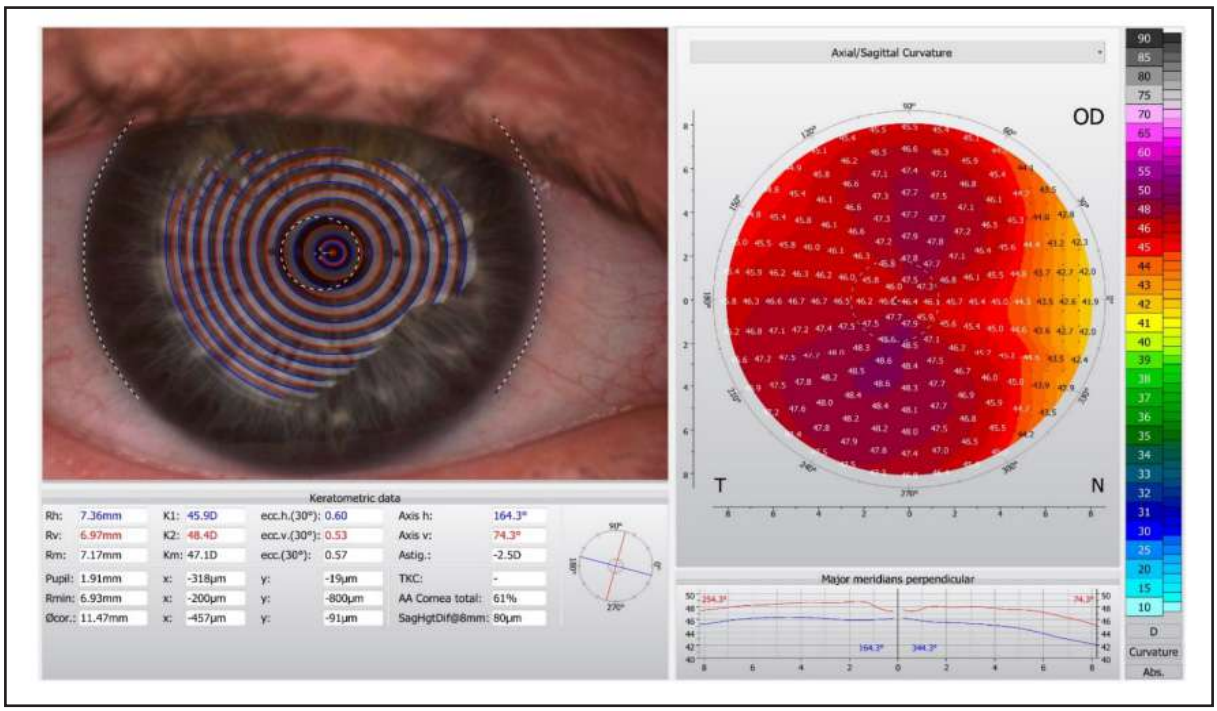

Table 1. Techniques employed for corneal topography in some of the currently used devices.

Technology	Details	Example Topographers
Placido disc	Large-cone topography	CSO Antares, CSO Sirius+ *, CSO MS-39 * Oculus Keratograph 5 M Topcon KR-1W Zeiss Atlas Ziemer Galilei *
Placido disc	Small-cone topography	Medmont E300 Optikon Keratotron
Color light-emitting diode	Point-to-point reconstruction of specular reflections	i-Optics Cassini i-Optics Cassini Ambient

* Devices that enable both corneal topography and tomography images to be obtained.

Corneal topographers can also be used for the non-invasive assessment of the tear film; in this case, texture analysis of the Placido-ring is employed to detect tear film anomalies.[20] Additionally, an infrared ring illumination can be provided to prevent glare-related artifacts [21]. Currently, the Oculus Keratograph 5 M (K5 M; Oculus GmbH, Wetzlar, Germany) is one of the most commonly used tools to analyze the tear film [22]. The noninvasive keratograph tear break-up time readings were shown to display superior discriminative ability in detecting dry eye compared to conventional tear-film stability measurements [23]. Corneal topography has also been combined with aberrometry, e.g., in the iTrace (Tracey Technologies, Houston, TX, USA) and OPD-scan (Nidek CO. Ltd., Tokyo, Japan) [24,25]. In these devices, corneal topography and the wavefront map can be linked to each other, which enables subtracting of the corneal aberrations from the total eye aberrations (Figure 2). Moreover, the aforementioned devices provide repeatable measurements of the near and distatance spherocylindrical refraction [26]

Figure 2. The Tracey iTrace device allows corneal aberrations to be analysed

Topographical images can also be calculated by projecting other-than-Placido images on the corneal surface. The PAR Technology Corneal Topography System introduced by Belin et al. produced a true topographic map by analyzing a projected grid on the corneal surface [27–29]. Another modality of corneal topography, which is currently available commercially, is color-LED corneal topography. The method was introduced in 1997 [30], and the device was released commercially in the last few years. The Cassini (i-Optics, Hague, Netherlands) corneal topographer is able to analyze the corneal shape based on point-to-point reconstruction of specular reflections of 679 pseudo-random colored points [31]. The potential advantage of this approach over Placido-based systems is that it is not affected by the Placido mismatch, resulting in a proper reconstruction of non-rotationally symmetrical or distorted corneal surfaces [32–34]. In a study by Klijn et al., the magnitude of corneal astigmatism obtained with the Cassini topographer was not different to that obtained with the Pentacam (Oculus Optikgeräte, Wetzlar, Germany), the Lenstar (HaagStreit, Koeniz, Switzerland) and the Keratotron (Optikon, Rome, Italy) [31]. With that, the repeatability of the cylinder measurements was higher than with the Pentacam or Keratotron ($p < 0.001$). Even though the keratometric values obtained with Cassini are similar to those of the Pentacam and IOL Master 500 (Carl Zeiss Meditec AG, Jena, Germany) [35,36] or the Orbscan IIz (Bausch and Lomb Surgical, Rochester, NY, USA) and Lenstar LS-900 (Haag-Streit Holding, Köniz, Switzerland) [37], the wide data spread discourages their interchangeable use to assess corneal power and astigmatism. Color LED topography also enables evaluation of the posterior surface using 2nd Purkinje imaging technology [38]. One might consider that measuring the total instead of anterior corneal astigmatism may decrease the residual astigmatism in toric IOL implantation [39]. The Cassini system has been shown to determine consistent measures of posterior corneal curvature and astigmatism in healthy eyes, but only measures of posterior astigmatism could be considered as interchangeable with those provided by the Pentacam [40]. In another study, for the astigmatism analysis, measurements from the anterior cornea obtained with color-LED topography showed an excellent agreement with Pentacam measurements, but the agreement was poor for the corneal posterior surface and particularly the magnitude of astigmatism [41,42]. Furthermore, when analyzing corneal aberrometry measurements obtained with the Cassini device in healthy eyes, they were not interchangeable with results provided by the Scheimpflug-based topography [43].

Corneal Tomography

Tomography is derived from the Greek words “cut section” (tomos) and “to write” (graphein). In medicine, the classic term computed tomography refers to a quickly rotating narrow X-ray beam, processed to generate cross-section images of an internal solid organ; based on these images, it is possible to produce a three-dimensional reconstruction of an anatomical structure. Similarly, corneal tomography allows the generation of a stereographic model of the cornea, enabling analysis of the front and back surfaces of the cornea, along with pachymetry mapping. Currently, the corneal tomography images might be obtained with (i) Scanning slit devices, e.g., Orbscan IIz (Bausch & Lomb, Rochester, NY, USA); (ii) The Scheimpflug cameras, i.e., the Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany), Galilei (Ziemer Ophthalmic Systems AG, Port, Switzerland) and Sirius (CSO, Firenze, Italy); the latter two have an additional large cone Placido disc incorporated; (iii) OCT-based devices, e.g., the Anterion (Heidelberg Engineering, Heidelberg, Germany) Visante (Carl Zeiss Meditec AG, Jena, Germany) (Table 2).

Table 2. Techniques employed for corneal tomography in some of the currently used devices.

Technology	Light Source (Wavelength)	Example Tomographers
Scanning slit	white flash light	Orbscan II
Scheimpflug imaging	blue-light emitting diode (470–475 nm)	CSO Sirius+ * Mediworks Scansys Oculus Pentacam Ziemer Galilei *
OCT	superluminescent diode laser (830–845 nm)	CSO MS-39 * Optopol Revo
SS-OCT	rapidly tuned laser with longer wavelength (1310 nm)	Heidelberg Engineering Anterion Tomey Casia SS-1000/Casia 2 Zeiss Visante OMNI *

* Devices that enable both corneal topography and tomography images to be obtained. Abbreviations: LCOR—low-coherence optical reflectometry, OCT—optical coherence tomography, PCI—partial coherence interferometry, SS-OCT—swept source-OCT.

Optical cross-sectioning for corneal analysis was first commercially introduced in 1995 with the Orbscan device (Bausch & Lomb Surgical, Rochester, NY, USA) [44,45]. The system employed slit scanning by a projection of 40 slits (12.50 mm high and 0.30 mm wide). The device calculated the corneal curvature based on the calculation of the front edge of the slits, but the images were not displayed for evaluation [45]. A significant problem was that the horizontal scanning did not have a shared point for the slits. Subsequently, the slit scanning system was combined with a Placido-disk attachment in the Orbscan II. Digital Scheimpflug tomography has been recognized as the evolution of slit scanning systems [45] (Figure 3). Within these devices, a rotating Scheimpflug camera is employed; these systems have the ability to measure the dispersion of light along the optical axis, allowing the detection of changes in the transparency of the lens over time [46]. Devices with a rotating Scheimpflug camera evaluate not only the cornea, but the entire anterior segment from the anterior corneal surface to the posterior lens surface [47,48]. Visualizing the anterior chamber morphology is critical to establish the long-term safety of phakic IOLs. One of the most threatened potential complications of any type of anterior segment surgery, and particularly after anterior chamber and iris-fixated IOLs, is accelerated endothelial cell loss [49,50]. This risk has been shown to be negatively correlated with the anterior chamber depth, and the position of these IOLs in the anterior chamber is one of the main safety parameters in both preoperative screening and follow-up [51]. Assessment of anterior chamber morphology is also critical for implantable collamer lens (ICL) assessment; if an inserted ICL is too large, it might bow anteriorly, causing anterior chamber shallowing and introducing a risk of pupillary block and angle-closure glaucoma [52,53] In contrast, if [52,53] In contrast, if the ICL vault is insufficient, it might potentially result in contact between the ICL and the crystalline lens, causing subsequent cataract formation [54]

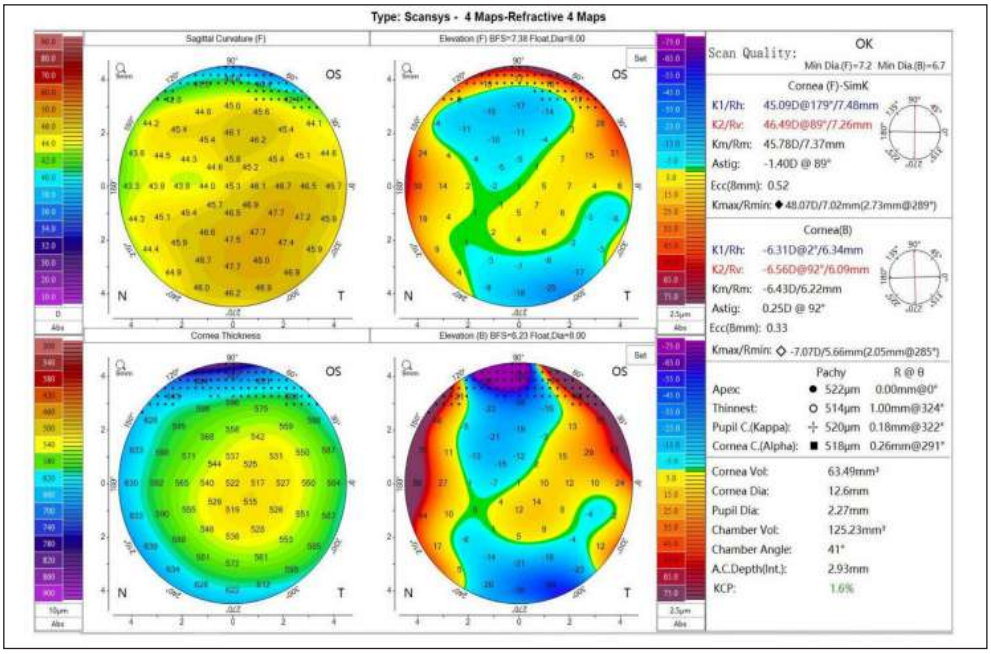

Figure 3. Scheimpflug corneal tomography in the Mediworks Scansys tomographer.

Corneal tomography characterizes the elevation of the front and back corneal surfaces and reconstructs the pachymetric mapping, which has significantly enhanced the sensitivity and specificity for detecting corneal ectasia [8,55]. A significant advantage of tomography compared to topography is the possibility to determine the true corneal power; to calculate it, it is required to assess the posterior corneal surface. In most keratometric devices, the relationship between the anterior and posterior corneal surfaces is considered as constant and estimated based on a theoretical “keratometric index”. Evaluation of the power of the posterior corneal surface is critical in IOL calculations in eyes having undergone laser vision correction. As in corneal refractive surgery, corneal tissue is removed for refractive purposes, and as a consequence, the altered relationship between the front and back surfaces invalidates the use of the standardized index of refraction. Moreover, recent investigations showed that in virgin eyes, the magnitude of anterior and posterior astigmatism is greater when the steep axis of the anterior astigmatism is oriented vertically [56]. Thus, neglecting measurements of the posterior corneal surface might result in overestimation of with-the-rule astigmatism, whereas in eyes with against-the-rule astigmatism, the magnitude of astigmatism can easily be underestimated. Therefore, accurate assessment of the total corneal power, and specifically its astigmatism, with corneal tomography devices could potentially increase the refractive outcome in cataract and refractive lens extraction surgery [57–60]. Currently, the Zeiss IOL Master 700, Oculus PenFigure 3. Scheimpflug corneal tomography in the Mediworks Scansys tomographer. Corneal tomography characterizes the elevation of the front and back corneal surfaces and reconstructs the pachymetric mapping, which has significantly enhanced the sensitivity and specificity for detecting corneal ectasia [8,55]. A significant advantage of tomography compared to topography is the possibility to determine the true corneal power; to calculate it, it is required to assess the posterior corneal surface. In most keratometric devices, the relationship between the anterior and posterior corneal surfaces is considered as constant and estimated based on a theoretical “keratometric index”. Evaluation of the power of the posterior corneal surface is critical in IOL calculations in eyes having undergone laser vision correction. As in corneal refractive surgery, corneal tissue is removed for refractive purposes, and as a consequence, the altered relationship between the front and back surfaces invalidates the use of the standardized index of refraction. Moreover, recent investigations showed that in virgin eyes, the magnitude of anterior and posterior astigmatism is greater when the steep axis of the anterior astigmatism is oriented vertically [56]. Thus, neglecting measurements of the posterior corneal surface might result in overestimation of with-the-rule astigmatism, whereas in eyes with against-the-rule astigmatism, the magnitude of astigmatism can easily be underestimated. Therefore, accurate assessment of the total corneal power, and specifically its astigmatism, with corneal tomography devices could potentially increase the refractive outcome in cataract and refractive lens extraction surgery [57–60]. Currently, the Zeiss IOL Master 700, Oculus Pentacam AXL and Anterion (Heidelberg Engineering, Heidelberg, Germany) allow measurement of the posterior corneal astigmatism [56] (Figure 4). Moreover, an ultra-fast Scheimpflug camera was implemented in the Corvis ST (OCULUS Optikgeräte GmbH, Wetzlar, Germany).

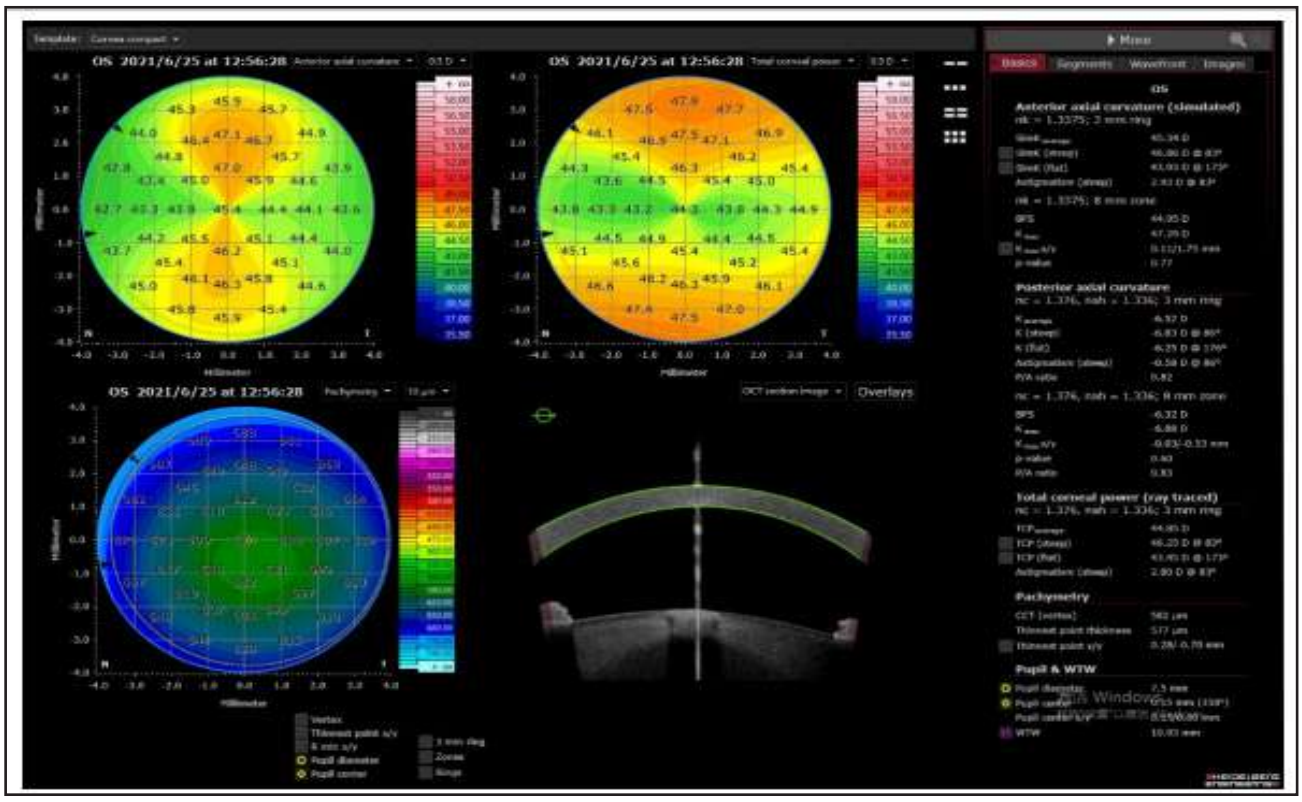

Figure 4. Corneal tomography in a swept-source optical coherence tomography device, the Anterion (Heidelberg Engineering)

Optical coherence tomography (OCT) systems analyze measurements of the echo time delay of backscattered or backreflected light by using an interferometer with a mechanically scanned optical reference path [63–65]. OCT devices can be classified into spectral-domain OCT (SD-OCT) and time-domain OCT (TD-OCT). SD-OCT is associated with a rapid scan speed, less noise and higher resolution compared to TD-OCT, but the imaging field is smaller [66]. Swept-source OCT (SS-OCT) devices use a short-cavity swept laser instead of the superluminescent diode laser typical for conventional SD-OCT [67]. The shorter the wavelength used in the OCT device (Table 2), the shorter is the imaging range. Both SD-OCT and TD-OCT allow visualization of the cornea, anterior chamber and iridocorneal angle [66,68–70]. The applicability of employing OCT for corneal tomography was demonstrated more than 10 years ago [71,72]. A problem in obtaining corneal tomography images with OCT is the fan distortion [71]; thus, some SD-OCT devices allow only pachymetry but not tomography images to be obtained. For example, the Optovue SDOCT (Freemont, CA, USA) is able to acquire eight evenly spaced 6.0 mm radial crosssections in order to provide corneal curvature data and corneal and epithelial thickness maps; however, it does not allow for the obtaining of precise maps of the corneal power [73,74]. In the Zeiss Visante OMNI platform, the OCT results are combined with those from a Placido-ring topography,to calculate a three-dimensional model [75]. Some other OCT devices, e.g., the Casia SS-1000 and Casia 2 (Tomey, Nürnberg, Germany) or Optopol Revo (Optopol Technology Sp. z o.o., Zawiercie, Poland), are able to calculate posterior corneal surface power and elevation, as in Scheimpflug imaging, but without topographic Figure 4. Corneal tomography in a swept-source optical coherence tomography device, the Anterion (Heidelberg Engineering). Optical coherence tomography (OCT) systems analyze measurements of the echo time delay of backscattered or backreflected light by using an interferometer with a mechanically scanned optical reference path. [63–65] OCT devices can be classified into spectral-domain OCT (SD-OCT) and time-domain OCT (TD-OCT). SD-OCT is associated with a rapid scan speed, less noise and higher resolution compared to TD-OCT, but the imaging field is smaller.[66] Swept-source OCT (SS-OCT) devices use a short-cavity swept laser instead of the superluminescent diode laser typical for conventional SD-OCT. [67] The shorter the wavelength used in the OCT device (Table 2), the shorter is the imaging range. Both SD-OCT and TD-OCT allow visualization of the cornea, anterior chamber and iridocorneal angle [66,68–70]. The applicability of employing OCT for corneal tomography was demonstrated more than 10 years ago [71,72]. A problem in obtaining corneal tomography images with OCT is the fan distortion [71]; thus, some SD-OCT devices allow only pachymetry but not tomography images to be obtained. For example, the Optovue SD-OCT (Freemont, CA, USA) is able to acquire eight evenly spaced 6.0 mm radial cross-sections in order to provide corneal curvature data and corneal and epithelial thickness maps; however, it does not allow for the obtaining of precise maps of the corneal power [73,74]. In the Zeiss Visante OMNI platform, the OCT results are combined with those from a Placido-ring topography, to calculate a three-dimensional model. [75] Some other OCT devices, e.g., the Casia SS-1000 and Casia 2 (Tomey, Nürnberg, Germany) or Optopol Revo (Optopol Technology Sp. z o.o., Zawiercie, Poland), are able to calculate posterior corneal surface power and elevation, as in Scheimpflug imaging, but without topographic data. Gjerdrum et al. have shown that OCT devices, in particular the Casia, might have a greater variability in simulated keratometry values than the Pentacam [76]. Szalai et al. have shown the utility of SD-OCT (Casia SS-1000) in measurements of eyes with keratoconus; although the results for keratometry, pachymetry and anterior chamber depth with Casia SS-1000 were different to those obtained with Pentacam, but the repeatability was similar.[77] Similarly, as with Scheimpflug cameras, OCT devices allow precise imaging of the anterior chamber, which is critical for, e.g., phakic IOLs or ICL assessment. One of the main limitations of Scheimpflug tomography is the low resolution and poor image quality; in these terms, OCT devices allow significantly better quality images with higher definition to be obtained [78]. OCT allows the corneal epithelium to be visualized, which, in certain conditions, might manifest as local thinning (e.g., in keratoconus) or thickening (e.g., adjacent to a corneal scar); this is an advantage over corneal topography, which presents solely the morphology of the corneal surface [79].

Discussion

Confusion in Terminology Although corneal topography and tomography are widely used, it is common that these technologies are confused. [4,6,41,80–84] This corrigendum could be associated with the fact that at the time when corneal tomographers were developed, the nomenclature was not yet defined.[8] The original Orbscan systems were designed to provide a three-dimensional reconstruction (tomography) of the cornea; however, the measurements were referred to as ‘topography’ (Orbscan topography system). The current version of the Orbscan device (Orbscan III) is referred to as an anterior segment analyzer but also as a multidimensional Orbscan topographer. Still, the Orbscan III displays Placido-discs but in a modified form and should rather be classified as a tomographer than topographer. Furthermore, the corneal module for Casia 2 (Tomey, Nürnberg, Germany) is advertised as corneal topography, although it does not have a Placido-cone and technically is an OCT corneal tomographer. Distinguishing topography and tomography is critical, as each of these examinations have their own characteristics. For corneal topography, we can expect excellent agreement in corneal power between measurements; for tomography the agreement limits are wider.[85] On the other hand, tomography allows critical stereometric data to be obtained, which are not available in corneal topography.

Limitations of Current Techniques

Both corneal topography and tomography are non-invasive measurements and carry no risk for the patient. However, they do require the patient to maintain a fixed gaze and can be inaccurate with eye movement. For Scheimpflug devices, it takes 2.0 s to obtain 25–50 scans as the camera rotates around the eye. Potential eye movements during the twosecond scan can occur; two cameras (e.g., in the Ziemer Galilei) allow measurements to be averaged and minimize decentration, such as in the case of involuntary eye movement [86]. On the contrary, Placido disk devices provide an instant picture of the cornea. It is known that Scheimpflug devices using a rotating camera can allow accurate measurements from highly irregular corneas that reflective Placido-based systems struggle to represent accurately. However, the distortion of the camera optics and of the cornea and lens itself distort the image, requiring automatic distortion correction.[87] Slit-scanning machines are imprecise when assessing the posterior surface after corneal refractive surgery due to the disruption of the corneal interface, causing light scatter. [88–90]

Scheimpflug devices also provide a good-looking image of the anterior segment in some particular meridian. However, this is just a reconstruction but not a true image of the corneal surface. Moreover, the true net power and keratometric power deviation have limited physical value outside of the central 2 to 3 mm. As Scheimpflug systems employ 470–475 nm wavelength light, they are sensitive to corneal opacities, resulting in hyperreflective images of an inaccurate contour [46]. Due to total internal reflection in the peripheral cornea, direct visualization of the anterior chamber angle is not possible. However, the extrapolation software is able to provide an estimate of the iris–corneal angle with relatively high accuracy [91]. OCT could be considered more practical for evaluating the peripheral corneal and corneo-scleral region [92]. OCT is particularly useful for a contact lens practitioner during both contact lens fitting and assessment, as the interaction of the lens and the cornea, as well as the edge with the conjunctiva, can be quantitatively assessed. [92]

Future Developments

Currently, we are encountering a significant development of optical technologies; they exhibit faster scanning speed and employ more reliable tracking systems. Still, conventional Placido-ring topography might provide the most realistic projection of the corneal surface. It is therefore unlikely that classical corneal topography will be completely replaced by corneal tomography. In the future, combining technologies in order to create more versatile devices could be a viable option (Table 3). In order to prevent refractive surprises and improve the predictability of intraocular lens power calculation, corneal topography has been employed in some optical biometers, e.g., the Aladdin (Topcon Corporation, Tokyo, Japan), or is available as an option in others, e.g., the Lenstar LS-900 (Haag Streit AG, Bern, Switzerland). On the contrary, optical biometry has been added to the new models of corneal tomography devices by adding a partial coherence interferometry SLED diode (e.g., Pentacam AXL) or low-coherence optical reflectometry with a superluminescent diode laser (e.g., Ziemer Galilei G6). Furthermore, a corneal tomography function has been added to a commercially available anterior/posterior segment SD-OCT device (the Revo NX, Optopol Technology Sp. z o.o., Zawiercie, Poland).[82] Many of these combinations would be considered practical, as with technological development, the number of devices required to provide a satisfactory ophthalmological standard of care has increased in recent decades.

Table 3. Devices combining topography or tomography with other technologies.

Corneal Topography + Ocular Aberrometry	Nidek OPD-Scan Tracey iTrace
Corneal topography + ocular biometry	Topcon Aladdin Lenstar LS-900
Corneal tomography + ocular biometry	Pentacam AXL Ziemer Galilei G6 Heidelberg Engineering Anterion
Corneal tomography + ocular biometry + posterior segment optical coherence tomography	Optopol Revo NX

Conclusions

There is a wide variety of imaging techniques to obtain corneal power maps. As different technologies are used, it is imperative that doctors involved in corneal surgery understand the science and clinical application of devices for corneal evaluation in depth. Advances in digital photography and computer processing have immensely increased the utility of corneal topography and tomography

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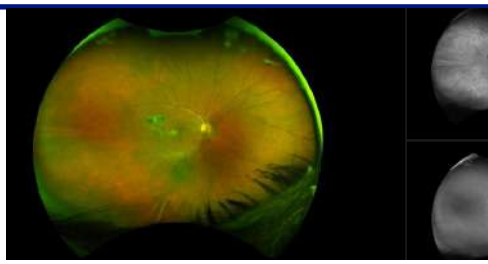
Review Article

Update on Multimodal Imaging in uveitis



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Abstract

Advances in multimodal imaging have significantly contributed to the management of many uveitis diseases in recent years. The most significant developments include the use of optical coherence tomography to obtain a more accurate and reproducible assessment of ocular inflammation, the application of optical coherence tomography angiography in choroiditis and retinal vasculitis, new possibilities for studying vitritis with ultrawide field imaging, and the most recent applications of fundus autofluorescence in uveitis. In this review, we provide an overview of the most significant advances in multimodal imaging of uveitis achieved in recent years.

Keywords: fundus autofluorescence, optical coherence tomography, optical coherence tomography angiography, ultrawide field imaging, uveitis

Introduction

Advances in multimodal imaging have significantly contributed to refining the diagnosis and management of uveitis in the recent years. Different imaging techniques have been applied to ocular inflammatory disorders and the most common indications are illustrated in Table 1. Recently, thanks to the introduction of new imaging modalities and improvements on those already available, significant achievements have been obtained in the field of uveitis. These include the application of optical coherence tomography (OCT) to obtain a more accurate and reproducible assessment of ocular inflammation. OCT devices have also been incorporated into surgical microscopes, gaining new insights into the management of the most complex surgical cases of uveitis. Other major contributions have been obtained with OCT angiography through a non-invasive study of the vascularization of the iris, retina, and choroid, with easier detection of ischemia and neovascularizations. More conventional imaging modalities, such as color fundus photography, have now been implemented into widefield cameras showing almost the entire retina in a single frame. These cameras can also perform fundus autofluorescence (FAF), which has a pivotal role in some posterior uveitis such as serpiginous choroiditis (SC) and white dots syndromes.

Table 1- Imaging techniques, principal indications and applications in uveitis.

Imaging technique	Main indications	Common applications in uveitis
Optical coherence tomography	Macular and optic disk pathology	Macular edema, retinitis, choroiditis, vitreoretinal disorders
Optical coherence tomography angiography	Retinal or choroidal vascular pathology	Retinal ischemia, retinitis, choroiditis, retinal and choroidal neovascularizations
Ultrawidefield imaging	Vitreoretinal or choroidal pathology involving the periphery	Retinal vasculitis, intermediate and posterior uveitis
Fundus autofluorescence	Retinal and retinal pigment epithelium pathology	Choroiditis, white-dot syndromes, masquerade syndromes
Fluorescein angiography	Retinal vascular pathology	Retinal ischemia, retinal vasculitis, posterior uveitis, intermediate uveitis, macular edema, retinal and choroidal neovascularizations
Indocyanine green angiography	Choroidal vascular pathology	Choroiditis, choroidal neovascularizations

In this review, we provide the most significant advances in multimodal imaging of uveitis achieved in recent years. OCT-Optical coherence tomography

OCT has become an indispensable ancillary test in the diagnosis and management of uveitis, allowing differential diagnosis and identification of many specific entities.[1–7] OCT has rapidly evolved in the last two decades from time-domain OCT to spectral-domain OCT (SD-OCT) and, recently, to Swept Source OCT (SS-OCT).[8–10] Although slit-lamp biomicroscopy still remains the standard method for assessment of inflammation of the anterior segment and vitreous, OCT-based methods for quantification of intraocular inflammation are gaining increasing interest as additional diagnostic tools. In a pilot study by Agarwal and colleagues,[11] inflammatory cells in the anterior chamber were visualized on OCT scans as hyperreflective dots. The ability of OCT to detect anterior chamber cells, even in eyes with corneal haze or edema, is one of the advantages of this new modality. A more recent study using a SS-OCT found that the objective measurement of anterior chamber flare and cells correlated well with other grading systems.[12] In particular, the authors used the optical density ratio between aqueous and air to evaluate the flare on OCT. OCT-based methods have also been applied for an objective assessment of vitreous haze.[13,14] These methods offer a better reproducibility and more objective measure of ocular inflammation, which can improve our endpoints for uveitis in future clinical trials.

Secondary complications of uveitis such epiretinal membrane and rhegmatogenous retinal detachment are associated with a high risk of vision loss. Pars plana vitrectomy can improve visual function in selected eyes with chronic uveitis, but surgery in such cases can be complicated. Given the complexity of these patients, intraoperative surgical guidance tools, like intraoperative OCT, have the potential to impact outcomes and intraoperative decision making dramatically. The Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/ Integrated OCT Visualization during En Face Retinal and Ophthalmic Surgery (DISCOVER) study evaluated the role of intraoperative OCT for ophthalmic surgery and concluded that intraoperative OCT is a valuable tool that can impact surgical decision making and may enhance surgical outcomes.[15] To date, there are limited studies on the use of intraoperative OCT in patients with uveitis.

Optical coherence tomography angiography-OCTA

The technique of optical coherence tomography angiography (OCTA) has completely revolutionized our understanding of the disease pathophysiology, management, and patient outcomes in the subspecialty of uveitis.[16–18] The improvement in technological innovations has resulted in better and more efficient OCTA devices, helping in complex differential diagnosis.[19,20] Swept-source (SS) OCTA combines the advantages of more than 100,000 A-scans in a short acquisition time with better depth resolution and dyeless angiography that provides vital anatomical alterations in ocular inflammation. In the context of uveitis, OCTA provides valuable information in conditions affecting the choriocapillaris/retinal pigment epithelium (RPE) such as white dot syndromes, choroidal stromal pathologies such as Vogt-Koyanagi-Harada (VKH) syndrome, and other infectious entities such as ocular toxoplasmosis and dengue maculopathy.

One of the most impressive developments due to OCTA is the finding of preserved choriocapillaris flow in eyes with multiple evanescent white dot syndrome (MEWDS; Figure 1).[21,22] The lesions in MEWDS, however, appear hypocyanescent on indocyanine green angiography (ICGA). These findings indicate that the pathology of MEWDS may not be related to choriocapillaris ischemia, but rather to a primary RPE disorder, which results in reversible hypocyanescence on ICGA and subsequent 'photoreceptoritis' for reasons not clearly elucidated yet.[21,23,24] Another possible explanation is that OCTA

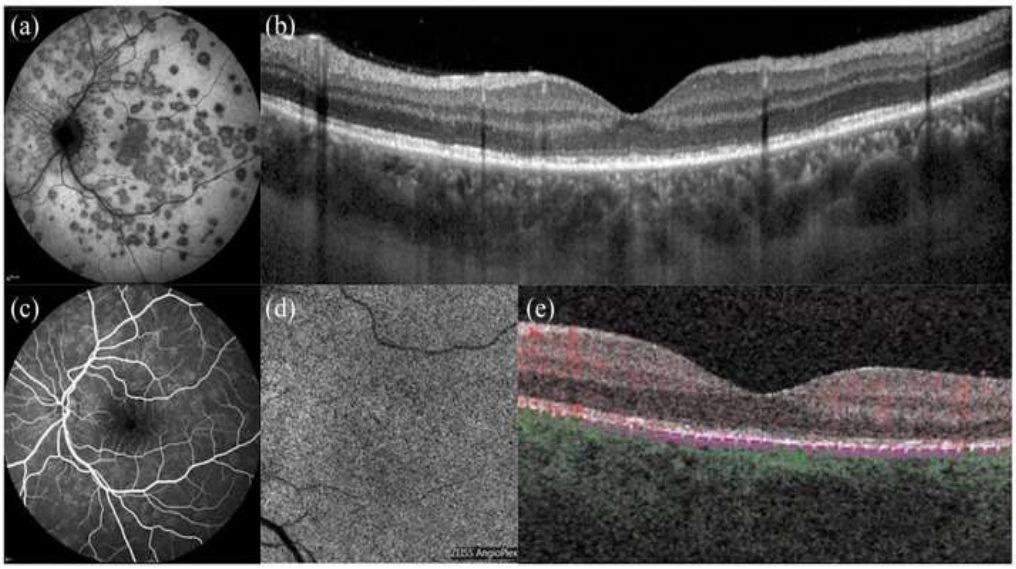

Figure1 -Multimodal imaging of multiple evanescent white dot syndrome (MEWDS). (a) Indocyanine green angiography illustrates scattered hypocyanescent dots. (b) OCT shows attenuation and irregularities of the ellipsoid zone. (c) Fluorescein angiography reveals minimal hyper-fluorescence with 'wreath-like' lesions. (d and e) On OCT angiography, the choriocapillaris slab shows a normal flow signal.

cannot be sensitive enough to detect subtle choriocapillaris inflammation, explaining the normal appearance observed in MEWDS.[25] Further research is needed to clarify the discrepancy between ICGA and OCTA in MEWDS.OCTA is very useful in autoimmune SC as well as tubercular serpiginous-like choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE; Figure 2), and multifocal choroiditis (MFC) in determining the area of choriocapillaris flow deficit corresponding to the active choroiditis lesions.[26–30] The area of choriocapillaris flow deficit appears predominantly 'dark' on en face OCTA and co-localizes with the active lesion on ICGA. OCTA can be also useful in monitoring the healing of the lesions, and the development of paradoxical worsening if the etiology of the choroiditis is tubercular. Once the choroiditis lesions have healed, the OCTA effectively shows choriocapillaris restitution (in case the choroiditis lesions are small in size), or choriocapillaris atrophy (in large choroidal lesions).[26,27]

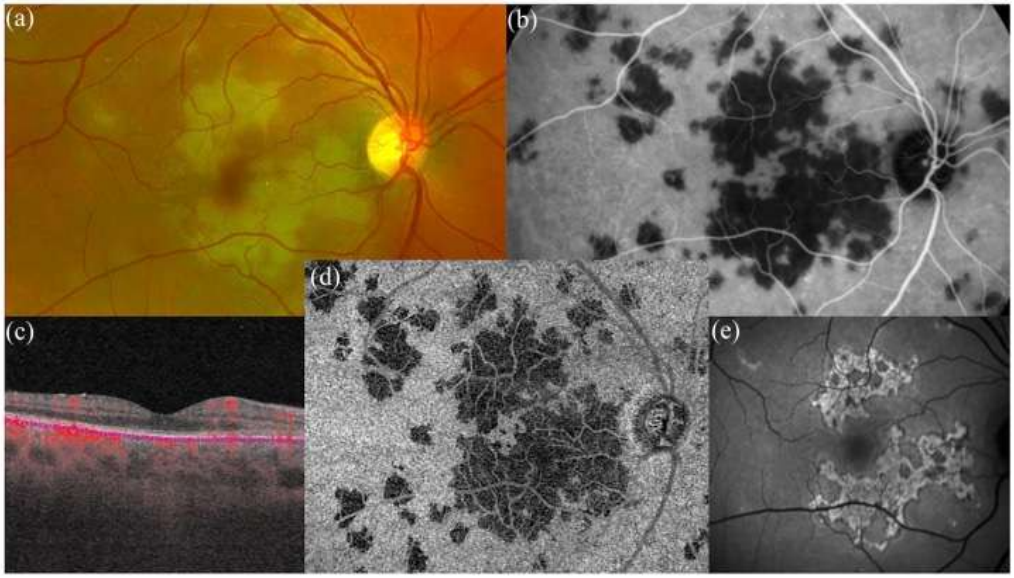

Figure 2-Multimodal imaging of acute posterior multifocal placoid pigment epitheliopathy (APMPPE). In the active phase, (a) fundus photos show multiple yellowish placoid lesions, (b) hypocyanescent on indocyanine green angiography, while (c and d) OCT angiography well delineates the dark areas of choriocapillaris hypoperfusion. Ten days after presentation, (e) fundus autofluorescence shows hyper-autofluorescent lesions.

OCTA is also valuable in detecting both type 1 and type 2 choroidal neovascularization (CNV) in eyes with choroiditis.[31–34] Type 1 lesions are extremely rare and have been reported in tubercular serpiginous-like choroiditis.[31] On the other hand, type 2 lesions are fairly common and easily detectable on OCTA in choriocapillaritis and other entities such as choroidal granulomas and toxoplasma retinochoroiditis.[34,35] Of note, caution must be exercised in distinguishing CNV lesions on OCTA from residual medium-to-large choroidal vessels in case there is an overlying choriocapillaris atrophy.[36]

Stromal choroiditis such as sarcoidosis, VKH disease, and sympathetic ophthalmia can be evaluated non-invasively using OCTA (Figure 3).[37,38] OCTA enables distinction between VKH and central serous chorioretinopathy (CSC) in atypical cases by visualization of hypo-reflective 'dark dots' in the choriocapillaris layer in VKH, which are absent in eyes with CSC.[38] In addition, OCTA enables determination of the level of inflammation and need for continued immunosuppression in VKH based on the appearance/disappearance of the hypo-reflective 'dark dots'. Similarly, in sympathetic ophthalmia, widefield OCTA has been shown to assess treatment response. On sequential imaging, flow deficits in the choriocapillaris improved following initiation of steroid and immunosuppressive therapy. Complete resolution was seen after 6-month therapy with a corresponding improvement in visual acuity.[37]

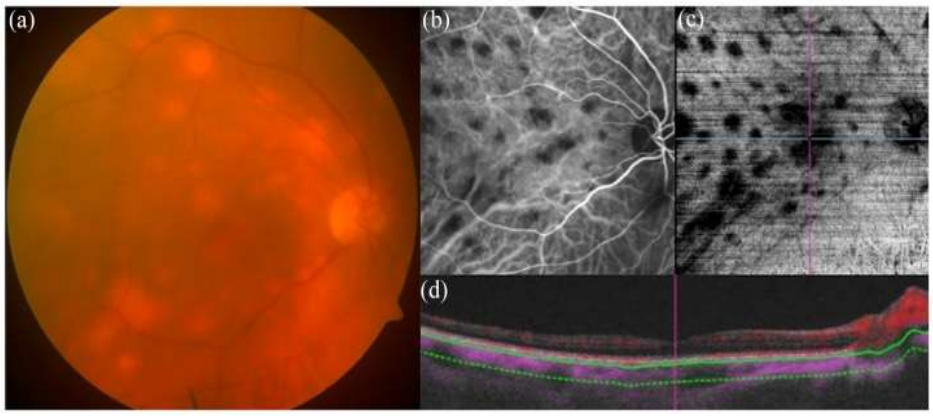

Figure 3 -Multimodal imaging of stromal choroiditis. (a) Fundus photograph shows yellowish scattered foci of choroiditis, corresponding to hypocyanescent area on (b) indocyanine green angiography (ICGA). On (c) *en-face* and (d) cross-sectional B-scan OCT angiography, the areas of choroiditis show the absence of decorrelation signal (black spaces), well correlating with ICGA.

OCTA can also be useful in emerging mosquito-borne uveitis. In dengue, maculopathy reveals a number of pathological alterations that include deep retinal plexus flow deficits. Other features include vitreous inflammation, and a yellow-orange foveal lesion (foveolitis). The analyses on OCTA show both ischemic and inflammatory processes that contribute to the development of these changes. This entity has been therefore named as dengue-induced inflammatory, ischemic foveolitis and outer maculopathy (DIII-FOM). The ischemic damage in DIII-FOM is irreversible, and the patients may have persistent scotoma despite healing of the foveolitis.[39]

Ocular toxoplasmosis has been extensively studied using OCTA including SS-OCTA. OCTA is very sensitive in detecting CNV in ocular toxoplasmosis.[35] Retinal vasculitis can also be evaluated using OCTA.[40–42] In Behcet's disease, retinal vasculitis may not be easily assessable over fluorescein angiography due to significant leakage. However, on OCTA, the microvascular changes including area of the foveal avascular zone can be easily assessed and quantified. Parafoveal capillary telangiectasia can also be observed in these eyes.[43,44] In other causes of retinal vasculitis, especially occlusive retinal vasculitis due to tuberculosis and other entities, OCTA can delineate the non-perfusion areas, and it may be superior to fluorescein angiography in detecting ischemic changes in conditions such as West Nile virus infection and HIV retinopathy.[41,45,46]

In summary, OCTA adds significant value in the armamentarium of multimodal imaging in uveitis. There are certain limitations including difficulty in OCTA image acquisition due to small pupil size/synechiae, vitreous haze, complicated cataract, and vitreous floaters in uveitis. With increasing knowledge, the technology of OCTA continues to provide novel valuable information in the assessment of patients with uveitis.

Ultrawide field imaging

Ultrawide field imaging refers to imaging modalities able to capture in a single frame, centered on the fovea, portions of the retina anterior to the vortex veins ampullae.[47] This technology can be applied to different imaging modalities, including color pictures, FAF, fluorescein angiography, and ICGA. In uveitis, ultrawide field techniques are progressively gaining a crucial role because of the more comprehensive nature of the information provided, rapid execution, and significant advantages associated.

Being able to provide simultaneous information of both the macula and the retinal periphery, ultrawide field imaging can offer added value when applied to fluorescein angiography. In occlusive retinal vasculitis, it can assess more accurately the entity of retinal non-perfusion and stratify the risk of retinal neovascularization (Figure 4). It can also guide laser photocoagulation, which can be targeted using the information provided by ultrawide field imaging.[48–50] On the other hand, users of ultrawide field imaging are often exposed to an excess of information and should be aware that not all the abnormalities shown are clinically significant. In a comprehensive cohort of uveitis patients, peripheral vascular leakage on ultra-widefield fluorescein angiography was seen in more than 50% of eyes. However, this peripheral leakage was not associated with any significant reduction in visual acuity or risk of macular edema, neither at baseline nor at the final follow-up. Also, patients with intermediate uveitis frequently show capillary leakage, which is often more prominent in the retinal periphery. Despite being found also in eyes active clinical inflammation, this peripheral leakage may have a low impact on visual acuity.[51]

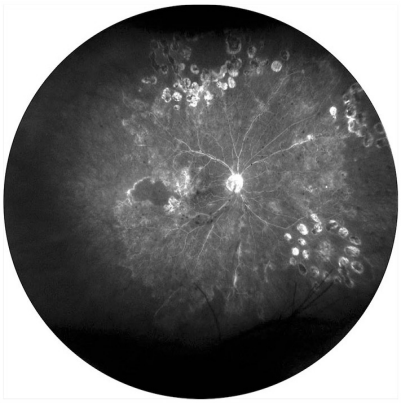

Figure 4-Ultrawide field fluorescein angiography of occlusive retinal vasculitis showing extensive areas of capillary nonperfusion, laser scars, and diffused vascular leakage.

Another key capability of devices using parabolic mirrors is their ability to provide information on the vitreous, which has traditionally been difficult to study because of its transparency and liquid nature. For instance, by applying this ultrawide field technique, we recently reported a peculiar pattern of vitritis along the vitreous fibrils in cases of vitreoretinal lymphoma (Figure 5).[52] In another paper, the assessment of vitritis with this technique was found to well correlate with the grade of vitritis observed clinically.[53] This application may provide an additional tool for monitoring the grade of vitreous haze, which is one of the main end-points in clinical trials for uveitis.

Figure 5-Ultrawide field imaging of biopsy-proven vitreoretinal lymphoma. The pseudocolor image shows the presence of vitritis along the most peripheral vitreous fibrils with an 'Aurora Borealis' appearance, as previously reported.

Another difficulty observed in uveitis patients is poor pupillary dilatation for posterior synechiae or iris inflammation. The possibility to obtain images of the retinal periphery with ultrawide field imaging even with undilated pupils offers a major advantage for the examiner.[54]

Other advantages of ultrawide field imaging in uveitis include a better staging of many ocular inflammatory disorders. The frequency of paradoxical worsening in tubercular serpiginous-like choroiditis has been found to be significantly higher when using an ultrawide field device as compared to conventional fundus cameras, which have a more limited field of view of the retina.[55] In that study, the information provided by ultrawide field imaging changed the management of more than one-third of patients. Also in cytomegalovirus retinitis, this technique proved to be helpful, with a better delineation of lesion borders and more comfort perceived by patients because of the rapid acquisition of the images.[56,57]

Ultrawide field imaging demonstrated clinical usefulness also in non-infectious uveitis. Based on this imaging modality, a simple way to assess and grade sunset glow fundus complicating VKH has been described.[58] Sunset glow fundus was classified into three progressive stages based on the severity of choroidal depigmentation, which could be better appreciated on ultrawide field images (Figure 6). Eyes presenting with more advanced depigmentation were also those that experience a higher number of recurrences and complications, like cataract and glaucoma. The more comprehensive assessment provided can also be helpful to identify disorders masquerading as uveitis, including retinal dystrophies and ocular tumors.[59,60]

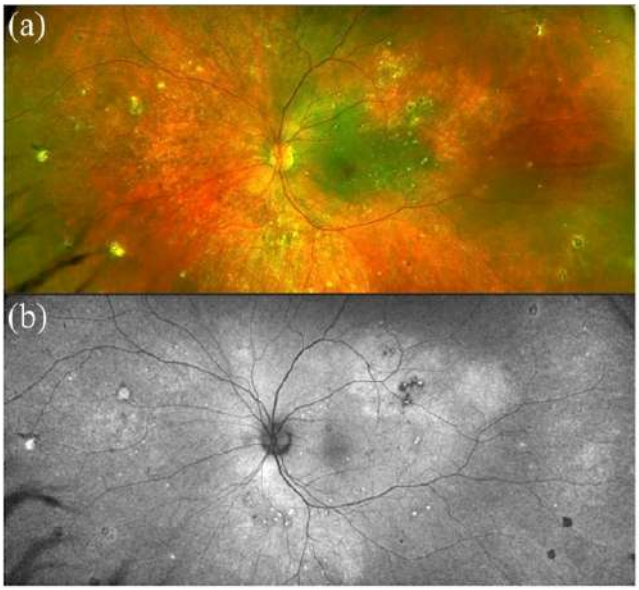

Figure 6-(a) Multimodal imaging of Vogt-Koyanagi-Harada (VKH) syndrome showing mild depigmentation of the retinal pigment epithelium on fundus photograph. (b) Fundus autofluorescence reveals scattered hypo and hyper autofluorescent areas.

Future goals of ultrawide field imaging should focus on the improvement of resolution and incorporation of additional imaging techniques, like OCTA. With the most recent machines, OCTA can already scan a significant amount of the retinal periphery, reaching wide field dimensions.[61] This will be particularly important in uveitis, where repeated examinations to monitor the treatment response are often required and should include the assessment of retinal periphery.

Fundus Autoflourescence-FAF

FAF provides a map of lipofuscin's distribution in the retina and different autofluorescence patterns have been found helpful in the differential diagnosis of many infectious and non-infectious uveitis, as well as masquerade syndromes. In most studies and ongoing clinical trials, FAF is performed using a confocal scanning laser ophthalmoscope (cSLO) with 488 nm blue-light excitation, but also other systems with different excitation light and barrier filters have been developed. Since FAF is the result of a cellular functional status, many studies have shown how this imaging modality can provide insights about the pathogenesis of posterior uveitis and be a useful prognostic tool.[62]

Multifocal choroiditis and punctate inner choroidopathy (PIC), once believed to be distinct pathologies, are now considered different spectrums of the same entity. Both MFC and PIC are mostly bilateral diseases characterized by development of circular scars with a high incidence of CNV and visual loss without treatment. A study showed that FAF detected more hypo-autofluorescent spots than chorioretinal scars seen clinically, in particular when smaller lesions (<125 µm) are considered.[62] In another study, FAF revealed hyperautofluorescence surrounding active lesions with associated CNV and hypoautofluorescence when lesions responded to treatment. The persistence of hyperautofluorescence raised the risk of persistent activity and recurrences.[63] For these reasons, FAF might be a sensitive measure of disease activity in MFC and PIC.[64] Recently, with FAF characterization, a new possible variant of MFC and PIC has been described in patients complaining acute vision loss or paracentral scotomas. This subset of patients presented large hyper-autofluorescent areas on FAF, not clinically visible, surrounding chorioretinal lesions (Figure 7).[65] These areas corresponded to attenuation of photoreceptor complex found on OCT and visual field defects detected on perimetry.

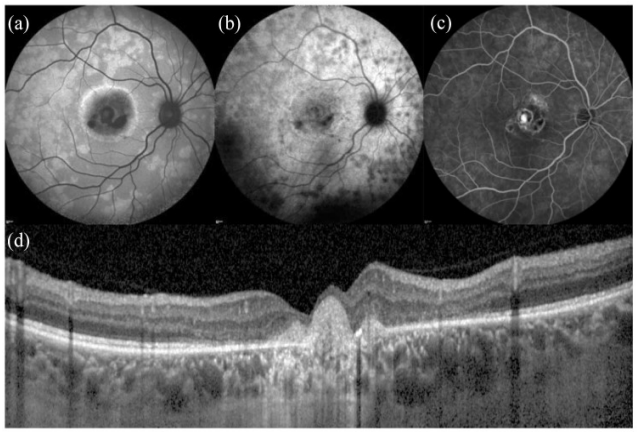

Figure 7- Multimodal imaging of punctate inner choroidopathy (PIC) complicated by light sensations and paracentral scotomas. (a) Fundus autofluorescence reveals scattered paracentral hyper autofluorescent areas next to a macular hypo autofluorescent scar. These paracentral areas appear hypocyanescent on (b) indocyanine green angiography and mildly hyperfluorescent on (c) fluorescein angiography. (d) OCT illustrates the hyper-reflective macular scar and mild disorganization of outer retinal layers.

Another uveitis where FAF can reveal more lesions than ophthalmoscopic examination is birdshot chorioretinopathy (BSCR; Figure 8).[66] BSCR is a stromal choroiditis associated with HLA-A29 characterized by the development of scattered hypopigmented yellow lesions with persistent chorioretinal inflammation.[67] FAF lesions mostly correspond to those detected on ICGA, but they may appear hyper-autofluorescent at first (Figure 8) and turn hypo-autofluorescent over time if the disease is not controlled. The hypo-autofluorescent spots seen on FAF correlate with persistent visual field defects.[66] These observations support the concept that an early and aggressive immunomodulatory therapy, before the appearance of permanent damage (e.g. hypo-autofluorescent spots on FAF), may improve visual prognosis.[68]

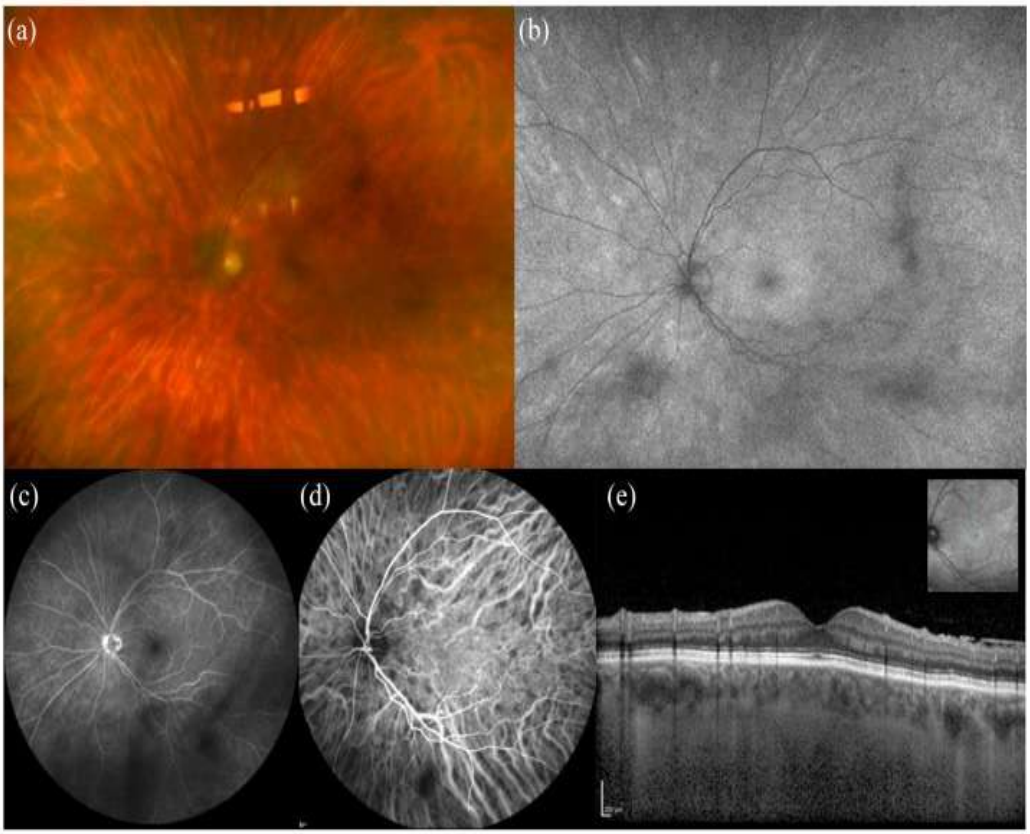

Figure 8- Multimodal imaging of birdshot chorioretinopathy. (a) Fundus photograph shows yellowish scattered foci of choroiditis, corresponding to hyper autofluorescent lesions on (b) fundus autofluorescence. (c) Fluorescein angiography shows some hypo fluorescent areas corresponding to vitreous opacities and (d) indocyanine green angiography reveals the presence of hypocyanescent foci of choroiditis. (e) OCT does not show significant changes in the macular scan.

Similarly, in MEWDS, FAF can identify the characteristic multiple hyper-autofluorescent spots during the acute phase, which correspond to the white dots observed clinically and ellipsoid disruptions on OCT. These dots fade away with the resolution of inflammation, but FAF can confirm the diagnosis of MEWDS even in the subacute phase.[69] Indeed, after the resolution of the patient's symptoms, FAF can detect new transient hyper-autofluorescent lesions in the previously affected areas, corresponding to subretinal deposits observed on OCT.[70] These secondary lesions, unlike the ones of acute MEWDS, remained hyper-autofluorescent after photobleaching on quantitative autofluorescence. This finding supported the theory that the acute hyperautofluorescence dots derived by a sort of window-effect toward RPE, while the subacute hyperautofluorescence was at least partially due to an intrinsic fluorescence of subretinal deposits.[70]

In VKH, two patterns were observed on FAF in the acute phase and, interestingly, depending on the timing of therapy. Patients treated with early intensive immunosuppression showed mild hyperautofluorescence which diminished up to the norm in disease remission. Conversely, patients either not treated or receiving a delayed treatment showed diffused zones of hyperautofluorescence which resolved within 6 months into patchy hypo- and hyperautofluorescence areas. Thus, prompt treatment could prevent permanent damage, as demonstrated by FAF.[71]

In acute zonal occult outer retinopathy (AZOOR; Figure 9), a rare syndrome presenting with acute loss of function of some retinal areas, photopsia, and minimal fundus changes, FAF has a pivotal role in diagnosis, because it depicts very well the typical trizonal pattern. In particular, normal autofluorescence area is observed outside a demarcating line (zone 1), a speckled hyper-autofluorescence is seen within the active lesion (zone 2), and hypoautofluorescence is detected where chorioretinal atrophy is developed (zone 3).[72] Furthermore, FAF allowed to discover other similar lesions, not clear on clinical ophthalmoscopy, also in periphery, suggesting that AZOOR may be a multifocal disease.[73]

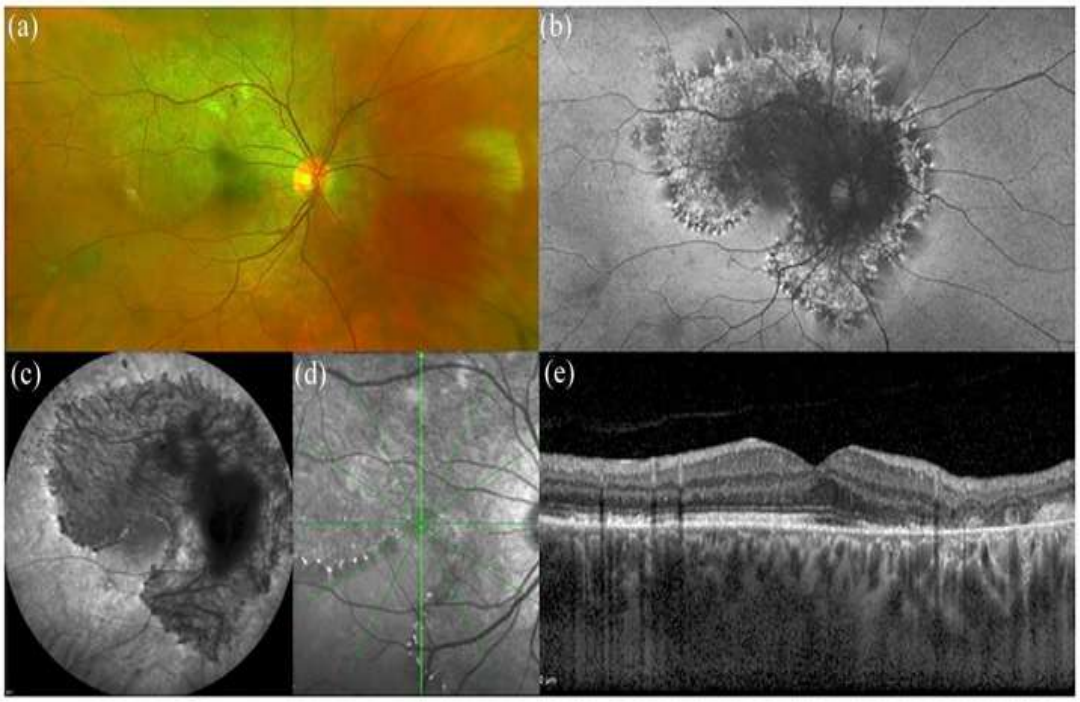

Figure 9 - Multimodal imaging of acute zonal occult outer retinopathy (AZOOR). (a) Fundus photography shows minimal outer retina and retinal pigment epithelium changes, while (b) FAF depicts very well the typical trizonal pattern. In particular, normal autofluorescence is observed outside a demarcating line (zone 1), speckled hyper-autofluorescence is seen within the active lesion (zone 2), and hypo-autofluorescence is detected where chorioretinal atrophy is developed (zone 3). Panels on the bottom row show (c) ICGA in the late phase, (d) infrared fundus image and (e) OCT.

In SC, FAF demonstrated to be more accurate than other exams in showing the extent and progression of RPE involvement (Figure 10). The area of hyperautofluorescence, marking active inflammation, corresponded to the final hypo-autofluorescent scar. Moreover, hyperautofluorescence at the scars' borders was a useful tool to identify early a disease's relapse.[73] FAF allowed also to distinguish active and resolved stages of tubercular serpiginous-like choroiditis, a distinct entity included in the spectrum of ocular tuberculosis. During the acute phase, FAF shows hyperautofluorescence of the lesions. As the disease begins to heal, it shows a stippled pattern of predominant hyperautofluorescence with a hypo-autofluorescent border surrounding the lesions. Gradually, the hypoautofluorescence border progresses and the lesions became mostly hypo-autofluorescent, still with a stippled pattern. On complete healing, the lesions become homogenously hypoautofluorescent.[74]

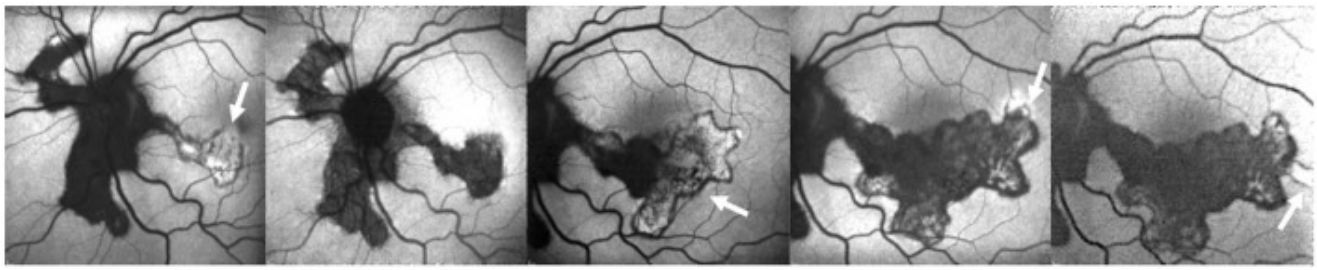

Figure 10-Fundus autofluorescence of serpiginous choroiditis showing the annual progression of the disease in the areas of activity (arrows). The active borders of choroiditis appear hyper-autofluorescent and the inactive areas show hypo-autofluorescence.

FAF could also help to monitor ocular syphilis since a hyper-autofluorescent pattern overlying retinal lesions and resolving with effective antibiotic treatment was described.[75]

FAF was also studied in the context of masquerade syndromes. In the majority of eyes with active vitreoretinal lymphoma (VRL), a subset of primary central nervous system lymphoma, a granular autofluorescence pattern could be observed and, interestingly, also in some patients where the classic leopard spot appearance was absent on fluorescein angiography (FA). Hyperautofluorescence could be the sign of sub-RPE infiltrate by lymphomatous cells, while hypoautofluorescence could be caused either by lymphomatous infiltrates' masking effect or by resulting RPE atrophy.[76] Taking together all these findings, abnormal autofluorescence could be a useful addition to monitor and detect possible relapses in patients with VRL. Hereditary retinal disorders which can masquerade as uveitis can also be easily recognized with FAF because they are characterized by specific patterns.[59]

Recently, a new confocal 450 nm blue-light FAF device has been introduced. This wavelength could excite a different range of fluorophores. Moreover, this new confocal light-emitting diode (LED) FAF system detects the full emission spectrum on a color sensor, providing so-called 'color' FAF and allowing to separate the emission spectrum into long-wave and short-wave components ('red' and 'green' component).[77] Studies are necessary to evaluate the potential role of this new imaging modality in uveitis.

Conclusion-

In conclusion, many recent imaging findings and new applications demonstrated the potential to change our clinical approach in the diagnosis and management of uveitis. In these patients, multimodal imaging may provide significant advantages because of the complex nature of many inflammatory entities, especially when guided by clinical presentation, personal and familial history. The treating physician should be familiar with the current advantages and limitations of each imaging technique to distinguish between specific uveitis entities. Implementation of imaging-based methods to quantify intraocular inflammation, either in the anterior segment or in the vitreous chamber, seems a promising strategy to obtain more objective and reliable endpoints for future clinical trials in uveitis. Future of ocular imaging in patients with chronic uveitis would be directed toward the implementation of non-invasive and wide field techniques.

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Review Article

Imaging in pathological myopia

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Abstract

Pathologic myopia (PM) is a major cause of irreversible visual impairment worldwide and especially in East Asian countries. The complications of PM include myopic maculopathy, myopic macular retinoschisis, dome-shaped macula, and myopic optic neuropathy. Posterior staphyloma is an important component of the diagnosis of PM and one of the hallmarks of PM. The photographic classification and grading system for myopic maculopathy has already been determined. Conventionally optical coherence tomography (OCT) was commonly used in PM and enabled investigators to image deeper tissue such as choroid and sclera. Today, the technological advances in OCT imaging including ultra-widefield OCT and 3-dimensional construction of OCT have given clinicians a novel insight on variable morphology in the PM.

Key words- Pathological myopia, imaging modalities

Complications from pathologic myopia (PM) are a major cause of visual impairment and blindness, especially in Asia, where the prevalence of myopia and high myopia (HM) is the highest.[1-4] According to the recent studies based on META-analysis for Pathologic Myopia (META-PM) Study Group, PM has been defined as the eyes having myopic maculopathy equivalent to or more severe than diffuse atrophy (category 2 in META-PM classification) and/or those having posterior staphylomas.[5-7] The causes of visual impairment in the eyes with PM included myopic maculopathy (mainly myopic choroidal neovascularization), myopic traction maculopathy (MTM) [myopic macular retinoschisis (MRS), macular hole and macular hole retinal detachment], and myopic optic neuropathy. And the important cause of developing these blinding complications is posterior staphyloma.

Recent advances in retinal imaging, especially optical coherence tomography (OCT), have enabled investigators to image the tissues deeper than the neural retina such as choroid and sclera. Among various types of OCT, swept-source OCT is a relatively new instrument that uses a wavelength-sweeping laser as the light source[8] and has less sensitivity roll-off with tissue depth than conventional spectral-domain OCTs. The current swept-source OCT instruments use a longer central wavelength, generally in the 1-µm range, which has improved their ability to penetrate deeper into tissues than the conventional spectral-domain OCT instruments. With this deeper penetration, evaluations of the choroid and sclera are potentially possible.

POSTERIOR STAPHYLOMA

Posterior staphyloma is a hallmark of PM.[7,9,10] It has been defined by Spaide et al[10] as an outpouching of the ocular wall with a smaller curvature radius than the surrounding ocular wall. Previous studies revealed that highly myopic eyes with posterior staphylomas had a significantly worse visual and anatomical outcome than highly myopic eyes without staphylomas.[6,11] Guo et al[11] investigated the relationship of eye shape, myopic maculopathy, and visual acuity in 95 relatively young HM patients with a mean age of 32.0 ± 14.0 years. Compared with eyes without posterior staphyloma, eyes with posterior staphyloma had a higher percentage having equal to or more serious diffuse atrophy (81.8% vs 54.8%) and having best-corrected visual acuity of <20/40 (50.0% vs 11.0%).

Despite its importance, the description of posterior staphylomas has so far been based mostly upon ophthalmoscopy. Based on their ophthalmoscopical appearance, Curtin[9] differentiated posterior staphylomas into 10 different types in 1977. Later, Moriyama et al[12] applied 3-dimensional magnetic resonance imaging (3D-MRI) and Ohno-Matsui et al[13,14] used a combination of 3D-MRI and ultra-widefield (UWF) fundus imaging to classify posterior staphylomas into 6 different types: the wide macular type, the narrow macular type, the peripapillary type, the nasal type, the inferior type, and other configurations, based on the size, shape, and location of the staphylomas.[12-15]

The 3D-MRI has an advantage of visualizing the shape of the whole eye including the anterior ocular segment. Such technique is, however, not as feasible as a screening technique, and due to a relatively low spatial resolution, subtle changes of shallow staphylomas are difficult to detect. Also, 3D-MRI cannot differentiate between the retinal, choroidal and scleral tissue. Since the 3D-MRI technique uses T2-weighted images showing intraocular fluid, 3D-MRI demonstrates the vitreo-retinal interface or the inner surface of the retina and does not show local variations in the thickness of the choroid and sclera.

Optical coherence tomography analyzes the curvature of the sclera in eyes with PM.[16,17] Due to the limited scan length and depth of devices previously available, the OCT technology was limited in its usefulness for visualization of posterior staphylomas. Comparing with spectral-domain OCT, the recently developed swept-source OCT technology improved the detectability of staphylomas, however, this was markedly limited by its relatively short length of the scan line.[18]

A new prototype of UWF-OCT system uses not only one but multiple scan lines and generates scan maps allowing the 3D reconstruction of posterior staphylomas in a region of interest of 23 mm × 20 mm and a depth of 5 mm. Applying UWF-OCT, we visualized posterior staphylomas in highly myopic eyes in their full 3D extent, and compared the detectability of staphylomas by widefield (WF)-OCT and by 3D-MRI.

On the WF-OCT images, all staphylomas — with the exception of 2 large staphylomas which were detected by 3D-MRI — were located in their whole length and width within the scanned region of interest (Fig. 1[19]). Morphological hallmarks of the posterior staphylomas as examined by WF-OCT were a smoothly configured border with a gradual thinning of the choroid from the periphery towards the edge of the staphyloma and a gradual re-thickening of the choroid in a direction towards the posterior pole. Additionally, there was a gradual thickening and inward protrusion of the sclera at the staphyloma edge. The 3D WF-OCT images also visualized the spatial relationships between the staphyloma and the optic nerve head as well as retinal vessels (Fig. 1[19]).

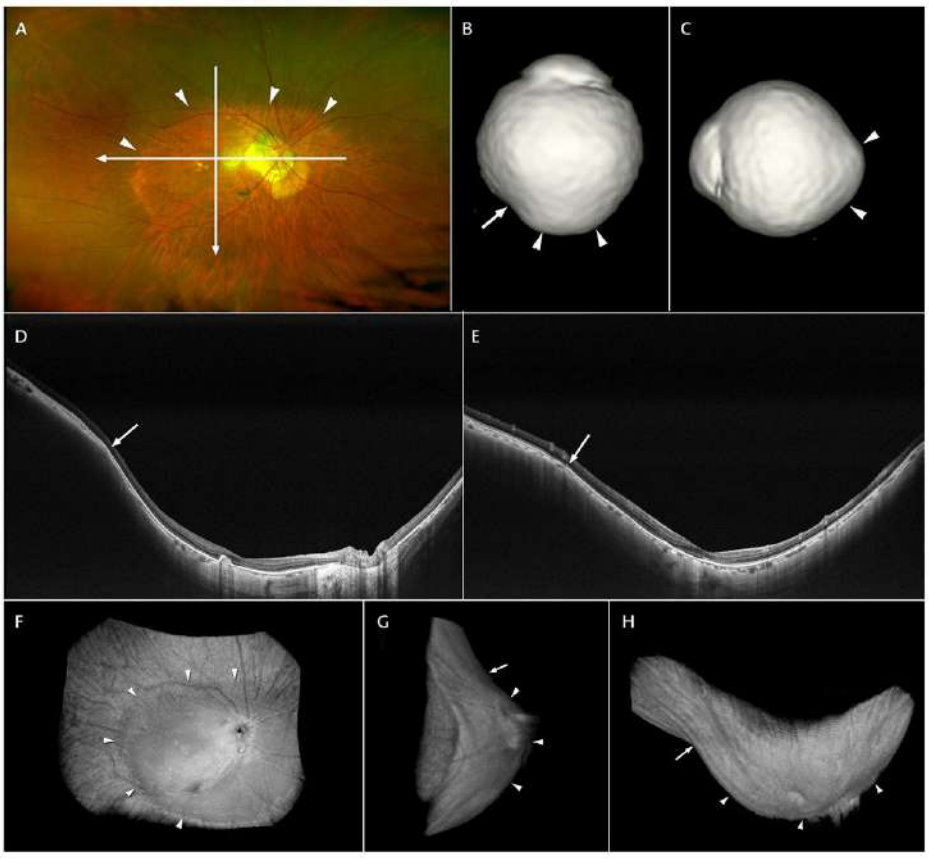
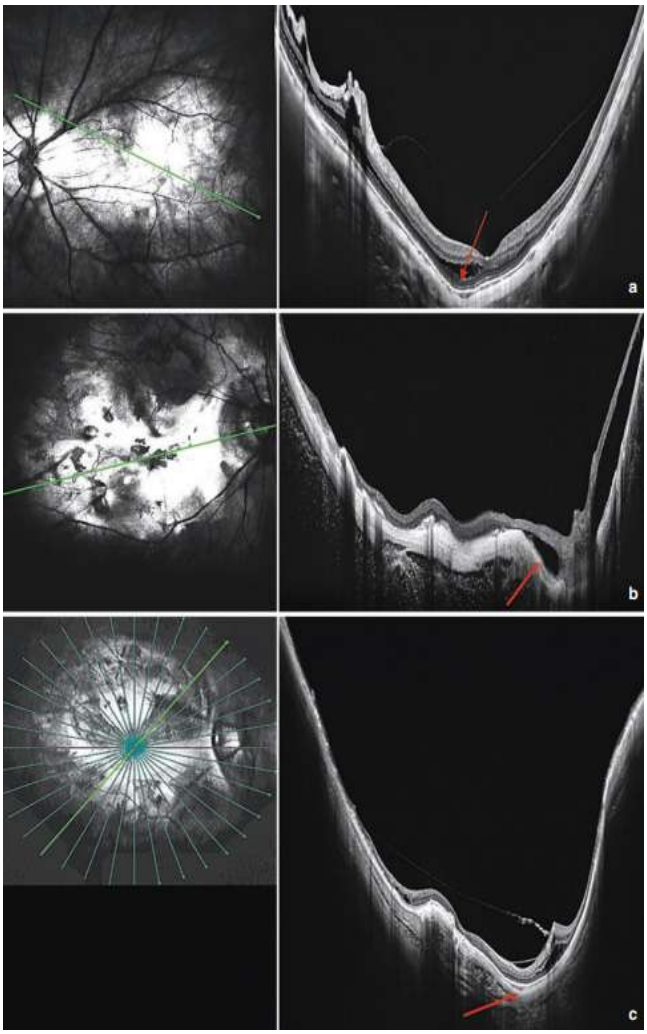


Figure1 -Wide macular staphyloma as visualized by widefield optical coherence tomography (WF-OCT) and 3-dimensional magnetic resonance imaging (3D-MRI).[19] A, Image of the left ocular fundus of a 79-year-old woman (axial length: 26.6 mm) showing the border of a wide staphyloma as indicated by pigmentary abnormalities (arrowheads). Arrows show the scanned lines of the WF-OCT images shown in D and E. B and C, 3D-MRI scans viewed from the inferior (B) and the nasal side (C) showing a wide macular staphyloma (arrowheads) with a notch at the temporal border (arrow in B). D and E, Cross-sectional WF-OCT images: horizontal scan (D) and vertical scan (E). An inward protrusion of the sclera and a thinning of the choroid are observed at the edge of the staphyloma in the horizontal section and in the vertical section (arrows). The staphylomatous region shows a posterior displacement of the sclera nasal to the staphyloma edge in D and inferior to the staphyloma edge in E. F to H, 3D WF-OCT images viewed from the anterior (F), the nasal (G), and the inferior side (H), showing a scleral outpouching (arrowheads) due to a wide macular staphyloma. In F, the staphyloma border is spatially associated with the optic nerve head and the retinal vessels.



(a) Limited macular posterior scleral staphyloma; (b) posterior scleral staphyloma around the optic disc; (c) posterior scleral staphyloma in the macular area on B-scan SS-OCT

MYOPIC MACULAR RETINOSCHISIS

Myopic traction maculopathy was first proposed by Pannozzo and Mercanti[20] as the pathologic features caused by tractions in the myopic environment. Such disorder is one of the major macular complications of PM, and frequently causes visual impairment in a natural course.[21,22] The representative retinal findings are retinoschisis and inner lamellar hole, and full-thickness macular hole is the progressed stage of MTM and becomes a cause of severe visual impairment.[21,23]

The traction mechanisms causing MTM were diverse and have been reported to include epiretinal membrane, remnant cortical vitreous plaques after posterior vitreous detachment, perifoveal posterior vitreous detachment with vitreomacular traction, elements intrinsic to the thinned retina such as a taut internal limiting membrane, and shortened retinal arterioles.[8,20,23-26] While all these mechanisms cause the anterior traction against the retina, posterior staphylomas which are thought to cause the posterior traction have also been considered to be associated with the development of MTM.[20,27-30] However, the earlier studies included a small number of cases with MTM and the diagnoses of posterior staphyloma were performed by ophthalmoscopy or color fundus photography which were rather suggestive. Therefore, the detailed association between posterior staphylomas and MTM was not elucidated yet.

A posterior staphyloma was detected significantly more frequently in eyes with MRS than those without MRS. In all eyes with both staphyloma and outer retinoschisis, the area of the outer retinoschisis was restricted to the area within the staphyloma (Fig. 2[31]). In one of the 19 eyes with outer retinoschisis but without staphyloma, the outer retinoschisis extended beyond the range of the scanned fundus area (Fig. 3[31]). Such information on a spatial relationship between MRS and staphylomas is considered important in making surgical strategies.

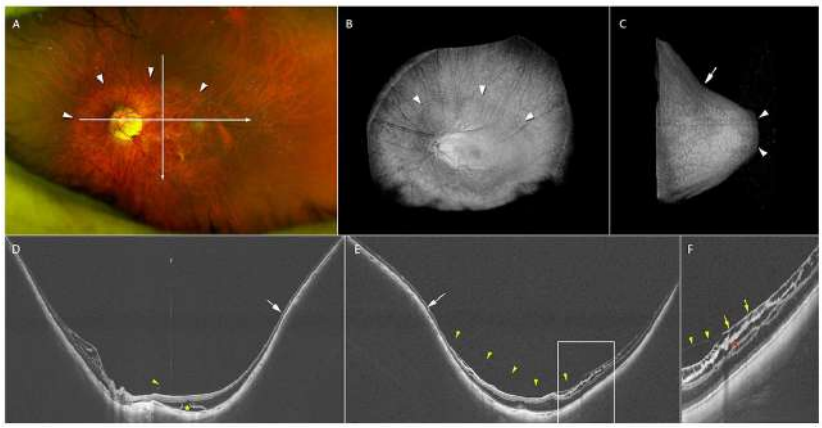
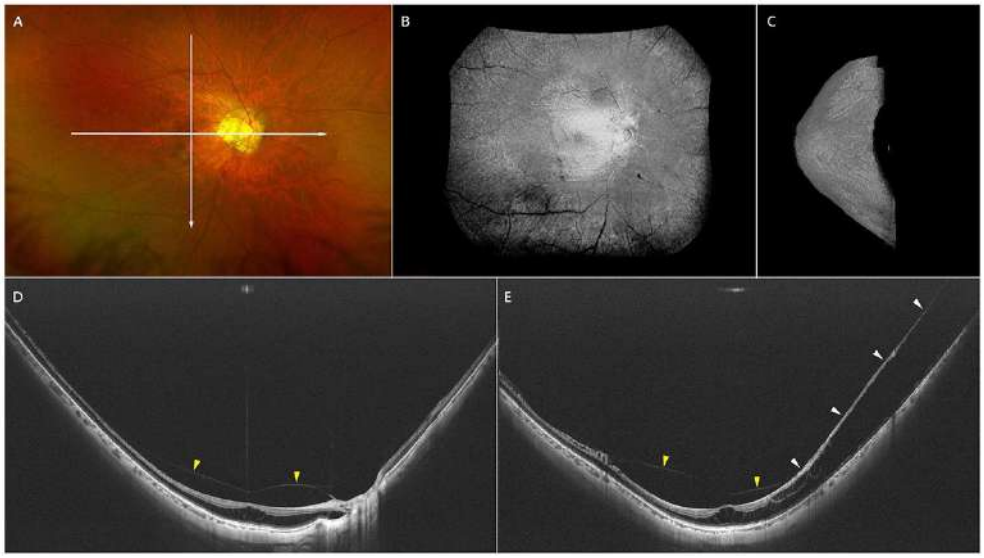
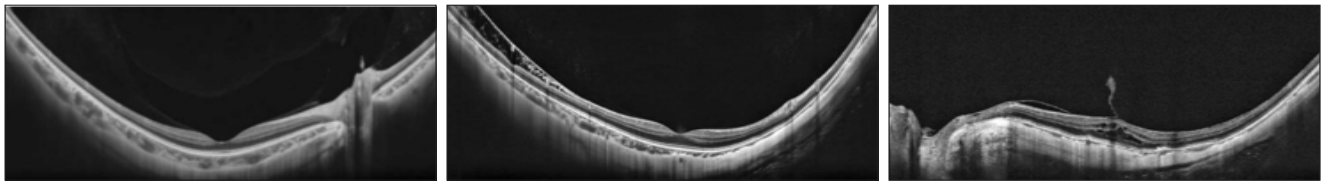


Figure 2-Outer and inner retinoschisis within the area of a wide macular posterior staphyloma in images obtained by widefield optical coherence tomography (WF-OCT).[31] A, Left fundus of a 72-year-old woman (axial length, 29.7 mm) with a wide staphyloma (white arrowheads). The 2 long white arrows show the lines scanned by the WF-OCT which are shown in D and E. B and C, 3D WF-OCT images viewed from the front (B) and the temporal side (C) showing a scleral outpouching (white arrowheads) due to a wide macular staphyloma. The edges of the staphyloma are marked by a notch (white arrow in C). D to F, Cross-sectional WF-OCT images: horizontal scan (D), vertical scan (E), and magnified image of E (F). White arrows in D and E show the staphyloma edge, associated with a slight inward protrusion of the sclera and a gradual thinning of the choroid coming from the periphery toward the staphyloma edge and a gradual re-thickening of the choroid coming from the staphyloma edge toward the posterior pole. An extended outer retinoschisis with a circumscribed macular retinal detachment (D, asterisk) does not extend beyond the staphyloma edge. Epiretinal membrane with internal limiting membrane (yellow arrows in F) can be seen within the area of the inner retinoschisis (E and F). The outer surface of the posterior vitreous is denoted by the yellow arrowheads (D, E, F), and a retinal vessel is marked by a red arrowhead (F).



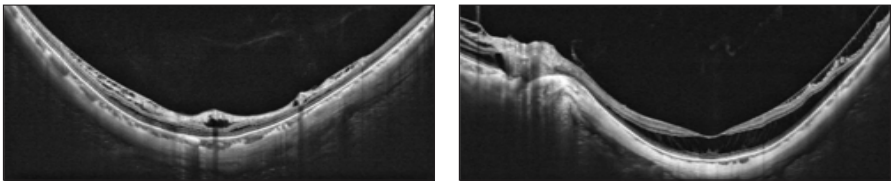
Figue 3-Widefield optical coherence tomography (WF-OCT) images of an outer retinoschisis without a posterior staphyloma.[31] A, Right fundus of a 59-year-old man (axial length: 28.2 mm). The 2 long white arrows show the lines scanned by the WF-OCT, and the images are shown in D and E. The edge of the staphyloma is not obvious in the fundus photograph. B and C, 3D WF-OCT images viewed from the front (B) and the temporal side (C). Both images do not show a posterior outpouching of the posterior segment which is typical for a posterior staphyloma. D and E, Cross-sectional WF-OCT images: horizontal scan (D) and vertical scan (E). An outer retinoschisis is observed in a wide area. In the vertical section, the outer retinoschisis spreads inferiorly. A diffuse adhesion of the posterior vitreous (yellow arrowheads) on the retinal surface is detected in the region inferior to the fovea (E, white arrowheads).



S0 MTM;
No retinoschisis

S1 MTM; Extrafoveal
macular retinoschisis

S2 MTM;
Foveal macular retinoschisis

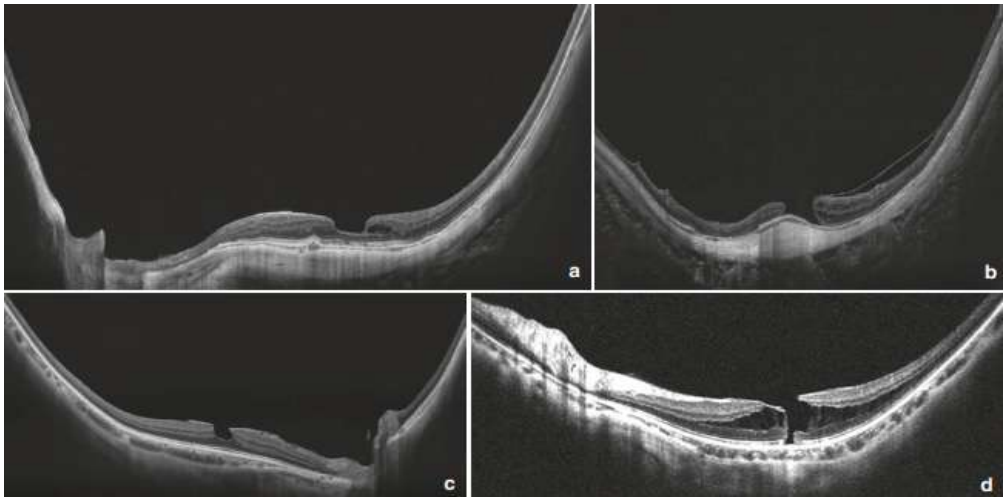


S3 MTM; Both foveal and extrafoveal
but not the entire macula retinoschisis

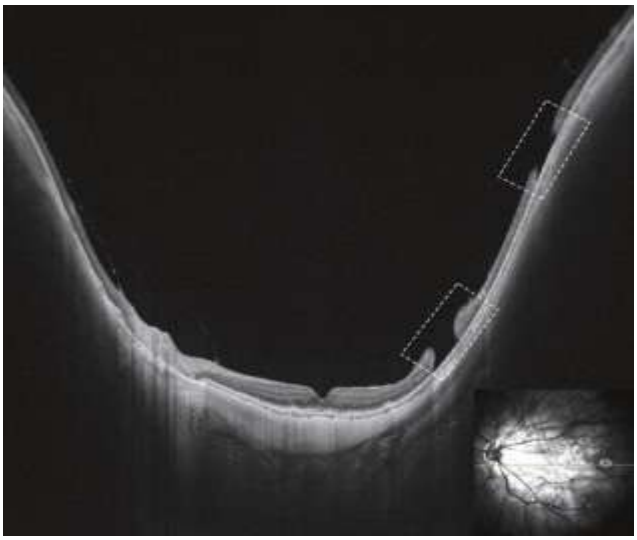
S4 MTM;
Entire macula retinoschisis

Myopic Macular hole

OCT has an irreplaceable role in the diagnosis of macular hole and can clearly display full thickness macular hole (b), lamellar macular hole (a, c), and macular hole combined with other fundus lesions (d)

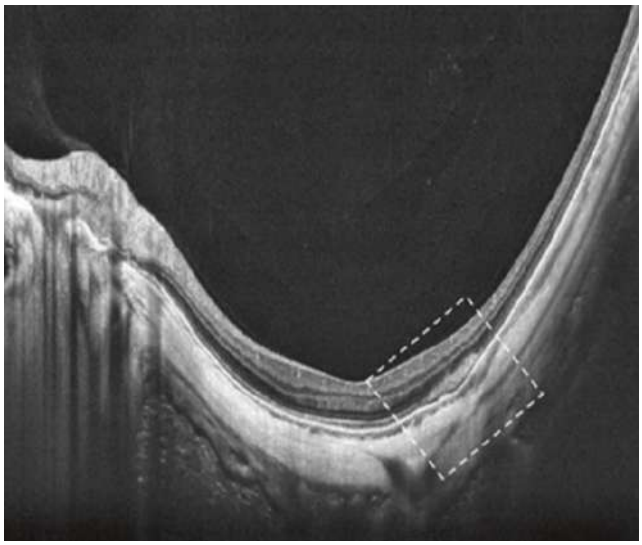


Retinal breaks

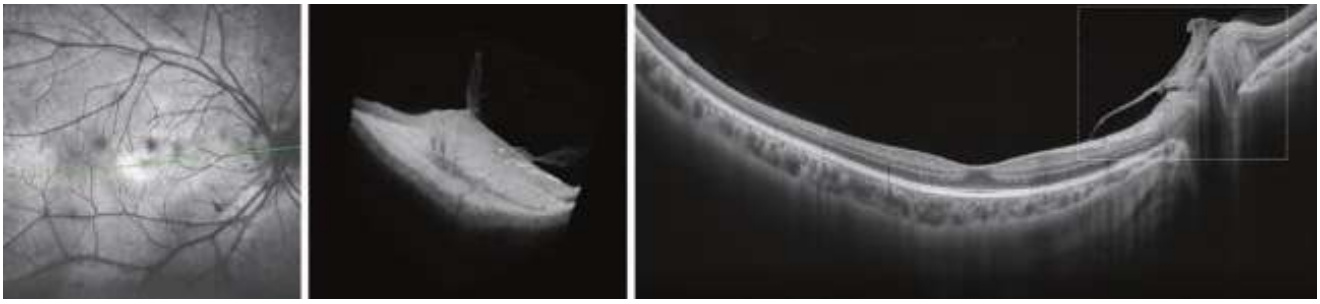


Two full thickness retinal breaks can be observed (dashed box)

Subretinal haemorrhage

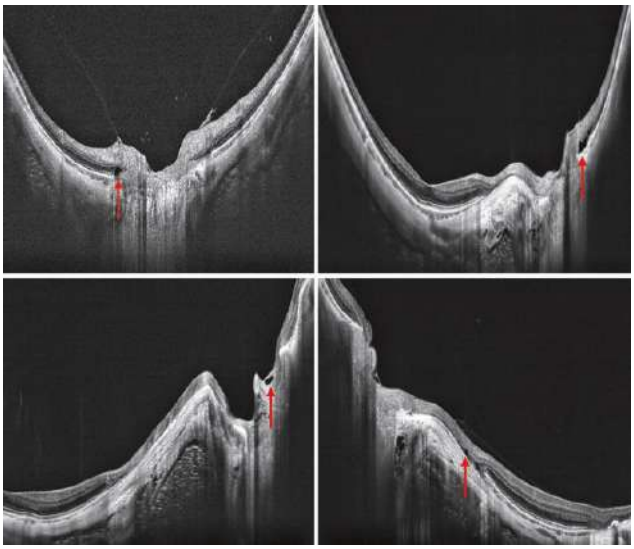


Subretinal hemorrhage as shown in the dashed box, which exhibits as a homogeneous moderate refective signal



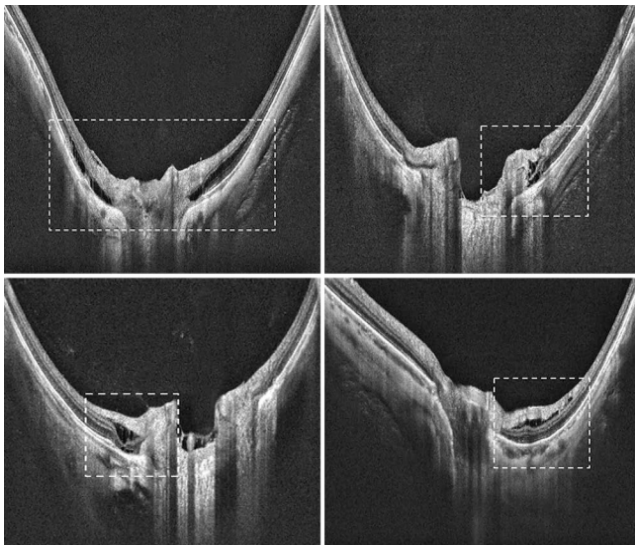
The preretinal fbroproliferative membrane stretching retina is clearly shown in front of the optic disc (dashed box)

Peripapillary Retinal Cavitation



A cyst-like retinal hyporefective signal (arrow) is display next to the optic disc; this presentation may be an early manifestation of peripapillary retinoschisis

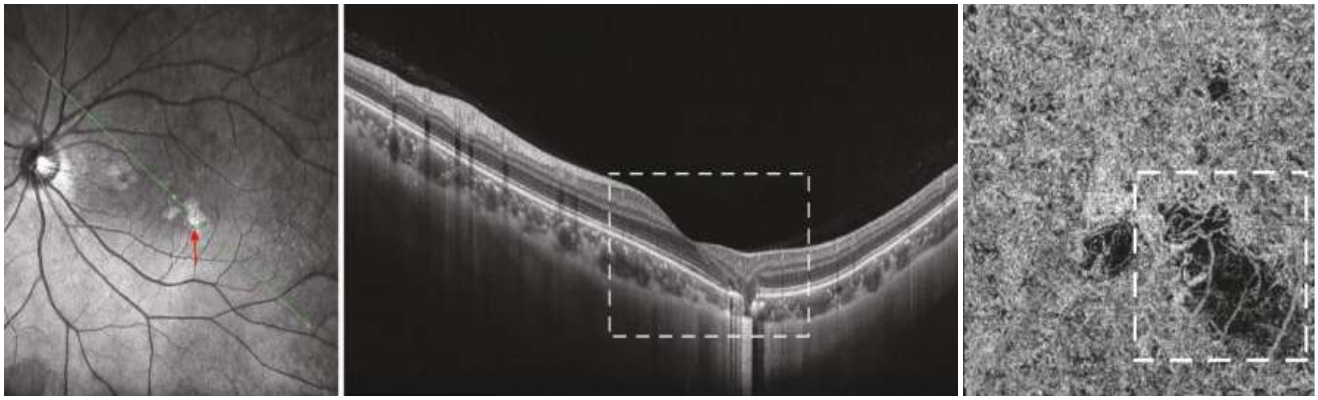
Peripapillary Retinoschisis

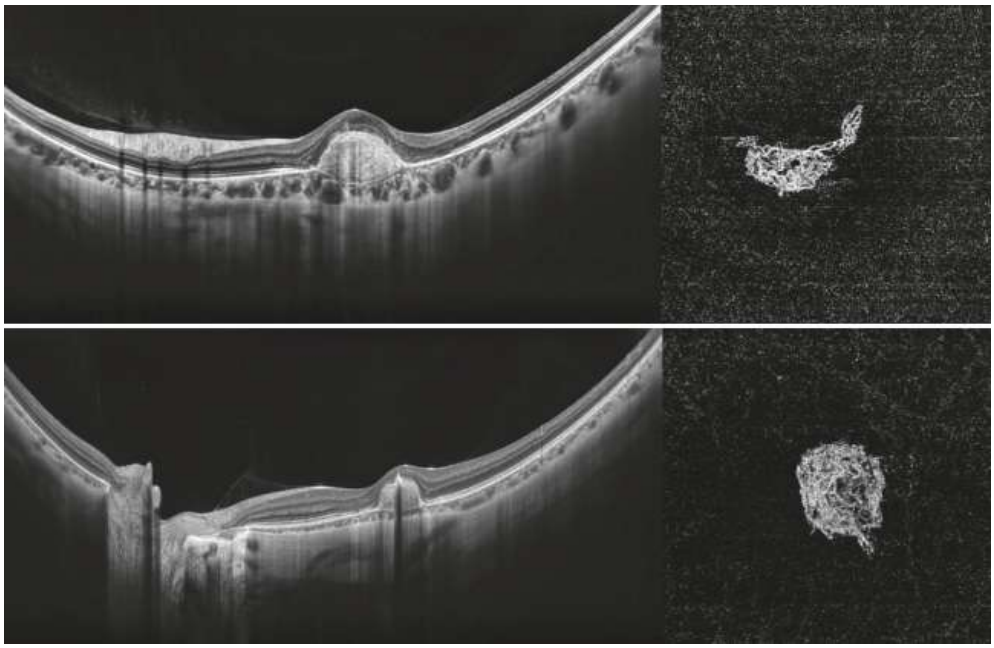


Retinoschisis located adjacent to the optic disc (dashed box)

Retinal Pigment Epithelial Tear

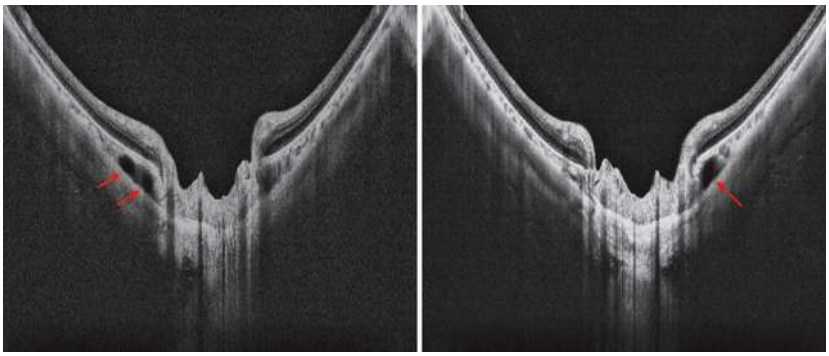
Localized retinal pigment epithelial tear is clearly shown in macular area (dashed box)





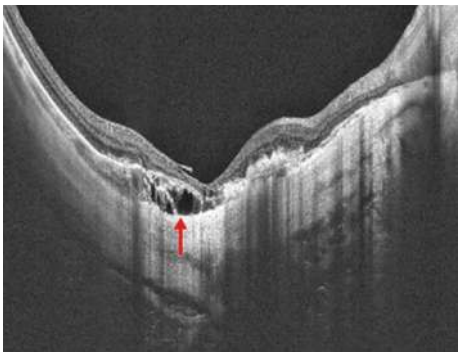
Myopic Choroidal Neovascularization (CNV)

B-scan SS-OCT shows a homogeneous hyperrefective subretinal bulge with Bruch's membrane depression; 3 mm × 3 mm SS-OCTA shows intertwined neovascularization with a clear border



Intrachoroidal Cavitation

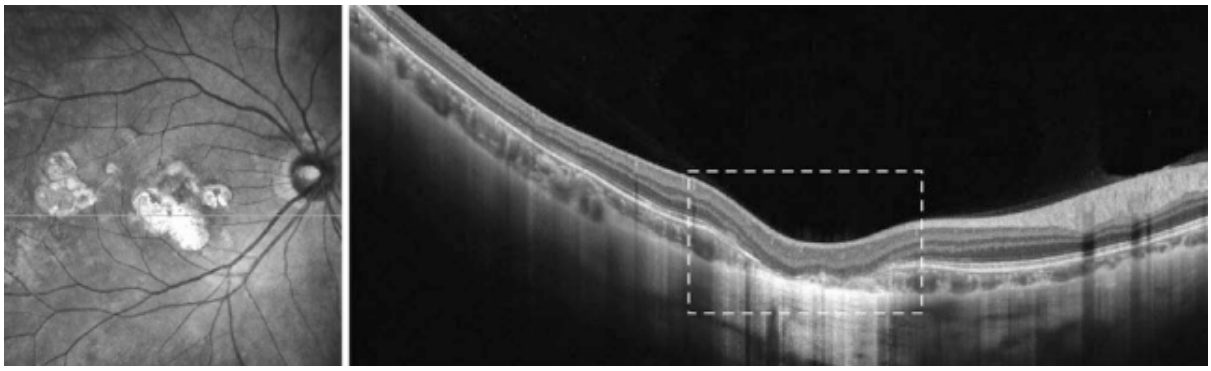
The choroidal thickness is thin next to the optic disc, and a hyporefective cavity-like structure is shown adjacent to the optic disc, indicating the accumulation of fuid in the cavity



The intrachoroidal cavitation may also be in the macular area, with multifocal hyporefective cavity-like structures (arrows) visible under the macular fovea

Choroidal Atrophy

Early focal atrophy of the choroid, corresponding to the choroidal defect on B-scan OCT (dashed box)



DOME-SHAPED MACULA

Dome-shaped macula (DSM) was first described by Gaucher et al[32] using OCT as inward bulge in the macular area inside the staphyloma which may cause visual impairment in myopic patients (Fig. 4). According to the definition of Ellabban et al,[33] DSM was defined as an inward bulging of the retinal pigment epithelium (RPE) line of more than 50 µm above a baseline connecting the RPE lines on both sides outside of the DSM. The prevalence of DSM in HM eyes has been estimated up to 20% in Japan[34] and approximately 10.7% in Europe.[32]

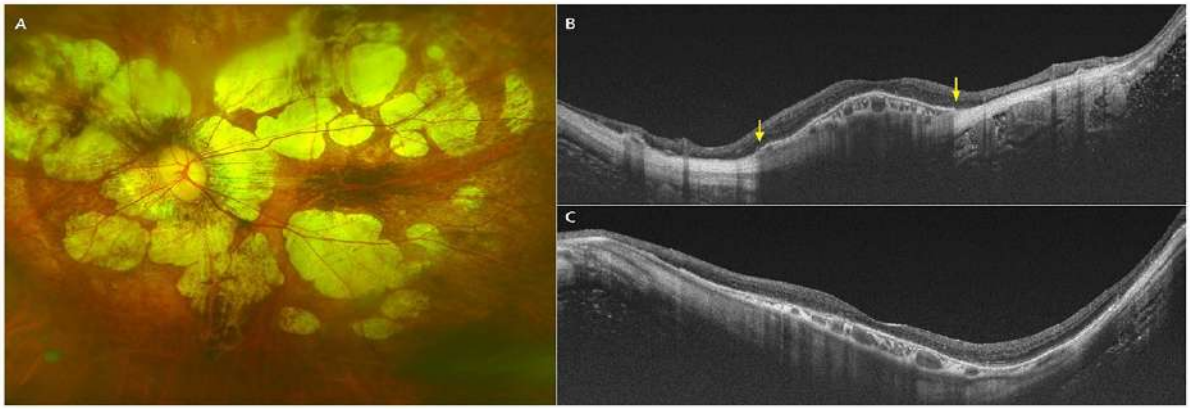
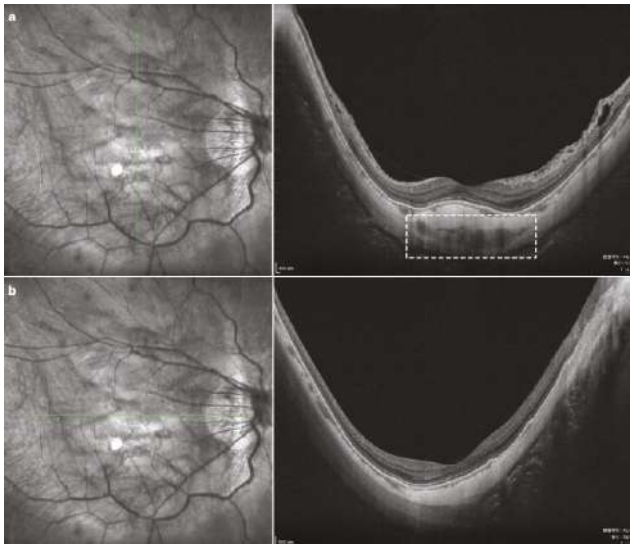


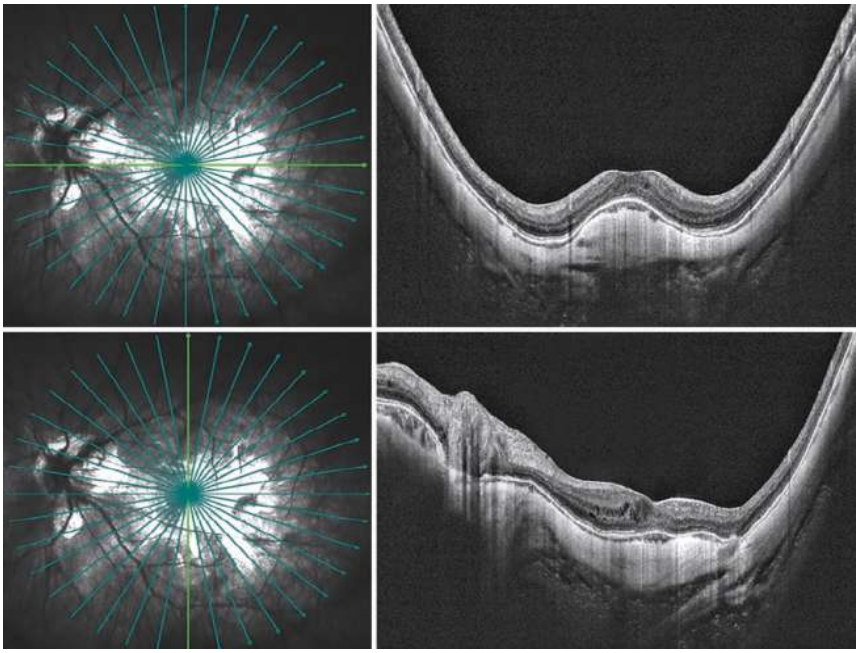
Figure 4-Optical coherence tomography (OCT) imaging of dome-shaped macula (DSM)[36]: A, Left fundus of a 65-year-old woman with an axial length of 33.2 mm showing multiple whitish, well-defined patchy atrophies superior and inferior to the macula. B, Vertical OCT section across the fovea shows an inward protrusion due to DSM. Bruch membrane remained at the center of macula, but stopped abruptly (yellow arrows) on both sides of the dome. C, The shape in the macular area was flat in horizontal OCT section across the fovea.



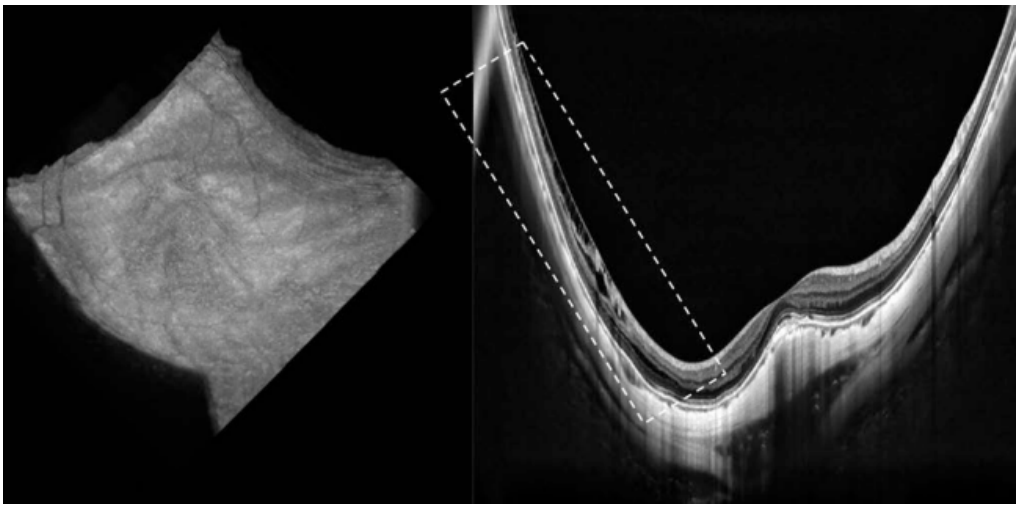
The dome-shaped macula is a special shape of the posterior pole of high myopic, characterized by a partial inward protrusion of the sclera in the macular area. A vertical dome-shaped macula is an oval dome that appears only vertically (a), not visible in other directions (b), with large scleral vessels visible at the dome macula (dashed box a)

Although the appearance of a horizontal ridge and macular pigmentation in fundus photographs may give some clues for the presence of DSM,[34] there is still lack of specific abnormality ophthalmoscopically. Examination by OCT is crucial for the diagnosis of DSM and 3D reconstruction of OCT allows precise investigations of DSM.[33,35] However, DSM is not always visible in all radial or crisscross OCT scans. Caillaux et al[35] classified DSM into 3 morphologic patterns: round dome, and vertically or horizontally oval-shaped domes. The typical dome was characterized by a round and radially symmetric

inward bulge which can be seen in both horizontal and vertical scans. However, the majority of DSM was not a typical round dome but a horizontally oriented, oval-shaped dome[33-38] in which the inward bulge can be detected only in vertical axis and horizontal axis was either slightly convex or flat. The prevalence of horizontal dome was approximately 62.5% to 91.6% in all types of DSM, whereas the typical round dome was 4.2% to 20.8%.[30,35-37] The third type was vertical DSM which is relatively rare in Japanese groups (0% to 4.2%)[33,36,37] that presented only in the horizontal sections. Significant variations of morphology may be observed in different orientation of OCT lines, radial scanning protocol or at least both vertical and horizontal scans should be suggested when imaging eyes with DSM.



Oval domes occur only horizontally



Oval domes are present in all directions,
often combined with retinoschisis (dashed box)

The pathogenesis of DSM remains unclear and disputed. Gaucher et al[32] observed in some eyes that the thickened choroid in the macular area may lead to the convexity of macula. However, Imamura et al[39] argued that a local thickening of the subfoveal sclera instead of choroid was more likely the cause of DSM. Targeting at the longitudinal observation of choroid, sclera and bulge height of DSM by OCT was helpful to understand the morphologic change in DSM.[40,41] Ellabban et al[40] found the height of dome increased with the sclera thinning which is more profound in parafoveal area than fovea center during 2 years. Although Soudier et al[42] confirmed the finding about apparent increase of DSM height over time, they considered that the reason is the deepening of the surrounding staphyloma instead of growing inward by itself. Fang et al[36] reported that macular Bruch membrane defect might also involve in the formation of a DSM by a focal relaxation of the posterior sclera that no longer pushed outward by an expanding Bruch membrane but partially bulged inwardly.

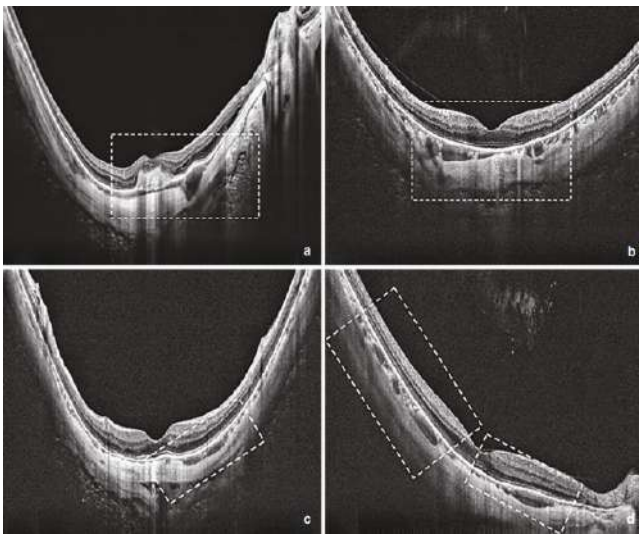
The macular complications in DSM include serous retinal detachment (SRD),[32,34,35,37-39,41] choroidal neovascularization,[43] and retinal pigment epithelial abnormalities.[32] The prevalence of SRD is markedly variable from 2% to 67%. The relationship between SRD and DSM is still mysterious. It was thought to be related to sclera thickening under the dome that resulted in resistance to choroidal fluid outflow.[39] Other factors such as a higher macular bulge height,[35,41] lower degree of myopia,[44] and vertically oriented oval-shaped domes[35] were also found to be associated with the presence of SRD in DSM. Tan et al[45] compared 2 groups with and without SRD in DSM/staphyloma/tilted disk syndrome and demonstrated that the eyes with SRD had a higher rate of abrupt change in choroidal thickness and associated pachyvessels which may cause RPE dysfunction and SRD. The treatment recommendation for SRD in DSM is still not solved.

In eyes with DSM, the best-corrected visual acuity usually remains stable over time, and SRD does not seem to be a significant cause of visual impairment.[44,46] Soudier et al[42] also found that the size of macular RPE atrophy seems to correlate with bulge height while subretinal fluid may increase or disappear spontaneously. However, a bulge height of more than 400 µm has been associated with lower visual acuity, subfoveal serous detachment, and greater RPE atrophy.[46] Recently, Xu et al[47] confirmed that DSM could be present in 9.2% of HM patients who are younger than 20 years. The young patients with DSM did not show the visual loss and the macular elevation was much lower (124 µm) than elderly patients with DSM (206 µm). It seems that the DSM itself, the inward contour in macular area, may not affect the vision. In case of the complication such as RPE damage induced by SRD, the vision impairment might occasionally appear after a long-time follow-up.

Although DSM is an important finding in HM, it was also found in mildly myopic[44] or even in emmetropic eyes.[48,49] A better understanding of those morphological changes in macula will help us elucidate the pathological process of myopia.

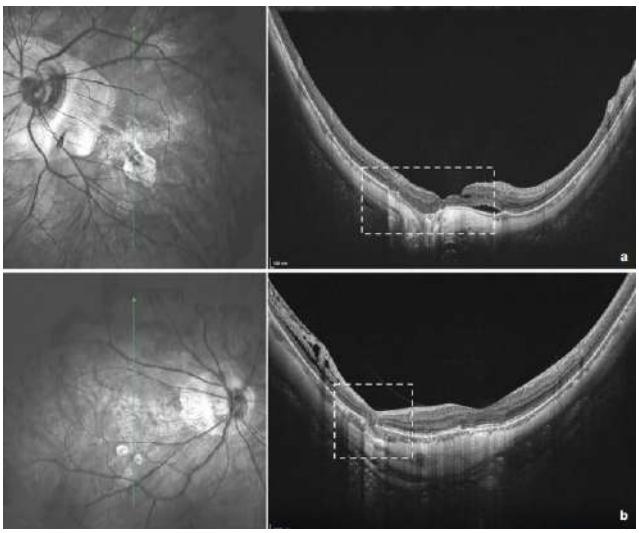
Uneven Diameter of Choroidal Vessels

The choroidal Haller layer is unevenly sized (dashed box), and the dilated Haller layer sometimes communicates with the scleral vessels to form penetrating branches (a, b). Local dilation of the choroidal Haller or Sattler layer (c, d)



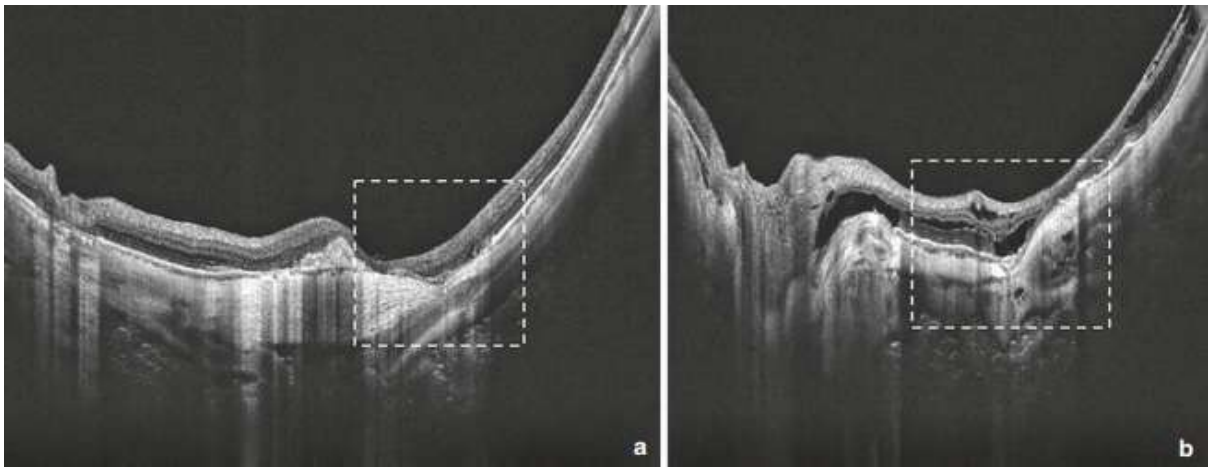
Bruch's Membrane Depression, Fracture

Localized Bruch's membrane breaks and depressions are seen in the macular area (a–b, dashed box), and scleral depressions may sometimes be combined at the lesion (a)



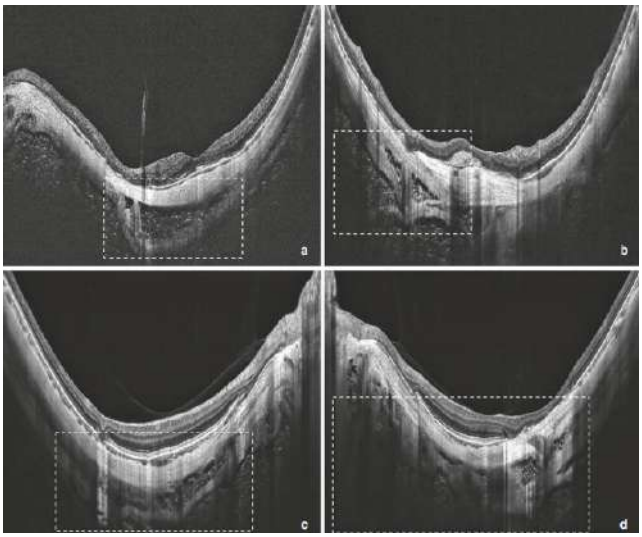
Scleral Depression

Sclera partially depressed, uneven in thickness (a), and often combined with retinoschisis (b)



Scleral Splitting

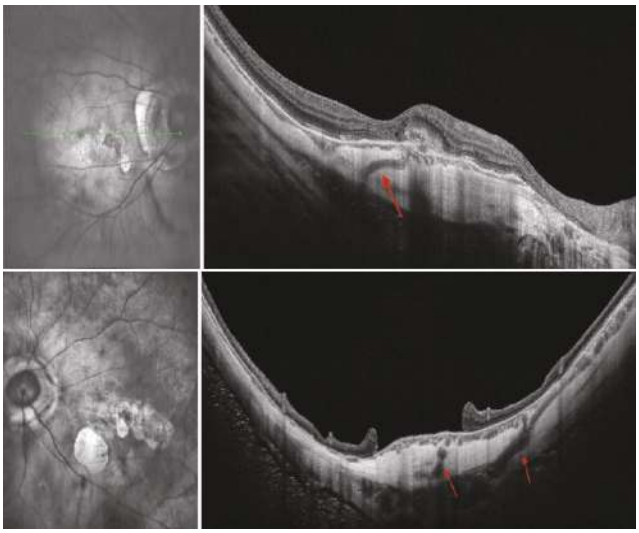
SS-OCT clearly shows post-scleral adipose tissue; as shown in the dashed box, the outer sclera partially splitting, and the splitting space is flled by adipose tissue (a–d); some of these lesions may be combined with CNV (b) and choroidal atrophy (d)



Scleral Penetration of Blood Vessels

SS-OCT can clearly display the pathway, structure, and morphology of scleral vessels (arrows).

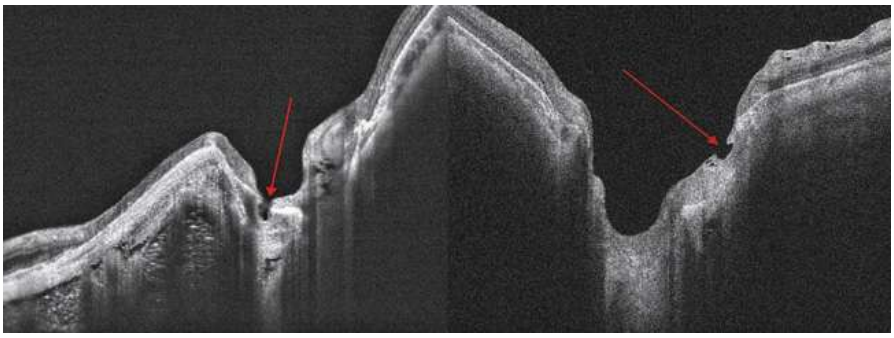
Note the dilated scleral blood vessels with uneven shape, which are often associated with other fundus lesions



Optic Disc Pit

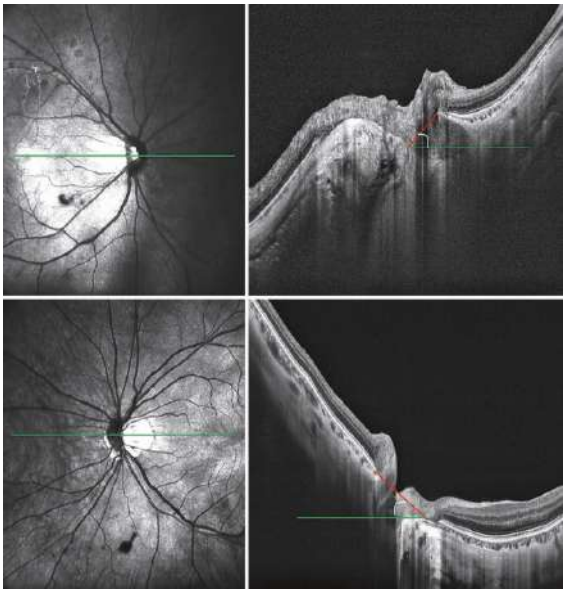
Optic disc pit is round or polygonal in shape, often covered by a grayish fbrous membrane, and is usually seen on the temporal or inferior temporal side of the optic

SS-OCT can visualize the details of the relevant structures of the optic disc (arrows), and can clearly show the structure of the optic disc pit



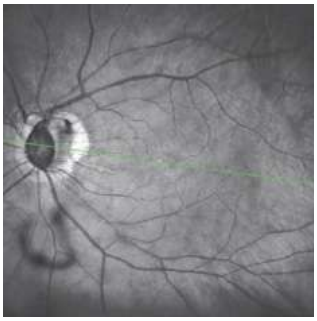
Tilted Disc

The tilted disc is due to posterior bulging of the eyeball wall in high myopia and the tilting entry of the optic nerve into the eyeball, resulting in one side of the optic disc to shift backwards (mostly temporal); the shape and structure of the tilted disc can be clearly observed under the horizontal cut of the optic disc

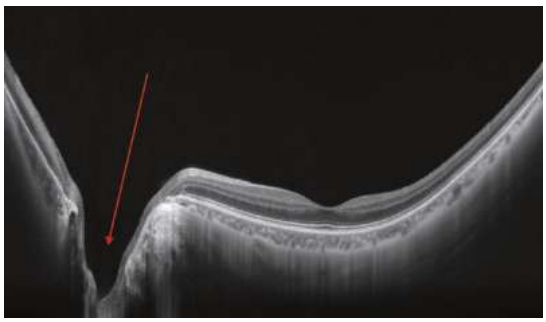


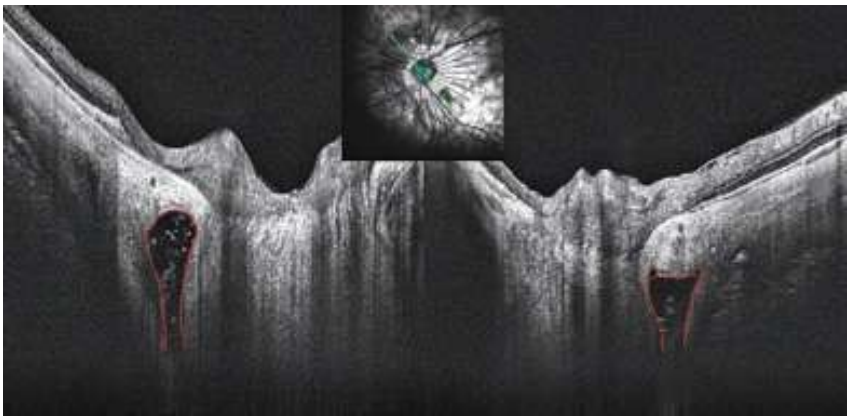
Deepening of the Optic Cup

Subarachnoid Cavity



The optic nerve is surrounded by cerebrospinal fuid, and sometimes the subarachnoid space terminates in the posterior wall of the eye at the scleral rim, and can therefore be visualized on OCT. The red line shows the subarachnoid space, which is a normal tissue structure and is useful for determining scleral curvature and other related pathologies





NEW CLASSIFICATION OF MYOPIC MACULOPATHY

Although the META-PM classification is well-suited to identify the various stages of myopic maculopathy, this classification is only based on fundus photographs which could affect an accurate diagnosis of atrophic lesions because of different looks according to the degree of fundus pigmentation among races. In addition, other myopic macular lesions such as MTM and DSM were not included. Thus, OCT-based classification has been developed.[50] The cut-off value of choroidal thickness may be useful to accurately diagnose peripapillary diffuse choroidal atrophy and macular diffuse choroidal atrophy regardless of the degree of pigmentation in fundus photographs.

Recently, Ruiz-Medrano et al[51] published a prestigious review summarizing the main feature of PM and proposed a new, more comprehensive classification system based on 3 key factors — atrophy (A), traction (T), and neovascularization (N) — called the ATN classification system.[51] This proposed classification system does not make any changes to the current atrophy classification (5 categories in META-PM), but it does include new proposals for the classification of the tractional and neovascular components which are considered a "plus sign" in META-PM. The simple, universally accepted classification system for myopic maculopathy might be used in future studies to ensure comparability among the studies.

Conclusion

Advances in retinal imaging, especially OCT, have clarified morphology of various tissues affected by PM in a very wide and deep range. These data provide great knowledge for understanding the pathophysiology of PM and new therapeutic approaches for PM.

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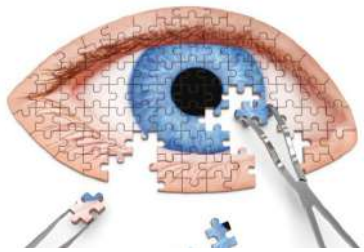
Point / Counterpoint

Should immidate Sequential Bilateral Cataract Surgery (ISBCS) Be Offered Routinely ?



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Introduction

The 2019 world report on vision of the WHO indicated that at least 2.2 billion people are visually impaired. [1] Of these people, 1 billion suffer from a visual impairment that could have been prevented or has yet to be addressed. Cataract is among the main diseases causing this preventable blindness, with an estimated number of 65.2 million people in need of treatment.[1] To date, phacoemulsification cataract surgery with an IOL implantation is one of the most commonly performed types of surgery worldwide, with low complication rates (1.2%) and high success rates (93%). [2,3] Moreover, it is considered one of the most cost-effective interventions in healthcare. [1,4,5]. However, currently, an estimated 6.9 billion U.S. dollars are needed to cover the gap of costs for unaddressed cataract globally.[1] Meanwhile, the world is facing an ageing population, and the number of patients in need of cataract treatment is therefore assumed to increase as well. [6] Coinciding with this rising demand for care, an increase of healthcare expenditures is expeced, which requires improvements in efficiency and logistics of the care that is provided.

Immediate sequential bilateral cataract surgery

Although cataract surgery on one eye is effective in restoring functional vision, it is known that cataract surgery of the second eye leads to faster visual rehabilitation and further improvements in quality of life and patient satisfaction. [7-10] At present, most patients with bilateral cataracts undergo cataract surgery in both eyes on separate days, referred to as delayed sequential bilateral cataract surgery (DSBCS). In this procedure, a period of days, weeks or even months is left between both surgeries. An alternative procedure involves operating on both eyes on the same day, but as two separate procedures, known as immediate sequential bilateral cataract surgery (ISBCS).[11] Although ISBCS is increasingly performed in some countries [12,13], the procedure is not recommended in most national clinical practice guidelines due to concerns regarding complication risks. [14,15] Nonetheless, the ISBCS procedure gained more interest and has been adopted more rapidly due to advantages such as a reduction in the number of patient visits to the hospital. [16-21]

Potential advantages of ISBCS include faster visual rehabilitation with no visual imbalance (anisometropia) between first eye surgery and second eye surgery, avoidance of additional day-care admission, less use of home care, a reduction in hospital visits and a reduction in costs. [15] Especially in the face of an ageing population and increasing global healthcare expenditures, this reduction in costs may have a substantial impact on a national and international level. To date, ISBCS is mainly performed in selected patients due to remaining concerns regarding safety and effectiveness of the procedure in comparison with DSBCS. These selected patients mainly include people who need cataract surgery under general anaesthesia, as the risk of receiving general anaesthesia twice is often higher than the potential risks of bilateral cataract surgery.[13]

The main reasons for delaying second-eye surgery are the risk of bilateral complications such as a severe infection of the eye (endophthalmitis) and refractive surprise. In order to minimize risks when performing ISBCS, general principles have been developed. [22] Recommendations described in these guidelines include that relevant ocular or periocular diseases have to be managed, and that complete aseptic separation of first eye surgery and second eye surgery is mandatory. This means that nothing that has been in physical contact with the first eye can be used during second eye surgery, instruments for the surgery of each eye have to go through complete and separate sterilization cycles, no cross-over of instruments, drugs or devices is allowed, different OVDs and different manufacturers or numerous surgical supplies should be used where reasonable and possible, separate sterile routines and operative field preparations should be performed for the first eye compared with the second eye, and the use of intracameral antibiotics at the end of surgery is strongly recommended. Furthermore, if a complication occurs in the first eye, this must be resolved before proceeding with the second eye and deferral of second eye surgery should be considered.

Endophthalmitis

The fear of endophthalmitis, most importantly a bilateral manifestation of the disease, has been identified as a predominant reason for not performing ISBCS. [23-26] Recently, a Cochrane review on immediate sequential bilateral cataract surgery for bilateral age-related cataracts has been published.[27] This review showed that there is likely no significant difference in endophthalmitis rates between ISBCS and DSBCS. However, because of the low incidence of bilateral endophthalmitis, none of the included studies was large enough to detect a bilateral case, and the amount and certainty of the evidence were graded low. In addition, the calculated risk of a bilateral event is very rare, with reported calculated rates of one in 70 million (using an incidence of 0.007%, assuming dependency between both eyes) [11] and one in two million (using an incidence of 0.07%, assuming no dependency between both eyes).[28] In order to increase the level of certainty of the evidence regarding endophthalmitis rates, additional large nonrandomized studies or (randomised) registry studies were found to be needed. Recently, three of such larger studies became available. [28-30] The study by Friling *et al.*[29] provides Swedish national data on endophthalmitis incidences for 1 457 172 cataract extractions, of which 92 238 were performed according to the ISBCS procedure. A significantly lower incidence of endophthalmitis was found for ISBCS compared with DSBCS, though it should be noted that independent risk factors for developing endophthalmitis were less frequent in the ISBCS group. Nonetheless, one case of bilateral endophthalmitis occurred in the ISBCS group compared with no bilateral cases in the DSBCS group. In contrast, the study by Lacy *et al.*[28] which included 165 609 ISBCS patients and 5 408 030 DSBCS patients, showed no significant difference in unilateral endophthalmitis rates between groups. In addition, they found no cases of bilateral endophthalmitis with clinical data supporting the diagnosis in the ISBCS group compared with seven cases in the DSBCS group. So, despite the time available for evaluation of first eye outcomes prior to second eye surgery, bilateral endophthalmitis occurred. Finally, the study of Malwankar *et al.*[30] provided demographics and postoperative rates on endophthalmitis and cystoid macula oedema in 4014 ISBCS patients and 1 940 965 DSBCS patients. Again, no evidence was found for major differences in complications between the groups.

In general, endophthalmitis rates following cataract surgery have decreased over the years. [31,32] This is likely to be a result of the increase in the administration of intracameral antibiotics. [33-35] Currently reported rates range from 0 to 0.08% with the use of intracameral cefuroxime and from 0 to 0.053% with the use of moxifloxacin. [36] However, the other side of the coin is that the decrease in absolute endophthalmitis numbers combined with the increase in the use of intracameral antibiotics potentially leaves us with predominantly drug-resistant strains. This is also shown in the bilateral endophthalmitis case described by Friling *et al.*[29], as the pathogen involved was a methicillin-resistant and therefore cefuroxime-resistant coagulase-negative staphylococcus. Similarly, many of the other cases of endophthalmitis reported in that study involved bacteria that were resistant to the intracameral antibiotic cefuroxime, which is the antibiotic of first choice of many European countries. As an alternative, other antibiotics reported for prophylaxis include vancomycin and moxifloxacin [12]. Although these cover a broader spectrum of pathogens, there are increasing concerns of resistance for moxifloxacin and concerns regarding off-label use of these antibiotics. [36-38] In addition, vancomycin has been associated with haemorrhagic occlusive retinal vasculitis (HORV), which causes severe and permanent vision loss. [36]

Refractive surprise

Nowadays, the level of success for cataract surgery is mostly determined by postoperative refractive outcomes. Currently accepted deviations from target refraction lie within 1.0 and 0.5 D, and success rates of 93 and 72.7%, respectively, have been reported in a large European database study (the EUREQUO database). [3] In addition, some studies set forth that in case of bilateral cataract surgery, the refractive outcomes of the first eye can be used to further optimize the prediction accuracy of the second eye. [39-41] On the contrary, a study by Jabbour *et al.*[42] showed no improvement in prediction accuracy for the second eye when using first eye outcomes, and most of the studies that do indicate a significant improvement are retrospective. Even though it is not certain to what extend this adjustment method is applied in current practice, the possibility of adjusting second eye IOL power based on first eye refractive outcomes is lost when performing ISBCS. Therefore, the risk of refractive surprise has been described as an important reason for not performing this procedure. [15,26]

The Cochrane review on ISBCS found moderate (one randomized controlled trial) and low-certainty (three nonrandomized studies) evidence that there was no difference in the percentage of eyes that did not achieve refraction within 1.0 D of target 1-3 months after surgery. [27] Furthermore, Owen *et al.*[43] recently published a retrospective cohort study on visual outcomes of ISBCS and DSBCS using population-based data from the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) Registry. They found that ISBCS was associated with slightly worse visual outcomes compared with DSBCS. However, the small statistical significant differences that were found may have been caused by a nonrandom surgery group assignment, the presence of confounding factors and a large sample size. In addition, no information on differences in relevant parameters (e.g. IOL calculation formulas or axial lengths) between groups were provided. Although it was suggested that refractive adjustments during the interval between first and second eye surgery may have accounted for better outcomes in DSBCS, no data were provided on whether these adjustments were performed or not and no sensitivity analyses were performed. Future randomized controlled trials can provide more insight in refractive outcomes of ISBCS compared with DSBCS

Other complications

Apart from endophthalmitis and refractive surprise, the risk of other complications (both intraoperative and postoperative) was found to not be significantly different for ISBCS compared with DSBCS in the current Cochrane review. [27] However, the certainty of the evidence was graded very low, and a high heterogeneity was found in the definition of complications between studies. In general, ISBCS is only recommended if any intraoperative complication in the first eye is resolved before continuing with the second eye and if patient safety and benefit are taken into account while deciding to proceed or not. [22] As for postoperative complications, the risk of some complications, such as retinal detachment and macular oedema, is likely to occur at a later postoperative stage than the time of 2 weeks usually left between first and second eye surgery in DSBCS.

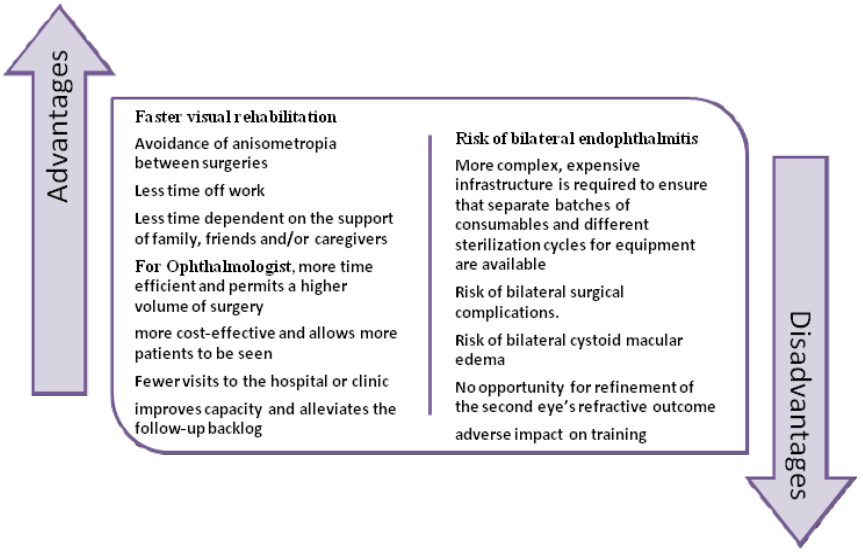
Costs and cost-effectiveness

As the world faces a rising demand for cataract care and healthcare expenditures as a result of an ageing population, further improvements of efficiency in healthcare and a reduction of healthcare costs are inevitable. Apart from patient benefits, potential cost-savings related to ISBCS are an important advantage compared with DSBCS. For example, potential cost savings in ISBCS can be related to surgical costs, day-care admission costs, a reduction in the number of outpatient visits, a reduction of travel cost, less use of home care and informal care, and less productivity loss. Previous studies already showed that cataract of the first eye, as well as cataract surgery of the second eye are cost-effective. [7,45] Available studies that compare costs for ISBCS compared with DSBCS found lower costs in ISBCS. [46-51] However, the Cochrane review showed there was a lack of cost-effectiveness studies on ISBCS versus DSBCS. [27]

Future studies on cost-effectiveness (e.g. from a societal perspective) are needed to support implementation of ISBCS and to provide information in a standardised way that allows for comparison of cost-effectiveness on a range of subjects or diseases. However, a limitation of this standardized method is that results from one country are not directly interchangeable with healthcare systems in another country. Therefore, calculation of exact hospital costs savings require a customized approach and changes in reimbursement strategies should not be based solely on cost reductions reported in cost-effectiveness studies.

Carbon footprint with immediate sequential bilateral cataract surgery

Another field for improvement of future cataract care involves its sustainability. The need for environment protection is high, as is reflected by the recent United Nations climate change conferences. Climate change is thought to be the biggest treat of the twenty-first century, and an estimated 250 000 additional deaths per year are expected by the WHO from 2030 until 2050. [52-54] Therefore, there is a clear need for cataract surgeons to critically evaluate the carbon footprint of cataract surgery. When performing ISBCS, the amount of waste is not likely to be reduced due to the need for separate sterilization requirements, and potential improvements in this regard are yet to be evaluated. However, a study by Morris *et al.*[55] showed that travel accounts for approximately 10% of CO_2 emissions in cataract surgery. Therefore, the more efficient follow-up that is achieved in ISBCS (e.g. reduced number of visits to the outpatient department, homecare combined for both eyes) can already contribute to the reduction of the cataract surgery carbon footprint.



Conclusion

Recently available evidence shows that ISBCS is an effective and cost-effective alternative to DSBCS, provided that patients are selected carefully and safety guidelines are taken into account. Additional randomized studies can provide valuable information on (bilateral) endophthalmitis rates and complications. Furthermore, future randomized studies and cost-effectiveness studies are needed to provide information on noninferiority regarding refractive outcomes and cost-effectiveness of ISBCS compared with DSBCS.

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Post Graduate Corner

How to turn a thesis to journal article for publication

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Doing a thesis or dissertation during a masters (MD/MS) or DNB residency is a colossal task that requires a lot of effort and commitment. Having put in all the efforts to do a good thesis, it is important that you are not content with its submission to the university but strive to publish it in a peer reviewed indexed journal.

Before we begin to understand how to do this, let's understand the difference between a thesis and scientific publications in a journal. **Firstly**, a thesis write up is extremely exhaustive and includes a lengthy review of literature; detailed methodology including standard operating procedures if any and every possible result derived using every possible research tool. **Secondly**, it is usually more than 10,000 words, 10-15 tables, a lot of figures, graphs and illustrations and usually has more than 100 references. And **finally,** the thesis may answer many relevant clinical questions as part of the entire project.On the other hand, an article
intended to be published in a scientific journal needs to be crisp in writing respecting the IMRAD (introduction, methods, results and discussion) format, within the journal word count, have limited references and answer a specific question that would be of interest to the journal readership. With these differences in mind, you can

1. **Writing an abstract:** A journal article requires you to submit an abstract which is a stand-alone précis for your study findings. A structured abstract is required by most journals with the following sub-headings: Purpose, Methods, Results and Conclusions. You will need to try and highlight the salient points of your study under these sub-headings within a word count between 250 – 350 words depending upon the journal. Remember that the abstract is freely available online, and after the title, the abstract is the most widely read part of your future publication. Hence concentrate on making it the best resume for your study.

2. **Writing the Introduction:** For a thesis, you will write a review of literature and show your exhaustive understanding of the topic. However, the main goal of the introduction of a journal article is to be succinct and narrow down a readers' attention from **what is known to what is unknown** about the topic, thus pique their attention and provide a rationale for your study. It is best to restrict the introduction to about 250 - 300 words.

3. **Writing the Methods:** This section is easiest to write since you have done the study already. However, it is by no means a copy – paste job. The main purpose of the methods in a journal article is to show what was done so that someone else can replicate your study. Omit unnecessary details from this section that do not add value to the manuscript. Yet try and retain the essentials. It is important to mention inclusion and exclusion criteria, sample size calculation, study design, execution (what was done a every step) protocols in short, outcome measures and statistical tests used. It is best if you can show the methods in a flowchart so that it is easy for the journal reviewers as well as readers to easily understand what you did by just eye-balling your paper.

4. **Writing the Results**: The thesis write up will have a lot of results with tables and figures for just about every variable you have measured. Remember that journals hate repetition of results in the written

imagine that a journal manuscript is essentially a précis from the thesis. However, you need to follow certain guidelines when you are looking to convert your thesis to a journal article. Remember that you have all the material for a good article if you have done your thesis well. It's just a matter of reorganization and goal directed writing to come up with an unbeatable article for a journal, especially if you follow what's given below.

Now that we understand the basic differences between a thesis and journal article, it will be easy to understand how to go about converting the thesis into an article. Lets take a step-by-step approach to this process:

In conclusion, turning your thesis into a journal article can be frustrating with frequent rejections from journals if you don't follow the correct approach, but can be enjoyable if your approach is right. These concepts are applicable not only for a thesis but for any manuscript you wish to submit to a journal. Another caveat is that you need to do the thesis well and derive robust results that cannot be easily refuted or doubted. The foundation for this should be laid even before you begin the thesis. You can explore extensive material and online courses on Sengupta's research academy to learn more about every aspect of clinical research.

text, tables and figures. A practical approach to writing results for a journal article is to mention the demographics first, followed by results of the primary outcome measure and then results from other outcomes you might have measured. Limit the outcomes you report to those that are meaningful for the particular paper. Before writing, understand your results and decide which results will be in written text, which will go into tables and which results are best represented by a diagram, chart, graph or illustration. It is best to restrict the total tables and figures between 5 and 7 to retain readers' attention. If you find that you are unable to fit everything nicely into the results, then you might consider splitting the data into 2 different papers which will both be equally consequentially. Avoid salami slicing which means unnecessarily splitting data into multiple papers.

5. **Writing the Discussion**: There is not much difference between writing the discussion for the thesis and journal article other than the length. Since you are reporting only meaningful results and not every result you found, the discussion is automatically shortened. It is best to discuss the results of your primary outcome measure first followed by others. Limit comparing your particular outcomes to 2-3 previous studies alone. Choose which ones are closest to your methodology and compare – contrast your discussion as to why your results are similar or different from these previous studies. To learn more about manuscript writing, click here.

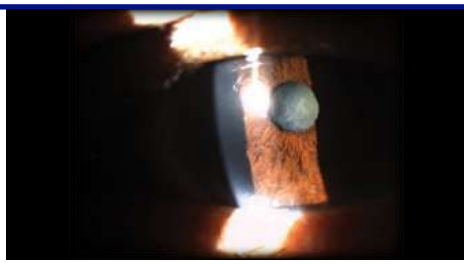
6. **References**: Restrict the number of references as per the journal instruction to authors. In fact, it is critically important to understand all aspects of the instruction to authors including referencing style, number of references allowed, instruction for figures (dpi, colour scheme, sizing etc.), restriction on number of tables and figures, word limits etc. To know more about referencing and reference managers, click here.

7. **Choosing a journal of choice**: This is a critical decision and should be done keeping in mind the merit of your paper, your target audience, the journal reputation, impact factor, scope and rapidity of decision making. For more detailed approach to choosing an appropriate journal, click here.

8. **A checklist approach:** There are internationally accepted checklists that can be used to write manuscripts. In my opinion, since you already have exhaustive material, using checklists is the best way to convert your thesis into a great journal article without missing out on any of the above-mentioned points. To know more, click here.

Post Graduate Corner

Pearls for Ophthalmic Surgical Excellence for Residents



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Good surgeons are essential for patients. Even if surgical techniques change in the future, the fundamental relationship between surgeon and patient will remain unchanged. A competent surgeon is one who can "successfully apply professional knowledge, skills, and attitudes"[1] Almost all postgraduates and fellows want to get into surgery as quickly as possible. A surgeon›s traditional training seems old-fashioned in a period of artificial intelligence and robotics with the prospect of replacing humans in some surgical fields. Here I will share some thoughts about the requirements and training of ophthalmic surgeons. Some aspects may be valid for other surgical fields.

During my training in ophthalmology, I learnt three principles: "You can teach anyone to operate", "Not everyone will be a master" and "To operate makes stupid". Meaning: Surgery is a craft that can be learned, but mastery of the craft may make it an art. The performance of routine surgery alone does not guarantee medical quality. Ophthalmic surgery is a delicate craft that requires precise execution, as evidenced by common operations of the anterior and posterior segments of the eye, such as suturing the cornea to avoid distortion or peeling the membrane on the macula with care not to damage the foveal tissue. To be a good surgeon, certain requirements must be met.

What are the prerequisites?

Physical requirements-Almost everyone can learn to be an eye surgeon. However, some physical conditions will help to make a successful eye surgeon. It is useful to have four healthy extremities to perform ocular microsurgery, as it is done with two hands and two feet at the same time. Being ambidextrous is an ideal characteristic for a surgeon. Robert Machemer, the father of vitrectomy, tested dexterity with match sticks that needed to be picked up single-handed. For right-handed people, a more advanced test was to use chopsticks with the left hand. Manual dexterity should be practiced and developed with both hands. Stereopsis should be normal to avoid depth perception problems, and normal color vision is favorable to correctly perceiving the red reflex during cataract surgery. Physical deficiencies may be overcome by unique engagement and adaption as psychomotor skills can be developed.[2]

Mental requirements -To learn a craft, manual dexterity and good eyesight are important. However, mental requirements are equally or even more critical, talent alone is not enough. As Theodor Fontane said, "Gifts, who would not have them? Talents - toys for children. Only seriousness makes a man. Only diligence makes a genius".[3] What is more important than dexterity is the mindset. In order to be successful, the student should possess certain traits.

Desire to learn and deliberate practice- In order to improve one's skills, one must focus, study, actively recall, identify gaps, simplify and practice. Having the right mindset is essential, which includes determination, passion, and persistence.[4] Adult learning involves active, focused learning and getting rid of distractions. The key element is full immersion. This is how many fields, such as surgery, foreign languages, and swimming, can be learned. To become an expert in any field, it is vital to have experience and practice deliberately with a focused goal, slow and attentive perception, and total concentration for many hours.[5] surgical success demands repetition.

Ability to plan- Surgery is a contiguous decision-making process. Planning is essential to achieve a successful outcome. Good surgeons take the time to consider every step before and after surgery. There are lessons to be learned from the masters of surgery, many advocate for preoperative planning in order to be successful. By nature many are not manually skilled: When operating, therefore one

need to think carefully about every single step and try to understand it rationally.[6] Every operation should be thought through by the surgeon once - with conceivable surprises - beforehand in peace. In rare and predictably tricky situations, write everything on paper step by step up to the choice of the instrument, often drawing. The higher the level of competence, the greater the flexibility one is afforded.

Attention to detail and quality awareness-Surgical failure is often the result of a minor initial mistake, as the consequences may be significant. Therefore, attention to detail is mandatory. Eisner's book "Eye Surgery" explains the intricacies of ophthalmic surgery, including preparation of the surgical field, use of instruments, and the importance of pressure chambers.[6] knowing the physical facts is crucial for making the right decisions and getting better results. Following this methodology, a sensible combination of options can help solve surgical problems.During childhood every child wll be taught to be patient and cautious while solving puzzles and the same applies to eye surgery: don't use force. Quality in real time can be seen through good craftsmanship. The tools and skills of the surgeon are important factors, but it is more important to be aware of your abilities and not be deceived. The man with enough insight to admit his limitations comes near perfection.[7] However, perfection should not be the main goal, but leaving the comfort zone and striving to be better than "good enough" is necessary to achieve quality.

Behavior and respect -Beginners should have basic knowledge of their field, self-criticism, and a little confidence. Preparation is key in ensuring success: one should familiarize themselves with the microscope before going into surgery and sit properly. Young surgeons should not practice alone but instead should begin their surgical career with a mentor for guidance and correction. Mentee and mentor need patience and time. They should demonstrate a friendly, courteous, quiet, and team-oriented attitude in the operating room. Respect must always be paid to the patient's eye, as no eye should be harmed.

Training of a surgeon

Learning surgery: general aspects-To become a good surgeon, it is necessary to understand surgical indications and interventions, gain experience through observation, participation, and research, and learn from the knowledge and mistakes of other surgeons. Therefore, it is useful to assist to gain the necessary prior knowledge. Instead of making your own mistakes, learn from others. Knowledge without action is useless. Progress in surgical practice can be made quickly by having seniors provide mentorship and later by researching and emulating top performers (by video or visit (Eye must travel). One is stuck in the zone of mediocrity when one is complacent with what one has learned without exceeding the comfort level. Continued medical education and self-education are necessary for independent learning. Evidence-based medicine combines the best research evidence, clinical expertise, and patient values to optimize medical practices. It requires measuring what can be measured and finding ways to measure what can't so that medical skills can be advanced.[8] Intraoperative checkpoints are recommended for things that cannot be quantified, such as the ideal amount of peripheral vitrectomy. In-depth analyses of surgical processes are now achievable, making it possible to analyze the inter-patient variability of surgical workflows.[9]

The Dunning-Kruger effect is a cognitive bias in which people with low abilities overestimate their abilities while those with high abilities underestimate them.[10] It can be measured by comparing self-assessment to performance. To ensure that beginners meet a certain standard of performance, a standardized, internationally valid tool such as the ICO-Ophthalmology Surgical Competency Assessment Rubric (ICO-OSCAR) is useful.[11] Furthermore, experts must be evaluated by their peers to ensure that surgeons are performing satisfactorily, as there will always be differences in skills even if all surgeons are performing adequately. As surgeons continue to learn and refine their skills throughout their professional lives, they should strive to reach the highest point of their knowledge and skills.[12]

Surgical training -Surgical training should be standardized and structured for newcomers, using simulators and rubrics to reach milestones and improve performance.[13] Becoming a surgeon is a long process that requires commitment and passion. It is important to plan each surgery and start with the simple tasks, proceeding to the difficult ones. Each surgery has a signature part showing how you can do it (e.g., capsulorhexis, hole localization, or peeling).[14] Recording and watching surgeries, asking for help when in doubt, and practicing extensively are key to success. Surgeons should be familiar with different techniques and use the most appropriate and least invasive form.

Mentee and mentor- The stages of a surgeon's life involve being a mentee learning from an experienced mentor by watching and getting guidance. The mentor discusses and interprets successes and failures. Most challenges a mentee faces don't arise from something challenging to learn but rather from the teacher, making it seem complicated. As a young surgeon, perform the surgeries your mentor allows while remaining cognizant of your limitations and striving to improve.Preparation and deliberate practice are essential in gaining the confidence to perform adequately. A successful operation involves not only knowledge but also skills that are often acquired subconsciously. Visual control alone is not enough, as gaining experience and expertise requires more than just a description of how to do the operation. Analyzing intuitively acquired information is difficult and requires feedback

from a mentor who can distinguish between conscious and unconscious (in-) competence. A mentor should be respected to achieve the best results when learning to be a surgeon. You get more motivated when you work with someone you admire. Mentor-apprentice relationships are challenged by the shift to outpatient surgery, which reduces the opportunities to learn from mistakes and refine skills. To be "good" at surgery, one must strive for perfection while being content with doing their best. "Good" is opposed by both "perfect" and "good enough". Perseverance and resilience are key to getting better at surgery in the long run, as time and effort are required to do so.

Books, videos and simulators- A comprehensive book can provide a framework for continuous self-learning. It should provide clear information supported by photographs and videos and emphasize critical decision points. A well-edited book's argumentative strength and well-organized information lead to more clarity and a better-integrated view and understanding. Videos allow sharing of many technical tricks and complications. Simulated surgical training tools can be used to practice skills, but there is no evidence that virtual reality training is better than conventional methods.[15]

What makes a good surgeon

Characteristics of a good surgeon- The expert surgeon is distinguished by their skills, judgment, experience, and craftsmanship. Their work identifies them. Real-time results are an outstanding feature of ophthalmic surgery. Even if mastery is hard to describe, others - patients and peers - can see when you're doing good work. Mastery involves regularly performing an activity - experts can recognize intricate patterns of information and apply them with ease and flexibility. Mastery is characterized by simplicity in instruments and techniques.[16] However, even when instruments and technical equipment are absent, a great surgeon can bring out good results.[17] Mastery is a path, not a destination. It requires instruction, practice, dedication, intentionality, and excellence. Poor lifestyle, ineffective learning and teaching, lack of ambition, laziness, inconsistency, and vanity impede perfection. This journey will never end, and it's impossible to forgo any part of it. We'll never get to the point where we can no longer learn from others. Those who are no longer striving to become better will not remain good.

Reputations are brittle and challenging to uphold. There is a belief that the value of surgical services is determined by the name of that service rather than by the surgeon's skill or the matter to the patient. Such a system would be logical only if all the physicians were equally competent. But all surgeons (and most people who are not) know this is as wrong as believing that all cooks are similarly qualified. Good surgeons can provide a better outcome for the patient than poorer surgeons.

A skilled and ethical surgeon must deliver instead of selling or becoming complacent. It is of no benefit to medical science to report successful cases that follow accepted rules, as this does not provide any new knowledge. What is of scientific value are discoveries made on either known or newly taken paths, but it will be of little value if the reporter is not completely truthful. Therefore, it is essential to report all facts correctly and not leave out any circumstances to support a preconceived opinion.[18]

Patient orientation-As a doctor, always remember that the patient is your only client. Make sure they receive excellent care with equity and integrity and a positive outcome. Don't focus on the image (OCT), examination, or disease, but on how it affects the patient.[19, 20] Put the patient's needs first, and don't be tempted to strive for perfection over care.

Ensure that patients understand the goals and results of surgery. The patient should request an operation from you after your consultation, not the other way around. Inform them that sometimes their issue may require multiple surgeries. Complete each task to the best of your ability. The initial procedure has the highest chance of solving the issue, and the likelihood of success decreases with every additional surgery. A good beginning speaks to a good end. One should try to perform the procedure in a way one would like to receive. After having surgery on oneself, one may change perspective and even better understand good surgery. One can then be referred to as an "experience expert", someone knowledgeable not because of having studied surgery but because of having experienced it.

Setting the indication- Preoperative planning, postoperative management, and patient discussion are key to surgical success. Setting the indication for surgery is a crucial and increasingly important decision for a physician. A shift towards an economic approach in medical practice has resulted in a subtle re-polarisation of physicians. It takes talent to recognize when to operate on a patient but delaying surgery can sometimes be the best option. The maxim "a cataract is not operated on if it troubles the ophthalmologist, but if it bothers the patient" (Thomas Neuhann) is now more relevant than ever.

Avoiding and handling complications-Complications should be avoided. We distinguish between preventable, complex, and intelligent failure. Simple errors, such as sending the wrong patient to the OR, are preventable failures; complex failure occurs when a procedure is convoluted (vital emergency in the operating room); and intelligent failure is exploratory, such as the development of vitrectomy by Machemer. Checklists help to prevent mistakes.[21] Surgeons must take care that their team is educated well. Nobody works alone, and good education and preparation prevent many complications. By following

these strategies, surgeons can minimize the risk of complications. A good surgeon needs to be able to deal with complications effectively without creating new ones. The way the complication is handled is more important than the complication itself. It is important to remain calm and consider all options when faced with an unexpected challenge rather than rush into a decision. Taking a moment to breathe and think can make a big difference. Failure is not the end but a lesson to use going forward. There is always a solution. Use mistakes and failures as data to find better solutions.[22] In essence, handling complications involves learning what we can influence, what we can control, and what we cannot.

Quality and quantity of surgical interventions-Quality does not usually come before quantity in surgical success (visual success and lack of complications). It depends mainly on a surgeon's competence, judgment, experience, and the number of cases. Decisions for one-time surgery or multiple interventions, knowledge of various surgical options, and ability and flexibility to adapt to the situation are all key factors successful results. High-volume cataract surgery leads to improved visual acuity outcomes and decreased complication rates, making it a valuable practice in developing countries with a backlog of cataract cases and a high patient-to-surgeon ratio.[23] While a larger number of surgeries does not result in further improvement of visual acuity, a surgeon›s experience and skill can be developed through years of deliberate, sharp practice. Short-term operating room numbers make a surgeon sharp, deliberate practice over the years makes a surgeon skilled, and the overall volume of a career makes him wise.

Innovation- Inquisitive surgeons who are curious and ask questions are essential to the advancement of the field of medicine. Progress is achieved when unconventional methods are considered. Quickly, what was once astonishing becomes ordinary. Innovation involves developing something new and combining, reexamining, and reviving what has been forgotten.[24] Playing and working can be complementary, with play helping to develop creativity. To much old information can lead to less openness to learning new things, so it's important to remain mentally agile and open-minded to new ideas. Therefore interests and hobbies outside surgery are useful.

Surgical learning as a function of the medical education system- Ophthalmology separated from general surgery due to the success of ophthalmologists in performing surgery. This and the overall progress of knowledge led to subspecialization. Today, ophthalmic surgery has multiple subspecialties, but it is possible to learn more than one surgical field in ophthalmology once one has had a good surgical introduction. Surgeons work in a health system that influences their decisions and spectrum of possibilities. The initial start of surgical learning is the most difficult phase. Beginners in countries lacking formal surgical fellowships face added challenges. A desire to learn, combined with goals and a plan, is essential for learning surgery, along with mentorship and self-education. You need resources and a plan, and successful execution. Passion, enthusiasm, and energy play a big role, too.[25]

Conclusion- Understanding and treating surgical conditions will benefit surgeons, their patients, and new generations of ophthalmologists, even as robots take over certain interventions.The right mindset and skills are necessary to become a competent surgeon. An excellent surgical mentee needs Physique for extended operations and work night hours, Passion for learning and helping patients, Perseveranc e, Patience, and Psyche to endure failures, Participation in being a valuable part of the surgical team, Planning and Portioning of surgical procedures, Practice and Precision until Perfection is close. Sometimes you need a Prayer.A master surgeon possesses expertise, is observant of outcomes, is innovative in treatment, can identify complex clinical problems, asks important questions to improve care, disseminates knowledge and expertise, and trains future surgeons.

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Surgical technique

Blepharoplasty

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Age related changes in the eyelids and periorbital region have a significant impact on the youthful appearance of the face and often account for major concern for those seeking facial rejuvenation. These include laxity of skin, orbital septum, canthal tendons and orbicularis muscles. Prolapse of the orbital fat and development of malar festoons add to it.

The demand for restoration and rejuvenation of eyelids and periocular area has increased in the last ten years and various non-invasive procedures and minimally invasive surgeries have become popular, one of them being blepharoplasty.

Blepharoplasty is done for cosmetic or functional reasons, both for upper and lower eyelids. It is one of the most frequently performed cosmetic surgery on the face.

Upper blepharoplasty constitutes the surgical repair or reconstruction of the upper eyelid including management of loose upper eyelid skin, orbital septum, any underlying ptosis, and excess preaponeurotic and medial orbital fat.

Indications

An upper blepharoplasty may be indicated for **functional reasons.**[2]

- **Excess laxity with temporal hooding** can interfere with superior and supero-temporal vision and may make the patient constantly raise their brows or the chin in order to see. Patients may complain specifically of having difficulty driving and seeing traffic lights. Visual field testing could objectively show the superior visual field constriction.
- **Constant use of the frontalis muscle** (frontalis overaction) in the presence of dermatochalasis and ptosis may give rise to frontal headaches.
- **Eye irritation** may be caused by eyelash ptosis or entropion because of the dermatochalasis.
- Skin-on-skin irritation may cause dermatitis.
- **Down-gaze ptosis** is the drop of the upper eyelids that occurs because of redundant upper eyelid skin and interferes with reading.

Cosmetic Indications

Cosmetic blepharoplasty is done for rejuvenation of the periocular area. It involves removing excess loose skin, creating a more defined skin crease and improving the fat prominence in the upper eyelids. Depending upon a particular patient's anatomical changes, browlift procedure, may need to be combined with blepharoplasty.

Contraindication for upper lid blepharoplasty -The presence of severe dry eyes, active thyroid disease, proptosis and clotting disorders are relative contraindications.

Prior to revision blepharoplasty procedure, the patient should be carefully examined for presence of adequate skin and good orbicularis function as well as absence of pre-existing lagophthalmos.

Medical history

A detailed medical history is essential for the assessment of safety of undertaking blepharoplasty as well as choosing the type of anesthesia for the patient. Review of illnesses such as diabetes mellitus, hypertension, thyroid disease, respiratory diseases, dermatologic diseases, kidney disease, recurrent edema, and any bleeding disorders is done. Medications and supplements need to be reviewed as many drugs can increase the risk of bleeding. Excessive smoking and alcohol can affect wound healing. A review of antiplatelet and anticoagulant medication is vital with a discussion with the patient's primary physician who monitors these to ensure that it is safe to withhold these for 1 week before surgery and for up to a week following surgery. This is more important

for lower lid blepharoplasty.

A review of the psychiatric history and any evidence of a narcissistic personality disorder, body dysmorphic disorder or tendency to histrionic behaviour should be noted and are red flags for cosmetic blepharoplasty procedure.

Ophthalmic History

Previous ocular surgery, including any refractive surgery, need to be reviewed as many such patients would need frequent lubrication in the post operative period.

Blepharitis and meibomian gland dysfunction need to be treated. History of prior blepharoplasty or any other eyelid surgery should be elicted.

Examination

Examination of upper eyelids should always start with a review of the forehead (to look for frontalis overaction), position of brows (to look for brow ptosis) and then upper eyelids. Underlying ptosis needs to be assessed. It is well-recognized that when upper eyelid surgery is performed with or without ptosis repair, the position of the brows will drop, unmasking the brow ptosis, especially in men.[4] The symmetry of the upper eyelids or lack of it needs to be measured and documented. The amount of upper eyelid skin excess, it's thickness, evidence of any inflammation or presence of skin lesions should be noted. It is important to look for and document facial (brow, eyelid, forehead and cheek) asymmetry. In Asians and certain other populations, epiblepharon may be present and should be noted as the placement of the upper eyelid incision will affect the eventual scar and result. Patients may have one or more (primary, secondary, tertiary) skin creases and the creases may be asymmetric.

Schirmer's test with topical anesthetic may be performed. Review of the blink, closure, lower eyelid laxity (the distraction and snap-back tests) and assessment of the corneal tear film is done. Bell's phenomenon is assessed as 15% of the population will have a neutral or negative Bell's phenomenon.

Tarsal platform and eyelid crease: central to any blepharoplasty is the creation of an eyelid skin crease, below which is the tarsal show or tarsal platform. The skin crease is defined by the insertion of the anterior fibers of the levator aponeurosis into the dermis through the orbicularis oculi muscle. The skin crease height varies depending upon ethnicity, age, and gender. In men, upper eyelid crease is generally lower than that in women. However, even within a particular ethnic group, the skin crease height varies. We assess photographs taken at a younger age, to decide suitable skin crease for the patient. In Asians, the skin crease is low (1 to 3 mm) because of the lower insertion of the orbital septum on the levator aponeurosis and weaker dermal attachments by the levator aponeurosis. Aging causes a decrease in skin elasticity, weakening of the aponeurotic attachments to the tarsal as well as the dermis, and an overall reduction in the periorbital fat, which should all be assessed. Hollowing of the periorbital tissues together with the elevation of the skin crease and "skeletonization" of the orbit in advanced age can occur.

Corneal reflex-lid margin distance in Caucasians measures 3.5 to 4 mm. If it is below 3 mm or there is asymmetry, ptosis should be measured and corrected. Levator function should always be measured; normal is more than 12 mm.

Fat pads in upper and lower eyelids -The upper eyelid has a medial and central fat pad. These fat pads can be accentuated by pushing gently on the globe with the eyelids closed or on the lower eyelid. The central fat pad often spreads laterally, but any lateral "bulge" should be assumed to be that of the lacrimal gland which may prolapse forwards with age. The medial fat pad which is a lighter color than the central fat pad is more rounded and medial to the levator aponeurosis separated by a weak septum from the central fat pad. The central fat pad sits on the levator aponeurosis. The lacrimal gland is in the lacrimal sac fossa in the superolateral orbit. There is also preseptal retro-orbicularis fat present which can contribute to upper eyelid fullness. Any lateral upper eyelid bulge should be noted as it may be a prolapsed lacrimal gland. Understanding these anatomical details allows one to examine the various bulges on the upper eyelid accurately.

Assessment of the position of the eyebrow and the brow fat pad is essential. A full brow gives a youthful look. Rarely is it necessary to remove some amount of brow fat pad. Some degree of droop of the brow fat (retro-orbicularis oculi fat) can occur, necessitating a surgical repositioning rather than removal.

The following **measurements** and assessments are made:

• Brow ptosis: Absent or present, mild, moderate or severe. Presence or absence of lateral brow ptosis (leading to secondary dermatochalasis)
• Brow shape
• Corneal reflex-lid margin distance (MRD-1). Normal measurement is 3.5 mm to 4 mm
• Levator function (more than 12 mm)
• Eyelid contour and height
• Pupils (any anisocoria)
• Ocular movements

• Examine the corneal surface (pterygia, scars, evidence of LASIK or radial keratotomy, conjunctival blebs, corneal dystrophies)
• Tear breakup time (BUT) and Schirmer's test are often performed
• Bell's phenomenon. If the patient has a neutral Bell's phenomenon or a negative one, conservative blepharoplasty is indicated.
• Lagophthalmos: May indicate underlying thyroid disease or prior eyelid surgery.
• Proptosis or enophthalmos. These can give rise to pseudo ptosis or eyelid retraction
• Hypertrophic or redundant orbicularis muscle
• Scleral show
• Examine the lower eyelid for laxity, position and canthal laxity.
• Beware of underlying blepharospasm which can give rise to orbicularis hypertrophy and redundancy and associated dermatochalasis and also an appearance of ptosis because of the tonic squeezing of the eyelids.
• Look for tarsal laxity (floppy eyelid syndrome). Patients will have a rubbery tarsal plate which may need horizontal shortening before being elevated.
• Consider blepharochalasis when the patient presents with recurrent eyelid swelling, sometimes unilateral. There will be associated eyelid atrophy and superior sulcus deformity. Patients will eventually develop ptosis, steatoblepharon and excessively thin eyelid skin (cigarette paper skin).
• Fluid retention in the upper and lower eyelids (and festoons) are often seen in patients with kidney failure and in patients on CPAP machines.
• Hereditary angioedema should be suspected if there is intermittent swelling of the eyelids: C1-esterase inhibitor levels are assessed.

Technique

Skin Marking

The upper eyelid skin crease should be marked either where it is or where the desired skin crease should be. Symmetry is important. The degree of skin excision is variable and is marked with a lateral raise in the incision. The amount of orbicularis muscle resection again has to be determined based upon numerous factors and the same applies to fat removal. More conservative blepharoplasty with tissue preservation (fat and muscle) has become more popular to retain or recreate normal periorbital fullness.

The medial extent of the markings are no more medial than the punctum, and the lateral markings are kept within the lateral orbital rim. A medial "W" plasty may be necessary if a more profound degree of skin removal is necessary. The amount of skin removal depends upon the position of the brow, keeping in mind any brow elevation. Some surgeons mark the amount of skin to be removed by pinching the skin with the patient lying down. This can be a useful technique to ensure that not too much skin is removed. I mark the removal of the skin with the patient sitting up. Certainly, at least 10 mm should be left between the upper incision and the inferior border of the brow. The normal distance between the lid margin and the inferior border of the brow is more than 25 mm in unoperated adult face. Although guidelines have been given (leave at least 20 mm between the upper lid margin and the inferior border of the brow, for example), this amount varies and depends upon numerous factors, including whether a concurrent brow repositioning is being performed, history of prior surgery, orbicularis strength, Bell's phenomenon and any underlying dry eye.

The shape of the excision is such that more tissue is resected laterally with the maximal resection being at the lateral canthus. Modifications in the incision designs have been made with even more tissue being removed laterally in some patients with brow ptosis where no brow elevation is being performed but the temporal hooding needs to be improved. Incisions carried low laterally will affect innervation of the orbicularis oculi muscle with resultant lagophthalmos.

Volume Augmentation

Attention, of late, has turned to volume augmentation rather than just subtractive surgery.[7] It is not uncommon to have volume loss of the brow fat as well as the middle fat pad. The medial fat pad is often prominent. This is probably because the central fat pad gets pulled back together with the levator aponeurosis and the orbital septum with the inevitable enophthalmos that occurs with age and posterior movement of the orbital fat. The medial fat pad does not sit on the levator aponeurosis and becomes more prominent. The orbital septum is also less substantial over the medial fat pad, allowing the anterior dislocation of the fat. Fat grafting may be performed or fat may be preserved and transposed into the hollow areas.[8]

Instruments required

No specialized equipment is needed for upper blepharoplasty other than standard plastic surgery and oculoplastic surgery instrument set.

Anesthesia

Upper blepharoplasty may be performed with local anesthesia with or without monitored sedation. These procedures can be performed safely in an office, surgical center or hospital operating theater. I do the procedure in hospital operating theatre, usually under local anesthesia. Local anesthesia injection with lidocaine and epinephrine subcutaneously with care being taken not to inject too deeply so the levator muscle is not affected The surgeon must be familiar with the procedure of blepharoplasty and also have the experience and knowledge to address any preoperative and postoperative complications that may arise.

Incisions

Incisions may be made with a 15 Bard-Parker blade, an electrocautery, a CO2 laser or a radiofrequency needle.

Removal of Orbicularis

Stretching of the skin can cause some degree of redundancy of the orbicularis oculi muscle but care must be taken to remove conservative amounts of orbicularis muscle. Pretarsal orbicularis must always be preserved. A variable amount of orbicularis over the preseptal region is removed, depending upon the patient's age, the degree of redundancy and whether any brow lifting is being performed. Removal of a small strip of orbicularis, together with work on the septum and fat (see below) can create a more defined crease.

The Orbital Septum

In some cases, the orbital septum may not need to be opened. Simple cautery to the surface of the septum does not give long-term tightening as there is tissue restitution over time. In most cases, the orbital septum is opened and planned fat removal is performed.

Fat

Unsatisfactory blepharoplasty results may be seen if the medial fat pad is not adequately debulked.[9] On the other hand, if the central fad pad is removed aggressively, an "A frame" deformity with a hollow superior sulcus will form. In some patients, especially when a repeat blepharoplasty or revision blepharoplasty is being performed, fat transposition may be performed to reacquire the natural sub brow fullness of a healthy, attractive eyelid. On rare occasions, a pedicle from the medial fat pad can be brought to the central zone if there is volume deficiency there. The art of blepharoplasty is to know how much to remove, how much to preserve and how much to reposition.

Closure can be with interrupted 6-0 catgut sutures which allow for a good wound but 6-0 nylon or prolene may also be used.

Fig 1A. Before and after Upper Lid blepharoplasty

Fig 1B .Skin Flap excised

Fig 2A Before Upper lid blepharoplasty

Fig 2B After Upper lid blepharoplasty

Postoperative Care

Patients are advised to use topical antibiotic eye ointment twice a day to the sutures and use artificial tears as needed. Most patients do not need prescription analgesics. Anticoagulants are usually recommenced by day 2. Patients are advised to ice their eyelids on-and-off for the first 24 hours.

Complications

All patients will have some bruising and swelling, which may last up to 2 weeks. If ptosis correction is done along with blepharoplasty, some amount of dryness is inevitable. Most patients will need topical lubrication during the day. Some patients need a topical lubricating ointment at night.

Eyelid Sensation

As the eyelid margin is supplied by branches of the supraorbital nerve centrally and laterally and the supratrochlear nerve medially, upper eyelid incisions will result in decreased sensation along the eyelid margin for six to eight weeks. Although most patients recover by 8 weeks, some numbness can persist for longer.[10] Females will recognize the numbness when they apply makeup on the eyelid margin.

Lagophthalmos and Dry Eyes

Early in the postoperative period, almost every patient will experience some lagophthalmos. However, within a few days, this settles and there is complete closure of the eyelids. This is where the experience of the surgeon is important as a number of factors affect the height of the upper eyelid and its ability to close. Peroperatively, local anesthetic injections will partially paralyze the orbicularis muscle, giving the levator a mechanical functional advantage. If there is diffusion of any anesthetic into the levator and Müller's muscle, the lid elevation will be affected. Most surgeons will aim for a slight lagophthalmos on the table, especially when ptosis correction is also undertaken. Topical lubricants with drops and ointment are useful for the first few days to weeks until the lagophthalmos resolves.

Even without lagophthalmos, the patient may experience dryness of the eyes. This is because the lid blink and amount of closure (firmness of closure) are affected in the first few weeks after surgery. Furthermore, any other underlying conditions that contribute to dryness (Meibomian gland disease, blepharitis, acne rosacea, lower lid laxity, etc) will exacerbate the postoperative dryness..

Hemorrhage

Ecchymosis is not uncommon. However, a retrobulbar hemorrhage is an emergency which necessitates opening of the wound and the deeper tissues to release the hematoma.[11] Bleeding may occur from vessels within the preaponeurotic fat or from sub-orbicularis vessels just below the incision. Patients will present with pain, proptosis, nausea and vomiting and reduced vision. It should be remembered that blepharoplasty generally causes little discomfort. Therefore, any severe pain after blepharoplasty should be assumed to be because of retrobulbar hemorrhage until proven otherwise. Immediate opening of the wound with or without a canthotomy and cantholysis is necessary.

Assymetric Eyelid Creases

When making a skin crease incision, it is important to remember that the final crease often ends up about 2-mm higher. Lowering a high skin crease is difficult and the results are unpredictable.[12]

Asymmetric Height and Eyelid Adjustment

Upper eyelid blepharoplasty is an art form, and small differences are often seen in all patients. It is wise to allow all the swelling to settle to determine if additional adjustments are needed. We rarely adjust before 2 months after surgery. Adjustable upper eyelid ptosis repair was described some years ago but is very rarely used.

Upper lid Blepharoplasty Refinements

Addressing Temporal Hooding

Some surgeons have recommended extending the lateral arc of the upper lid skin excision laterally and up close to the brow and have shown nice results with minimal scarring when the patient does not want to have a brow lift performed.[13] The concern is that one is extending the incision from the thin skin of the upper lid to the thick skin of the brow. Such a transition can give a scar that may be visible. This procedure should not be performed for purely cosmetic reasons where we would prefer to perform a combination of a brow lift and upper blepharoplasty. In some older patients, this is a reasonable approach.

Skin Crease Reformation

When a well-defined skin crease needs to be designed, we pick up the levator aponeurosis in the skin closure sutures. One can use buried vicryl sutures from the subcutaneous tissue to the aponeurosis or pick up the aponeurosis with the skin closure suture. Removal of a strip of the orbicularis oculi muscle and some preaponeurotic fat also allows a more defined upper eyelid skin crease.

Filling the "A" Frame Central Eyelid

As one ages, prominence of the medial fat pad and posterior dislocation of the central fat pad with stretching or disinsertion of the levator aponeurosis (and also age-related fat atrophy more posteriorly) gives a deep superior sulcus. Free fat grafts may be used to fill this space. Another options is to mobilize the upper eyelid fat pad behind the

orbital septum, bring the fat forwards and suture it to the orbicularis under the incision. This gives nice results without the need for free fat grafts. The medial fat pad can also be mobilized and transposed centrally, but the whole central concavity cannot be adequately addressed using this technique.

Lateral Brow

Botulinum toxin is injected in the lateral sub-brow orbital orbicularis to give a nice lift to the brow tail. A similar resection of a small amount of orbital orbicularis oculi muscle may be performed to provide a subtle brow lift. [14] This resection does not seem to give as impressive a lift as the use of botulinum toxin, so we reserve this for subtle lifts only.

Internal Brow Lifts

"Internal brow lifts" should be considered as brow stabilizing procedures. This does not give a long-lasting and substantial brow position and curve change and so"internal brow lift" procedure is not preferred.

Lower lid Blepharoplasty

In the lower eyelid, there are also two fat pads. The larger medial fat pad is often subdivided into two smaller collections by a septum in the region of inferior oblique muscle.The smaller lateral fat pad is separated from the medial fat pad by a fascial septum.

In younger patients, skin reduction is often not required in the lower eyelids. Fat alone may be reduced through a conjunctival approach. The skin approach allows reduction of both skin and fat. Fat prolapse is addressed by excision or redraping (transposition). Laxity of lower lid needs to be corrected at the time of blepharoplasty to avoid post operative ectropion or scleral show.

Examination

We look at the lower lid and cheek – we should look for excess skin, fat prolapse, scleral show

We look at the lateral canthi, whether they are low

We look for the presence of tear trough deformity, obvious nasojugal fold and supramalar sulcus

Detailed complete eye examination is done.

Choice of operation

1. **Skin flap blepharoplasty –** Surgery of choice in older patients with thin lower lid skin and poor tone in orbicularis muscle.

2. **Skin – muscle flap blepharoplasty –** In younger patient, if there is definite but limited excess skin, a skin – muscle flap blepharoplasty is preferred.

3. **Transconjunctival approach –** If there is fat prolapse and no skin needs to be removed , then only the fat can be removed from the conjunctival side

4. **Blepharoplasty with transposition of fat –** If there is severe tear trough deformity , then the prolapsed fat can be transposed or redraped by opening the septum and fixing the fat over the inferior orbital rim **,** to correct the hollow

Ancillary procedures

1. **Correction of lateral canthal laxity –** Canthal tendon laxity must be corrected. Tightening of lid is combined with elevation of canthus. If laxity is mild, then a simple plication suture between the tarsal plate and lateral canthal tissues is sufficient. If changes are more marked , then lateral tarsal strip is preferred.Marked changes require relocation of the lateral canthal tendon to a higher level on the lateral orbital rim.

2. **Correction of medial canthal laxity –** It is occasionally necessary to correct medial canthal tendon laxity

Skin Muscle Flap Blepharoplasty

This technique is used in older patients with thin lower eyelid skin and poor lid muscle tone.

Steps of surgery –

1. Incision is made 2 mm below the lash line, extending from just below the punctum medially to the lateral canthus, then extending slightly downwards towards the orbital rim.

2. Skin flap alone or skin muscle flap is dissected as far as the inferior orbital rim.

3. Remove excess fat from central , medial and lateral fat pads is done by making small openings in the septum

4. Then horizontal lid laxity is corrected and finally excess skin is excised. Vertical excess of skin is excised first, then horizontal excess excised.

5. Wound closed with continuous monofilament sutures along the lid and interrupted sutures along the lateral canthus.

6. Suture is removed in 5 days

Fig 3. A. Before Skin Flap Blepharoplasty

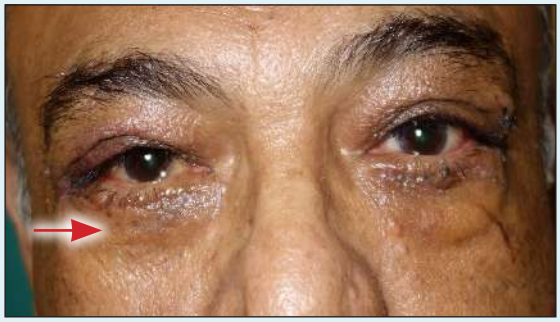

Fig 3. B. After Skin Flap Blepharoplasty

Complications

1. Lid retraction
2. Scleral show
3. Ectropion – if too much skin is removed or uncorrected horizontal lid laxity. Horizontal lid laxity is corrected in the standard way, shortage of skin is corrected by full thickness skin graft.

Transconjunctival Lower Lid Blepharoplasty

This technique is suitable for fat excision or redraping without skin excision. Preferred in young individuals, where skin need not be removed.

Steps of surgery –

1. Carefully assess and mark on the skin, the fat which needs to be removed. Compare and look for asymmetry between the two eyelids.
2. Then , retract the lower eyelid and infiltrate that area with 2% lignocaine with 1:10000 adrenaline , deep to the conjunctiva , along the lower eyelids
3. Incise the fornix a few millimetres inferior to the lower border of the tarsal plate , with scissors or monopolar cutting cautery needle
4. Open the fat pockets widely , prolapse the fat , clamp with artery forceps and then cut with monopolar cautery
5. The medial fat pad may be difficult to locate , gentle pressure on the globe will encourage the fat to prolapse
6. The inferior oblique muscle can be identified once the medial and central fat pads have been reduced
7. Finally conjunctiva is closed with interrupted absorbable sutures

Fig 4A. Before , intraoperative and 1 week after Transconjunctival lower lid blepharoplasty

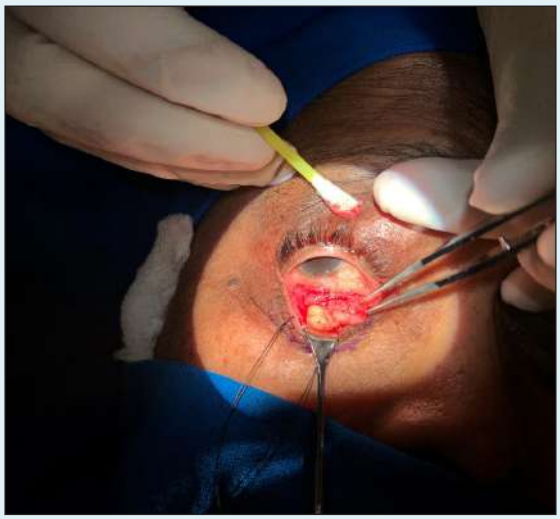

Fig 4B. Intraoperative picture showing prolapsing fat in Transconjunctival lower lid blepharoplasty

Complications

1. Residual fat prolapse – this is the commonest complication, commonly due to inadequate excision of fat or inappropriate redraping. Further fat can be excised at a second operation.
2. Over – excision of fat – If this is very marked, fat replacement or fillers may be needed.
3. Lower lid retraction – less common
4. Damage to inferior oblique muscle – uncommon , although transient weakness may occur
5. Retrobulbar hemorrhage – rare but possible.

Conclusion

In conclusion, conservative excision of intraorbital fat in either transcutaneous or transconjunctival blepharoplasty has proven to be predictable and esthetically acceptable procedure for rejuvenation of the eyelids. Optimal preservation of orbital fat is a better alternative than complete excision of the prolapsed orbital fat.

High patient satisfaction with the least postoperative complications is the objective of every surgeon. With the proper patient selection, adequate surgical training and meticulous dissection consistently reproducible esthetic outcome and harmony in facial rejuvenation following blepharoplasty can be accomplished.

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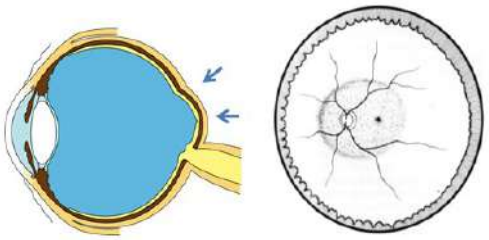
Surgical technique



Macular Buckle for myopic posterior staphyloma-related macular conditions

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Introduction

Pathologic myopia is one of the leading cause of secondary visual impairment worldwide and the most frequent cause in Asian subcontinent. Visual impairment in these eyes with pathologic myopia is mainly due to the development of different types of myopic maculopathies, closely associated with the type and grade of the staphyloma.[1] Various authors have classified them into tessellated fundus, lacquer cracks and patchy atrophy, diffuse chorioretinal atrophy, lacquer cracks, patchy chorioretinal atrophy, CNV, macular atrophy and posterior staphyloma.[2] Macular hole with or without macular retinal detachments, myopic foveal schisis are established associations of the posterior staphyloma.[1] These complications are managed surgically by pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling with intraocular tamponade. Scleral shortening procedures, episcleral buckling are some of the additional procedures performed to take care of the posterior staphyloma component pathological myopia with variable surgical success.

Pathophysiology

The pathogenesis of RD secondary to macular hole and retinoschisis in high myopia with posterior staphyloma are [4,5]

1. Posterior staphyloma leading to disparity in the length of the sclera and retina (mismatch).
2. Anteroposterior traction caused by the vitreous.
3. Tangential traction due to abnormal rigid ILM, stretched retinal vessels or epiretinal membrane.

Other possible explanations were weak adhesion between the neurosensory retina and retinal pigment epithelium due to the severe myopic chorioretinal atrophy and an incomplete detachment of the posterior hyaloid that will increase the anteroposterior and tangential traction on the retina. The macular buckle is proposed to support the posterior globe to counteract all the mechanisms involved in such cases. Buckle changes the configuration of the posterior pole from the concave profile of posterior staphyloma to a plano/convex protruding contour thereby relieving anteroposterior traction, tangential traction and sclero retinal mismatch (Fig. 1).History of macular buckle

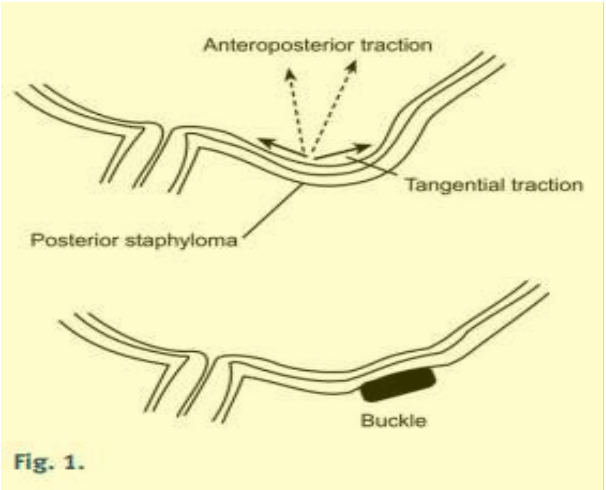


Fig. 1.

1957: Macular buckling was described for the first time by Charles L. Schepens, the father of modern retinal surgery, using a radially placed polyethylene tube.[6]

1966: Rosengren B described a silver ring and plomb technique to indent the macula. The ring is attached to the limbus and an arm fixed to the ring has a terminal ball, which was made to indent the macula. Photocoagulation is done after a day or two once the fluid is absorbed. The ring and plomb are removed after 4 weeks.[7,8]

1974: Theodossiadis used a silastic sponge rod placed between the inferior oblique insertion and the optic nerve. The rod was stretched vertically across the macula by fixing sutures to produce the required indentation. He followed his patients for upto 15 years.[9]

1980: Ando introduced the Ando plombe which is described in detail later.[10, 11]

Evolution of surgical treatment for myopic macular schisis, macular hole and RD

PPV with ILM peeling has been effective in terms of anatomical and functional success in the treatment of macular schisis and macular holes associated with high myopia.[12–14] Complications include formation or persistence of macular hole, macular hole retinal detachment (MHRD) and visual loss.[15–16]. Success of closure in these myopic macular holes following surgery is less than the idiopathic holes in emmetropia.[17] Ikuno et al showed 25% of macular hole closure following surgery in myopia with macular hole and foveoschisis with posterior staphyloma.[18] Failure of vitrectomy with ILM peeling in such cases lead to think about the other causative factors responsible for the macular complications in myopic eyes with posterior staphyloma. Cases which had failures following vitrectomy led one to consider additional or supplemental procedures which could negate the mismatch between the staphyloma and retinal contour. This led to the surgical options of macular buckle in myopic eyes with posterior staphyloma

Indications

- Myopic macular retinoschisis with posterior pole staphyloma with recent decrease in visual acuity.
- Posterior pole detachment associated with myopic macular hole with posterior staphyloma.
- Failed and recurrent cases of macular hole with or without RD following vitrectomy with or without tamponade.
- Optic disc pit maculopathy.

Macular buckle types

- Ando plombe
- T-shaped macular buckle
- AJL macular buckle
- L-shaped macular buckle
- Adjustable macular buckle
- Wire-strengthened sponge exoplant

Ando's plombe (Ondeko Corp)

Ando plombe consists of a T-shaped semirigid silicone rubber rod internally reinforced with titanium wires and an indenting head at one end. The length of the plombe is either 25 or 27 mm from head to tail, selected according to the size of globe. The size of the head is 4–5 mm. Mateo et al. coupled Ando's plombe with an internal 30-G optical fiber to enhance the visualization to place the indenting head correctly under the fovea.[19] Advantages include easy to insert the buckle, shape memory, customization of buckle with its embedded wire and eliminates the need for sutures on the staphylomatous sclera near macular area. Disadvantages include its stiffness, limitations in adjustment of buckle height, a less accurate positioning. The long-term safety of metal wire which is embedded in the Ando's plombe is not known.

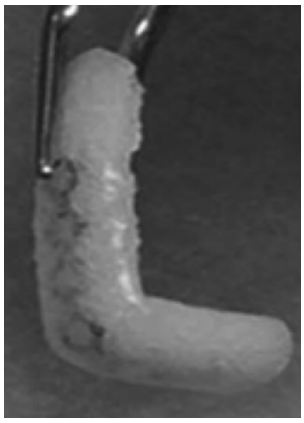
T-shaped macular buckle {France Chirurgie Instrumentation (FCI), Paris, France}

The T-shaped macular buckle20 is created by threading a 4-mm-wide solid silicone band through a 7-mm solid silicone macular wedge (Morin–Devin 'T'-shaped macular wedge) with a biconvex end. Macular wedge is negotiated under the lateral rectus muscle, manoeuvred further to be placed posteriorly under the staphyloma area. The 4-mm solid silicone bands are mobilized under the vertical muscles, behind the obliques to secure on to the nasal aspect, either side of the medial rectus. Advantages of T-shaped macular buckle are that it allows the adjustment for lengthening or shortening the band anteriorly while sliding the macular plate in the coronal plane; it does not require posterior sutures or direct access to the posterior pole, no need for muscle disinsertion which carries the risk of postoperative pain and diplopia. Disadvantage includes possibility of improper alignment under the fovea.

AJL macular buckle

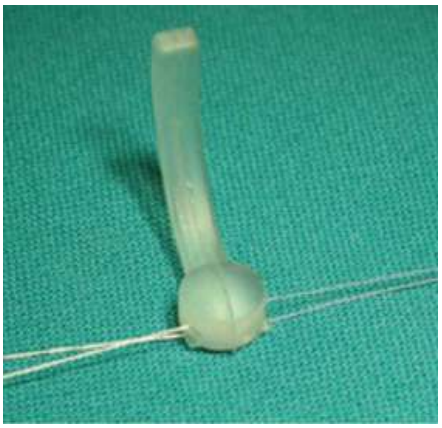
AJL macular buckle is made up of PMMA material covered by silicone in order to increase its biocompatibility. It has an indentation area with a spherical helmet in its superior area to indent the macular area. The arm's length and curvature is customized depending on the patient's specific eye. It can be supplied with an optic fiber light probe for the accurate positioning of the head under the fovea.

L-shaped macular buckle



L-shaped buckle is prepared using a silicone sponge (Labtician 507 oval sponge), 7 mm large and 5 mm thick and 3 cm long. A malleable titanum stent (Mod MCP6TP, Tekka, Pesaro, Italy) 15 mm long, 2 mm wide and 0.5 mm was inserted and hidden into the tunnel. The sponge could then be bent to obtain an L-shaped buckle by creating a 90° angle to fashion the curvature accordingly. Advantages are that it can be easily prepared in the operation theatre and the technique can be performed without the need of specially designed buckles, which are not available easily in all countries. Disadvantages include the unknown long-term safety of the titanium inside the orbit.[21]

Adjustable macular buckle (AMB)



The AMB is made up of silicone rubber, consisting of a handle or stalk designed for radial positioning and a terminal plate intended to indent the macular area. Two lateral winglets at the terminal plate helps to pass suture through it. The two mersilene sutures are brought on either side of the medial rectus, fixed to the sclera anterior to the equator. This procedure requires lateral rectus disinsertion. Postoperatively the buckle effect can be adjusted using these sutures under local anaesthesia.[22]

Wire-strengthened sponge exoplant

It consists of a 7 mm silicone sponge strengthened with a 0.5 mm orthodontic steel wire that is originally used for dental braces. First, the wire is bent into U shape at the middle with 2 mm separation between the 2 arms. Then, the wire is inserted inside the sponge and fed through its whole length. The distal end is bent according to the eyes which help to indent the macula.[23]

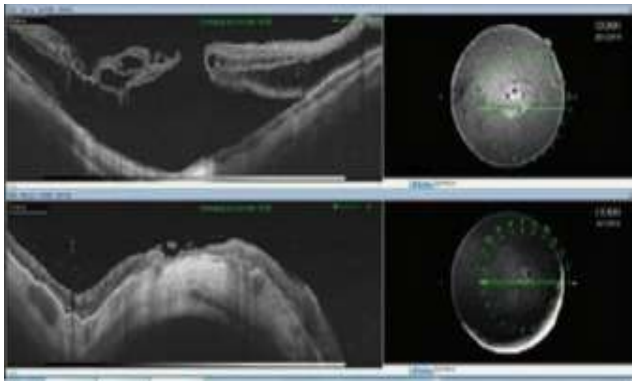
Limitations of macular buckle

- Possible damage to nerves and vessels in the posterior pole.
- Precised alignment of the buckle under the fovea is of concern.
- Thin sclera increases the risk of perforation and erosion is more.

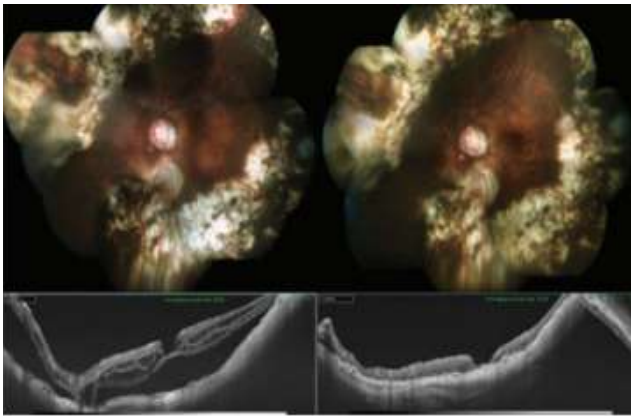
Precise alignment of the buckle under the fovea can be achieved by either

- External posterior landmarks.
- Trans illumination.
- Endo illumination.
- Using illuminated optical fiber along with the macular buckle.

We had an initial experience of three cases operated using the T-shaped macular wedge implants. Indications were recent central visual impairment due to progressive schisis, macular hole with macular detachment and persistent chorioretinal mismatch at the staphyloma in an oil filled eye. One patient operated for the staphyloma associated macular hole with localized detachment, had the macular buckle along with vitrectomy, ILM peeling and tamponade. We noted the anatomical closure of the macular hole and the foveal attachment as early as fourth post-operative period.



Another case had a persistent lamellar hole with a retinochoroidal mismatch post vitrectomy. This case was operated for the macular buckle alone in the oil filled eye. Patient had a progressive visual improvement with a gradual absorption of the subretinal fluid and the retinal apposition over a period of 5 months. Our initial short experience has been quite promising in terms of achieving anatomical restoration of the retina to match the contour of the ocular coats.



Complications

The intraoperative complications include inadvertent globe perforation, injury to vortex veins, ciliary vessels and nerves, malposition of the buckle, optic nerve abutting, subretinal hemorrhage, choroidal detachment and threatening suprachoroidal hemorrhage intraoperatively. Late complications include buckle displacement, exposure, infection, choroidal neovascular membrane progression, restriction of eye movements, diplopia, focal retinal pigment epithelium atrophy due to circulatory disturbances.[24]

Conclusion

Macular buckle can be a good option for myopic posterior staphyloma-related macular conditions such as progressive macular schisis, macular hole and posterior pole RD. The technique requires appropriate case selection and has a good anatomical and functional success as reported in many of the studies. Detection and correction of the retinoscleral mismatch would help improve functional outcomes in these eyes with high myopia-related maculopathy.

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Ophthalmic research

Pros and Cons of Collaborative research

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The contribution of India toward research globally is quite influential and hence has achieved the 6th rank for publication of research papers. This is growing at an annual rate of 14% and at the global level at an average of 4%. Collaborative research is a partnership between two or more parties who work together to achieve common goals. In the context of research, it is a way for researchers from different backgrounds to bridge the gap between the theoretical and the practical. Homogeneous collaboration involves researchers from a single discipline working together, whereas heterogeneous collaboration involves researchers from multiple disciplines working together.

When done correctly, collaborative research can lead to ground-breaking discoveries and innovations that benefit everyone involved. It refers to subjects in which several entities -generally of a different nature- share an interest in the execution of a project, the effort to develop it, the risks, and ownership of the results according to their diverse contribution to obtaining them.

Collaboration can be classified as voluntary, consortia, federation, affiliation, and merger and can occur at five different levels: *within disciplinary, interdisciplinary, multi-disciplinary, trans-disciplinary or national vs international*. Collaborative research has the capabilities for exchanging ideas across disciplines, learning new skills, access to funding, higher quality of results and radical benefits. Collaboration encourages the establishment of effective communication and partnerships and also offers equal opportunities among the team members. It honors and respects each member's individual and organizational style. Collaboration also increases ethical conduct maintaining honesty, integrity, justice, transparency, and confidentiality.

Advantages-Increased collaborations can save considerable time and money, and most often, breakthrough research comes through collaborative research rather than by adhering to tried and true methods. Further legislation, industry, and academia encouraged the collaboration between the private sector and academia

Various forms of collaborative research

Mentor–mentee-A mentor–mentee relationship is very crucial as the challenges experienced by the mentor will be faced by the mentees and it will be the duty of the current scientists to mentor the next generation of scientists. The mentor is responsible for holding regular meetings with mentees and making sure that they are familiar with academic and non-academic policies.

Collaborative research within disciplinary, interdisciplinary, multidisciplinary, and transdisciplinary- There are different kinds of collaboration such as interdisciplinary (team of researchers within the same department), interdisciplinary (team of researchers of different departments but different backgrounds), multidisciplinary (team of researchers of different backgrounds), or transdisciplinary (involvement of people from outside academia into the research process) and everyone aspire for common demands such as making of operational plans, communication between different research groups, sharing of credit, holding frequent meetings, and encouraging open communications. Miscommunications can also be caused by working among different research disciplines and can be due to different understandings of science, vocabulary, or methods. Each and every working researcher has their own perspective of working, for example, some prefer verbal agreements and some consider written contracts. On the other hand, few are in favour of publishing every new finding and others prefer a single large publication after the compilation of whole data.[1]

Challenges of Collaboration-Collaboration can be a frequent source of problems. This can be due to many reasons such as sharing of credit and responsibility after joining more than two people for a common

purpose. Sometimes, collaborations do not get initiated due to unwillingness of sharing or working together. Sometimes, collaborations are often spoiled because of misunderstandings among the participants due to disagreement about what and when to publish and also due to discontent with a slow collaborator.

Individual challenges-There is a scarcity of competent researchers in India. Most of the research going on in our country is not methodologically sound. As far as scholarship is considered, it is an individualized endeavour, and academic frameworks for recognition, rewards, and promotions are supposed at the individual level. For the promotion and tenure process, single-authored publications are given more credit as compared to collaborative work. Intellectual property rights are the central issue and occur in various categories of members in collaborative research.

Institutional challenges-This is because of differences in different approaches among the collaborating partners. For example, if collaboration occurs between industry and institutional level, discrepancies do occur between objectives, different hypothesis, cultural differences, and issues with technology.

Challenges regarding funds-The most important challenge is less funds granted for research to universities as compared to small elite research institutions. This leads to less focus on research and more on teaching by the universities resulting in the separation of education and research. Due to funding restrictions, most of the significant work of Indian research is in the theoretical domain.

Systematic challenges- In India, the success of the scientists is prioritized by becoming an administrative head in research institutions rather than advancing research. Furthermore, the prevalence of ineptitude among the spectrum has made incompetent scientists to strengthen their weaknesses. There is a culture of elitism in our Indian laboratories, where the manual work is done by laboratory assistants and scientists mostly just command orders.[2]

Pros	Cons
• Collaborations promote shared scientific credits. • Collaborations may lead to publication in high-profile research journals. • Collaboration can reduce the time needed to conduct experiments quickly (through sharing of resources). • There is an enhanced ability to share and exchange resources. Thus, collaboration is a mutually beneficial arrangement. • Collaboration provides the opportunity to learn about other disciplines, which leads to the development of innovative solutions because discussion can stimulate new ideas. • The collaboration uses the division of labor to complete tasks in a timely fashion by dividing the workload according to collaborator skills. As a result, work becomes more manageable. Each assigned activity targets members with the appropriate experience or expertise. • Collaboration provides the opportunity to lend credibility and validity to the project. Collaboration with many experienced researchers facilitates ongoing research efforts as well as future collaboration.	• There can be disagreements between researchers on what experiments to perform or how to analyze the results obtained. • Authorship is hard to define in collaborations. Researchers do not want to give up scientific credit because credit is integral to their scientific career and their research funding. • Graduate students who are the first author on a project can be confused by ideas from collaborators and spend time on projects that may not help the primary project. This can delay the research progress. Thus, it is important for senior authors to provide intellectual expertise.

Top 12 Barriers to Effective Research Collaboration
1. Lack of funding opportunities (42%)
2. Requires more time to conduct (41%)
3. Challenges of communicating with different audiences (38%)
4. Different assumptions about what constitutes adequate rigor (36%)
5. Travel required (35%)
6. Goals of academic research are not compatible with goals of practitioners (34%)
7. Scholarly research relevant to policy, education, or industry valued less (33%)
8. Lack of common terminology or language (33%)
9. Difficulties clarifying research problem and integrating objectives (31%)
10. Project organization or management structure inadequate (29%)
11. Issues of budget control or distribution (27%)
12. Lack of understanding of disciplinary differences (26%)

Conclusion

After a thorough understanding of collaboration, it can be assumed that language, financial commitment, inadequate regulatory frameworks, and diverse interests are among the potential challenges in collaborative research. This can be successful if the collaborators respect each other and without involving their ego and are also willing to give and take constructive criticism without being defensive. To conclude, the results of these collaborations will not only be seen in specific work done at the time of collaboration but also during the professional lifetimes of scholarship and publication.

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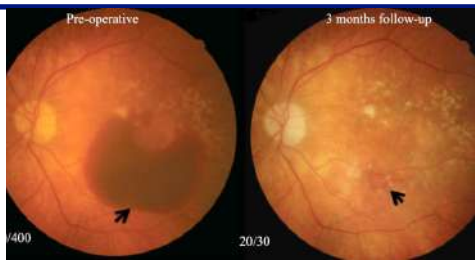
Original article

Fluorescein-Assisted Subretinal tPA delivery for Submacular Hemorrhage



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Abstract

Purpose- To assess the efficacy of fluorescein-assisted subretinal tPA delivery during Parsplana vitrectomy for submacular hemorrhage **Methods**- Prospective study of 18 eyes of 18 patients undergoing PPV with fluorescein-assisted subretinal delivery of tPA for submacular hemorrhage. Out of 18 patients, 10 had wet AMD and 8 had PCV. All patients underwent standrard 23 guage vitrectomy. 2 mL tPA (concentration:25 µg/0.1 mL) poured into a standard silicone oil syringe with attached 41-gauge cannula. A sterile fluorescein sodium strip was placed into the tPA creating an orange solution. Silicone oil syringe with 41-gauge cannula was then connected to the vitrectomy system and injection titrated to allow a slow trickle of tPA into subretinal space. tPA was delivered into the subretinal space until an adequate bleb formed. SF6 gas in 16 eyes and air in 2 eyes was used as tamponade. All patients post operatively assessed for successful postoperative displacement of submacular hemorrhage and change in visual acuity from baseline.**Results**- Mean age was 72 ± 9 years (range 51–79 years). At mean follow-up of 463 ± 262 days, mean Snellen visual acuity improved from 20/690 preoperatively to 20/234 postoperatively (P = 0.14). Overall, 9/18 eyes gained visual acuity, 8/18 eyes remained stable, and 1/18 eyes lost visual acuity. There were no intraoperative or postoperative complications.**Conclusion-** Fluorescein-assisted delivery of subretinal tPA during PPV for submacular hemorrhage allowed improved visualization of subretinal tPA and was not associated with a unique toxicity concern or intraoperative complication.

Keywords- Subretinal hemorrhage, Flourescein, Sub retinal tPA

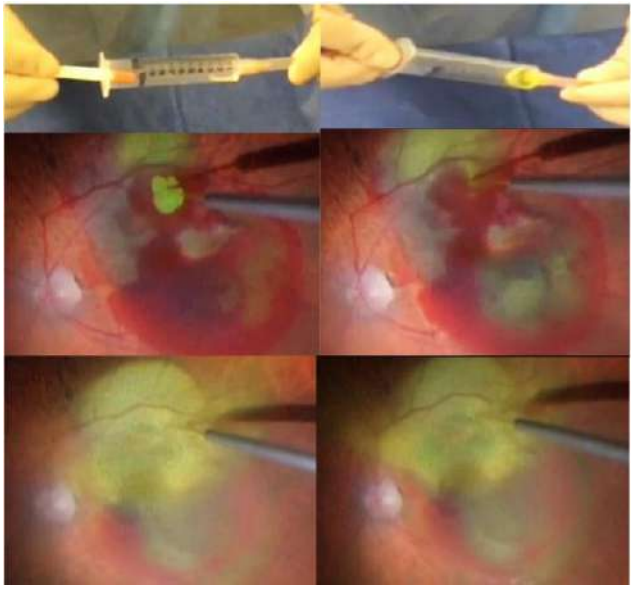
Introduction

Subretinal macular hemorrhage (SRMH) is an important cause of irreversible visual loss because it causes permanent functional and anatomical damage to photoreceptors, mainly as a result of 1) barrier effect (separation of photoreceptors from the retinal pigmented epithelium by the blood), 2) tractional changes (clot contraction causing sharing of the photoreceptors) and 3) toxic damage (hemosiderin from hemoglobin is toxic to the photoreceptors). In fact, Litts et al demonstrated histologically that cones overlying an SRMH become degenerated, with translocated mitochondria. Recent and small SRMH may be treated with intravitreal injections of perfluoropropane (C3F8) associated with or without tissue plasminogen activator (tPA) followed by patient positioning in an attempt to move the blood away from the fovea, to avoid the loss of central visual acuity. However, if the SRMH is massive, thick, subfoveal, and predominantly inferior, it should be displaced from the macular area using a more direct and invasive procedure. After pars plana vitrectomy (PPV), the most frequently used technique in such cases is subretinal injections of tPA, followed by fluid–air exchange and intravitreal injection of nonexpansible gas. The technique of choice for subretinal tPA or air injection for treating SRMH usually requires an assistant physician to push the insulin syringe plunger while the surgeon holds the syringe body caring for the cannula to be steady at the subretinal space. However, significant shaking both by the surgeon and the assistant may occur during the procedure, possibly leading to complications, such as hemorrhage, and if the plunger is pushed too fast, macular hole can develop. To reduce the risk of such complications the surgeon can connect the subretinal cannula to a specific flexible tubing; nevertheless, it continues to be assistant dependent and associated with an uncontrolled infusion pressure. To overcome some of these complications we describe a surgical technique for fluorescein-assisted subretinal tPA delivery during PPV for submacular hemorrhage. Use of fluorescein allows for improved visualization of subretinal tPA delivery and resulting subretinal bleb formation during PPV.

Methods

Patients with overt massive foveal SRMH and symptoms of central scotoma for up to 10 days were eligible. Patients with blood dyscrasia, anticoagulant drug therapy, and AMD with a history of poor visual acuity associated with macular scar or atrophy on complementary tests were excluded. All study participants gave their informed written consent. The following data were collected: age, gender, preoperative and postoperative Snellen visual acuity (VA), preoperative and postoperative intraocular pressure (IOP), past ocular history, medical history, medication use, and lens status. All cases were performed with peribulbar anesthesia with conscious sedation. Surgical eyes were prepped using 5% povidone-iodone (Betadine; Purdue Fredrick Co, Norwalk, CT). Standard, 3-port PPV was performed in all eyes using the Alcon Constellation 23-gauge Vision System (Alcon Laboratories, Fort Worth, TX). In each case, a core vitrectomy with elevation of the hyaloid face was followed by removal of peripheral cortical gel. A total of 2 mL tPA (25 µg/0.1 mL) was then prepared off the surgical field. The tPA was poured into a standard silicone oil syringe with attached 41-gauge cannula. A sterile fluorescein sodium ophthalmic strip was then transiently placed into the tPA creating an orange hued solution. The silicone oil syringe and tubing was then connected to the Constellation system with the viscous fluid injection pressure set to 12 pounds per square inch (psi). Outside the eye, viscous fluid injection pressure is titrated to allow a slow trickle of tPA out of the 41-gauge cannula (typically between 12 and 16 psi). The 41-gauge cannula then enters the subretinal space overlying the submacular hemorrhage. Using surgeon actuated foot pedal control, tPA is delivered into the

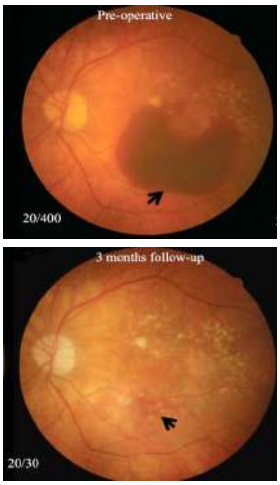
subretinal space until an adequate bleb is formed. A subtotal air–fluid exchange (approximately 75%) with non expansile gas concentrations or air follows. All sclerotomy sites were inspected and, if required, sutured. Patients were instructed to maintain upright positioning for 3 days post surgery.



The primary outcome measure was successful subretinal delivery of tPA. Secondary outcomes were successful postoperative displacement of submacular hemorrhage and change in visual acuity from baseline. Functional assessment is done with microperimetry and multifocal ERG in selected cases. We defined improvement of visual acuity equivalent to two or more lines on the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared with preoperative visual acuity as improved, a decrease of visual acuity equivalent to two or more lines as deteriorated, and the others as stable. The retinal sensitivity values are presented as the mean ± SD (db), evaluated on a 33-point scale using microperimetry. Best available Snellen visual acuities (present correction with pinhole) were converted to logarithm of the minimum angle of resolution (logMAR) equivalents for statistical analyses, with counting fingers (CF) and hand motions (HM) vision corresponding to 1.98 and 2.28, respectively. Statistical analysis of primary outcomes was performed using a Student's t-test. A p-value <0.05 was considered statistically significant.

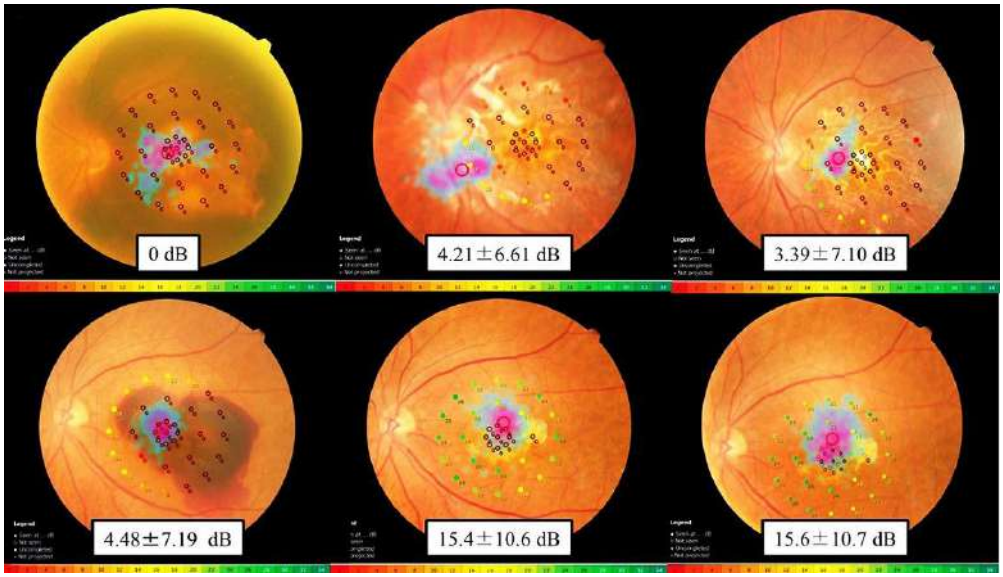
Results

Eighteen eyes (8 right eyes, 10 left eyes) of 18 patients (9 female, 9 male) were included. Mean age was 72 ± 9 years (range 51–79 years). In 10 patients, SRMH was caused by CNV-AMD and polypoidal choroidal vasculopathy in 8. None of the patients had baseline vision better than 20/200. Best-corrected visual acuity (BCVA) was hand motion in 40%, counting fingers in 40%, and 20/400 in 20%. The average duration of SRMH was 4.9 days (range, 2–10 days). Past medical history was notable for systemic hypertension in 9 patients. Preoperatively, two patients were on anticoagulant therapy with daily aspirin (325 mg). Ten of 18 eyes were previously treated with anti-vascular endothelial growth factor therapy, 4/18 eyes had prior history of focal laser and anti-vascular endothelial growth factor therapy, and 4/18 eyes were treatment naïve at the time of submacular hemorrhage diagnosis. Intraoperatively, all eyes had successful subretinal



delivery of fluorescein-stained tPA. Sulfur hexafluoride (SF6) gas tamponade was used in 16 eyes and air tamponade in 2 eyes at the conclusion of surgery. Postoperatively, displacement of the submacular hemorrhage was achieved in all eyes. At mean follow-up of 463 ± 262 days, mean Snellen visual acuity improved from 20/690(1.53 log MAR) preoperatively to 20/234(1.068log MAR) postoperatively (P = 0.14). Overall, 9/18 eyes gained visual acuity, 8/18 eyes remained stable, and 1/18 eyes lost visual acuity. There was significant improvement in retinal sensitivity post operatively. There were no intraoperative or postoperative complications.

Preoperative and postoperative retinal sensitivity



Discussion

Surgical management with PPV, subretinal injection of tPA, and intraocular gas tamponade is an effective treatment option for submacular hemorrhage. Fassbender et al compared outcomes in eyes treated with PPV and subretinal tPA with eyes treated with intraocular gas (pneumatic displacement) with or without intravitreal tPA. The authors noted that although both subretinal and intravitreal tPA improved visual outcomes compared with pneumatic displacement alone, eyes treated with PPV and subretinal tPA had smaller final scar area compared with those treated with intravitreal tPA. Fluorescein sodium has been used for the characterization and detection of retinal disease for over 50 years in the form of fluorescein angiography testing. Fluorescein sodium is eliminated from the circulation typically within 24 hours, and retinal toxicity has not been reported with intraretinal or subretinal fluorescein to date. In this study, subretinal instillation of fluorescein-stained tPA and subsequent hemorrhage displacement was successfully achieved in all eyes. Mean visual acuity improved from 20/693 preoperatively to 20/224 postoperatively at mean follow-up of 560 days. No intraoperative or postoperative complications were encountered, and no novel or unique toxicity with use of fluorescein-stained tPA was observed. Previously, authors have noted the importance of adequate subretinal tPA bleb formation for successful hemorrhage displacement. Bleb formation allows space for tPA enzymatic activity, reduces friction amongst red blood cells after clot dissolution, and provides a potential space for hemorrhage displacement. We believe that the described surgical technique with fluorescein-assisted tPA delivery will help in this aim with the following *advantages*:

1. Improved visualization of bleb formation
2. Full viewing of tPA distribution in the subretinal space
3. Fluorescein staining of 41 gauge puncture site edges allows reentry into initial puncture site
4. Ability to view reflux of tPA into vitreous cavity, allowing quick identification of unfavorable injection sites
5. With use of viscous fluid tubing and foot pedal, the surgeon can perform controlled subretinal instillation of tPA without need of a skilled assistant.

Notably, reflux of fluorescein-stained tPA was directly observed in 3 eyes in and allowed for quick cessation of subretinal injection and selection of secondary injection sites. Together with prior described techniques, including instillation of subretinal air, fluorescein-stained tPA may allow for improved surgical performance during PPV for submacular hemorrhage without additional surgical maneuvering or concern for added toxicity. This study has numerous limitations, including small sample size and lack of a direct control group. In summary, we describe a technique for fluorescein-assisted delivery of subretinal tPA during PPV surgery for submacular hemorrhage. Use of subretinal tPA allowed for improved visualization of subretinal tPA delivery and was not associated with a unique toxicity concern or intraoperative complication.

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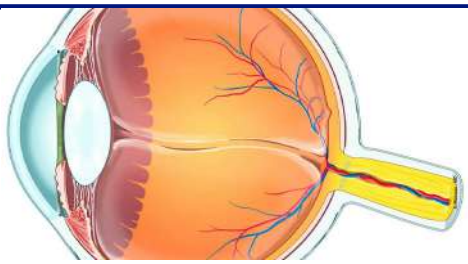

Thicknesses of sclera and lamina cribrosa in central retinal vein occlusion

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Abstract

Purpose: To evaluate thicknesses of sclera and lamina cribrosa (LC) in central retinal vein occlusion (CRVO). **Method**: Thirty-two patients with CRVO (mean age 62.2 ± 11.6 years, women/men 18/ 14) and 35 age- and sex-matched healthy volunteers were included into the study. Scleral thickness was measured at scleral spur and at 1 to 3 mm from scleral spur in four quadrants (temporal, nasal, super, and inferior) using anterior segment optical coherence tomography. Lamina cribrosa was measured using optic disk enhanced depth imaging optical coherence tomography. **Results**: The sclera was thicker in affected eyes of the CRVO group than healthy subjects at scleral spur in four quadrants (738.7 ± 30.9 mm vs. 702 ± 30.8 mm in temporal, 700.4 ± 19.7 mm vs. 673 ± 13.7 mm in superior, 693 ± 19.3 mm vs. 665.3 ± 24.2 mm in nasal, 810.7 ± 28.9 mm vs. 784.5 ± 23.7 mm in inferior quadrants, respectively; $P < 0.05$ for all). Lamina cribrosa thickness in affected eyes of the CRVO group was significantly higher than that of healthy subjects (285.2 ± 12.7 mm vs. 266.4 ± 10.7 mm, respectively; $P < 0.01$). The correlation between scleral thickness and LC thickness was moderate at scleral spur of temporal and superior quadrants of affected eyes ($r = 0.510$ and $r = 0.420$, respectively). **Conclusion**: Thicknesses of sclera and LC are increased in the CRVO, which may play a role in the pathogenesis of the disease

Key words: lamina cribrosa, sclera, central retinal vein occlusion.

Central retinal vein occlusion (CRVO) is a retinal vascular disease usually caused by diabetic retinopathy, and it can lead to the permanent loss of vision if not treated.[1–3] Multiple factors play a role in the progression of CRVO including diabetes, hypertension, hyperviscosity, lipidemia, shorter axial length, and primary open-angle glaucoma.[4] An intraluminal thrombus located in the lamina cribrosa (LC) has been implicated in the physiopathology of CRVO.[5,6] The LC is part of the corneoscleral shell, and its rigidity has a critical role in the biomechanical properties of the sclera. The rigidity and thickness of the sclera and LC provide biomechanical stability to the optic nerve head (ONH).[7] Abnmalities in the sclera and LC have been suggested to be responsible for the pathogenesis of CRVO. In color Doppler imaging, a uniform constriction of the bottle neck of retinal vein in the LC region was reported, and endothelial damage and thrombus formation were found as a result of increased shear stress.[8] Increased thicknesses of LC and sclera may cause more retinal vein constriction and may result in predisposition to CRVO development, which needs to be evaluated. The thickness and structure of the sclera can be assessed using magnetic resonance imaging and ultrasonic biomicroscopy. However, the tissues can also be noninvasively evaluated at high resolution using optical coherence tomography (OCT). Human and animal studies have shown a strong correlation between histological and OCT sections.[9,10] Increased LC and scleral thicknesses may cause more retinal vein constriction, which may predispose to CRVO development.

In the present study, we aimed to evaluate the scleral thickness and lamina LC thickness of patients diagnosed with CRVO.

Methods

Study Design and Population Thirty-two patients diagnosed with CRVO (Group 1; mean age 62.2 ± 11.6 years, age range 42–76 years, women/men 18/14) and 35 age- and sex-matched healthy volunteers (Group 2; mean age 57.9 ± 13.8 years, age range 45–78 years, women/men 17/18) were included into this case–control study. Patients with uncontrolled systemic disease, collagen tissue disease, refractive error greater than 5.0 diopters (D) of spherical equivalent or 3.0 D of astigmatism, previous surgery for ocular pathology, use of contact lenses, thyroid disorders, glaucoma, or systemic inflammation disease were excluded from the study. All study patients received intravitreal dexamethasone

implant injections for the treatment of macular edema. Medical history, demographics, smoking status, and systemic and/or topical drug use of participants were recorded. All subjects underwent a standard ocular examination, bilateral anterior segment OCT, and bilateral optic disk enhanced depth imaging OCT (EDI-OCT) in two groups. All examinations were performed between 9:00 and 11:00 AM Scleral and LC thicknesses were measured by an investigator blinded to the study groups. Right eyes of Group 2 were evaluated in statistical analysis. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All participants signed the informed consent form before the study.

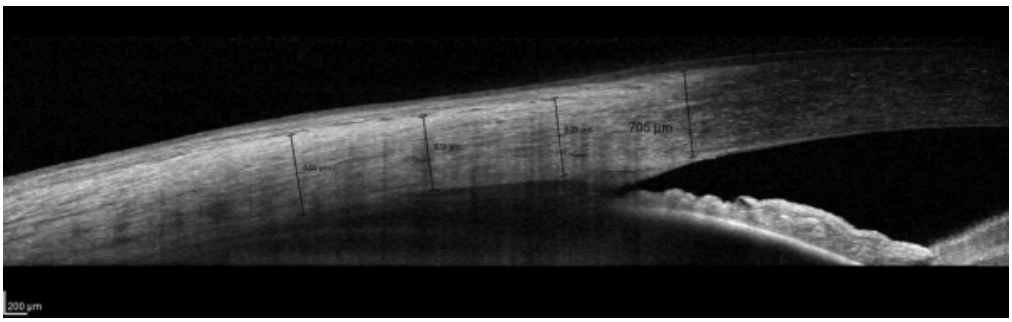

Fig. 1. Optical coherence tomography image of the temporal sclera. Calipers (in black) shown for scleral thickness measurements at scleral spur (SS) and 3 mm from the SS at 1-mm intervals.

Scleral Thickness Measurements

The scleral thickness of each patient was measured on his/her first visit in the acute phase, and spectral domain OCT (SD-OCT) with an anterior segment module was obtained in scleral mode EDI-OCT. We recorded a volume that consisted of 21 scans. These scans comprised the limbus with the orientation perpendicular to the limbus. The apex scleral spur (SS) location was determined as previously described.[11] The scleral thickness was measured manually in the SS and at distances of 1, 2, and 3 mm from the SS in the 4 quadrants (temporal, nasal, super, and inferior) in both the affected and fellow eyes of the participants in Group 1 and Group 2 (Figure 1). The episclera or the conjunctiva was not included in the measurements; the external limit of the sclera was determined by means of the episcleral vascular plexus.

Lamina Cribrosa Thickness Measurements

Lamina cribrosa thickness was evaluated after regression of optic disk edema, because contour delineation of the anterior and posterior borders of the LC was generally less definite in the presence of optic disk edema in the acute period of the disease. We evaluated only the highest quality images and the most centered vertical scans with clearly visible borders. Heidelberg Spectralis EDI-OCT mode was used in all images as described in a previous study.[12] We obtained an average of 45 images for each section, and measured the thickness manually from the vertical center of the ONH in these images. The center of the ONH was determined as the point where the retinal vessels originated from the ONH. Lamina cribrosa thickness was defined as the distance between the anterior and posterior margins of the LC, which were determined as a highly reflective structure below the optic cup (Figure 2).

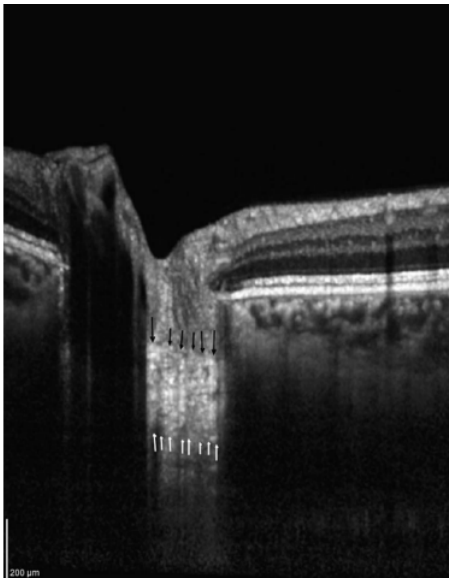

Fig. 2. The measurement of the LC thickness. The borders of the LC were considered to be where the hyperreflective region started and ended. White arrows indicate the posterior borders of LC. Black arrows show the anterior borders of the LC. Lamina cribrosa thickness was defined as the distance between the anterior and posterior borders of LC.

Statistical Analysis

The Statistical Package for the Social Sciences (SSPS, version 17.0, Chicago, IL) was used for the statistical analyses. The study data were summarized using descriptive statistics such as mean and SD, range, frequency, and percentage. The normality of distribution of data was tested with the Kolmogorov– Smirnov and the Shapiro–Wilk tests. The independent samples t-test and Mann–Whitney test were used to compare the groups for normally and not normally distributed variables, respectively. We evaluated the intraobserver repeatability using two OCT images obtained by the same operator; interobserver reproducibility was evaluated using two OCT images obtained from two different operators. Mean thickness and intraclass correlation coefficients were calculated to evaluate the repeatability and reproducibility

of the thickness. Intraclass correlation coefficient was determined on the basis of a mean rating (k = 2), absolute agreement, two-way random-effects model. Intraclass correlation coefficient values that were greater than 0.90 were accepted as excellent reliability. The level of statistical significance was defined as P < 0.05.

Results

In Group 1, the mean LC thickness was 285.2 ± 12.7 mm (range 263–308 mm) in the affected eye and 283.5 ± 12.6 mm (range 249–289 mm) in the fellow eye (P = 0.941). In Group 2, the mean LC thickness was 266.4 ± 10.7 mm (range 259–306 mm) in right eye (Table 1). The mean LC thickness in the affected and fellow eyes of Group 1 was significantly higher than that of the control group (P , 0.01 and P , 0.01, respectively). The scleral thicknesses of study groups on all quadrants were summarized in Table 1. Comparison of the affected and fellow eyes of Group 1 with the control eyes showed that the scleral thickness values of Group 1 were statistically significantly higher than those of the control eyes in all quadrants, with the exception of a 2-mm distance from the SS in the inferior quadrant (Table 1). In the temporal quadrant of the affected eyes, there was a moderate correlation between scleral thickness and LC thickness in the SS and at a 2-mm distance from the SS (r = 0.510 and r = 0.540, respectively). In the superior quadrants of the affected eyes, there was a weak correlation between scleral thickness and LC thickness in the SS and at a 2-mm distance from the SS (r = 0.420 and r = 0.450, respectively). In the inferior quadrant, a moderate correlation between scleral thickness and LC thickness was evident only at a 2-mm distance from the SS (r = 0.562). In Group 1, the mean intraocular pressure was 15.38 ± 3.51 mmHg (range 11–20 mmHg) in the affected eye and 15.36 ± 3.53 mmHg (range 12–20 mmHg) in the fellow eye (P = 0.8). In Group 2, the mean intraocular pressure was 13.12 ± 3.25 mmHg (range 9–20 mmHg). Comparison of the affected and fellow eyes of Group 1 with the Group 2 showed no statistically significant differences (P = 0.08 and P = 0.99, respectively).

Table 1. Lamina Cribrosa Thickness of Affected and Fellow Eyes of Patients in Group 1 and Healthy Volunteers in Group 2; and the Scleral Thickness Along 3 mm From SS at 1-mm Intervals in all Quadrants of Eyes

	Group 1			*P*	
	Affected Eye	Fellow Eye	Group 2, Right Eye	Affected Eye vs. Fellow Eye of Group 1	Affected Eye of Group 1 vs. Group 2
Lamina cribrosa thickness (μm)	285.2 ± 12.7	283.5 ± 12.6	266.4 ± 10.7	0.94	<0.01
Scleral thickness (μm)					
Temporal					
SS	738.7 ± 30.9	736.3 ± 31	702 ± 30.8	0.731	0.001
1 mm	689.3 ± 26.9	691.9 ± 22.5	659 ± 28.4	0.675	0.001
2 mm	678 ± 22.3	677.2 ± 23	649 ± 22.2	0.873	0.003
3 mm	696 ± 30.1	695.9 ± 31	655 ± 24.9	0.872	0.001
Superior					
SS	700.4 ± 19.7	698.81 ± 18.9	673 ± 13.7	0.933	0.002
1 mm	624.2 ± 29.1	622 ± 24.5	576 ± 24.5	0.465	0.001
2 mm	614.2 ± 28.91	615.6 ± 26.5	588 ± 26.8	0.772	0.005
3 mm	630.1 ± 17.7	628.5 ± 17.6	585 ± 16.9	0.714	0.001
Nasal					
SS	693 ± 19.3	690.5 ± 19.4	665.3 ± 24.2	0.998	0.002
1 mm	672.5 ± 21.8	670.1 ± 21.7	651.9 ± 21.7	0.793	0.001
2 mm	686.5 ± 28.3	684.2 ± 27.8	655.9 ± 26.7	0.971	0.002
3 mm	705.9 ± 22.3	699.1 ± 21.1	682.8 ± 21.9	0.493	0.005
Inferior					
SS	810.7 ± 28.9	803.9 ± 28.7	784.5 ± 23.7	0.897	0.005
1 mm	753.1 ± 32.2	750.7 ± 31.6	738.4 ± 32.5	0.812	0.002
2 mm	749.4 ± 18.6	747.2 ± 19.1	744.4 ± 15.6	0.783	0.145
3 mm	773.5 ± 17.1	774.3 ± 16.8	743.4 ± 20.8	0.80	0.016

Discussion

The sclera is the main supporting tissue of the eye sphere. It has critical importance for the integrity of the eye and in the response to external factors. The LC is a part of the scleral shield. The structure of the LC and the sclera are influential on the ONH biomechanics.[13] In this study, we analyzed LC thickness and scleral thickness in patients diagnosed with CRVO. We observed a significant thickening of LC thickness and scleral thickness in the study group compared to the control group. In addition, we found a correlation between LC thickness and scleral thickness. Several studies have defined corneal thickness as an indicator of LC rigidity, a significant marker of CRVO.[12,13] However, to the best of our knowledge, LC thickness and scleral thickness have not previously been studied in patients with CRVO An anatomical study described the narrowing of the retinal vein as it passes through the LC in six postmortem eyes. In this study, Opremcak et al[14] reported that CRVO is a compartment-like syndrome because of the anatomic "bottleneck-like" configuration of the LC. The luminal caliper of the CRV was slender at the LC plane, and the LC consists of denser connective tissue that circumscribes the retinal vessels. It was also defined

that retinal vein circulation is prone to occlusion.[15] Most CRVO cases occurred as a result of thrombus formation in the CRV adjacent to the LC. Williamson et al showed an increased blood velocity because of a reduction in the caliber of the retinal vein at the lamina cribrosa by color Doppler imaging.[8] Increased blood velocity causes increased shear stress and collapse of the vein. As a result, endothelial damage, endothelial proliferation, and thrombus formation develop at the LC region. For these reasons, we evaluated the LC thickness and scleral thickness in patients diagnosed with CRVO and compared the measurements with those of a healthy control group. In our study, the LC thickness in the affected and fellow eyes of the participants diagnosed with CRVO was greater than that in the control group. We suggest that increased LC thickness may contribute to narrowing of the retinal vein and compartment-like syndrome. Increased thickness of the LC may thus play a role in etiopathogenesis by exacerbation of existing endothelial injury. Previous studies have shown that glaucoma and ocular hypertension are risk factors of CRVO.[16–18] The relationship between glaucoma and retinal vein occlusion has been believed to result from LC compression. In previous studies, the researchers showed that the LC thickness in eyes with branch retinal vein occlusion and glaucoma was thinner than the LC thickness of control eyes, and there was no statistically significant difference between fellow and affected eyes.[17,18] These studies suggested that glaucoma and branch retinal vein occlusion have similar structural abnormalities in the LC. The cases with branch retinal vein occlusion were not included in the present study because of differences in the etiopathogenesis of CRVO and branch retinal vein occlusion. We found no statistically significant differences in LC thickness and scleral thickness between the affected and fellow eyes of the CRVO-diagnosed participants. For this reason, increased LC thickness and scleral thickness play important roles in promoting preventive measures for the fellow eye and in raising the awareness of the patient.

Sigal et al found that the most important factor affecting ONH biomechanics is scleral rigidity.[11] Scleral deformities have also been found to affect blood flow.[19–22] Imaging of LC is difficult in acute phase because of optic disk edema. In our study, we found a correlation between LC thickness and scleral thickness, especially in the temporal and superior quadrants. Increased scleral thickness in anterior segment OCT may be helpful in determining the role of LC thickness in the etiopathogenesis of disease, particularly if LC borders are not clearly visualized during the acute phase. The present study had a number of limitations. The first limitation was the small sample size. The second was that because of the difficulty of measurement of LC thickness in acute phase, LC thickness could be measured after regression of the optic disk edema, which makes it difficult to visualize the posterior of the LC. In addition, although EDI mode provides high image quality, and LC imaging is difficult in the acute period of disease. The border between LC anterior and posterior demarcation has been generally less definite in the presence of optic disk edema in the acute period. Further studies are needed to define this border with greater certainty using improved OCT modules in patients with optic disk edema. In conclusion, increased thicknesses of both LC and sclera may create a risk for the development of CRVO. Evaluation of LC thickness and scleral thickness in CRVO-diagnosed patients may be important for the detection of etiopathology of the disease.

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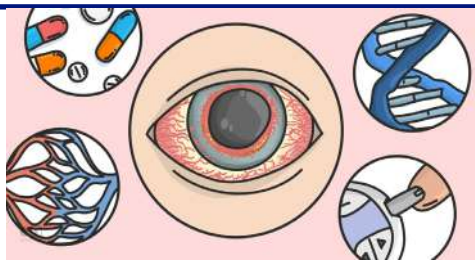

Effect of topical calcium channel blockers on intraocular pressure in steroid induced glaucoma

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Abstract

Purpose- To evaluate the effect of 0.125% verapamil and 0.5% diltiazem eye drops on intraocular pressure in steroid-induced glaucoma in rabbit eyes. **Methods:** A total of 18 rabbits with steroid-induced glaucoma were divided into three groups (A, B, and C; n=6 each). Right eyes in groups A,B and C received 0.5% diltiazem, 0.125% verapamil, and 0.5% timolol eye drops twice daily for 12 days respectively, whereas left eyes received distilled water. IOP was measured with Tonopen-XL at baseline, day 4, day 8 and day 12 of treatment.**Results:** Both 0.5% diltiazem and 0.125% verapamil eye drops significantly reduced IOP compared to control eyes ($p<0.05$). Reduction of IOP by 0.5% diltiazem, 0.125% verapamil eye drops were comparable to 0.5% timolol. No surface toxicity or systemic side effects were noted during the study period.**Conclusions:** Calcium channel blockers, verapamil and diltiazem significantly reduced intraocular pressure in rabbit eyes. This group of drugs may have a potential role in treatment of glaucoma

Key words: Calcium channel blockers, Intraocular pressure

Introduction

Glaucoma is second leading cause of blindness worldwide.[1]Characterized by progressive degeneration of retinal ganglion cells (RGCs) and optic nerve fibers, leading to gradual deterioration of visual field. If untreated, it can lead to irreversible blindness.[2] In most of the cases, glaucoma is associated with high intraocular pressure (IOP). Prophylactic medical reduction of IOP reduces the risk of progression to glaucoma from ~10 to 5 %.[3] There is a constant search for newer drugs that can lower the IOP and therefore possibly retard the progression of glaucomatous optic nerve damage.

Calcium is an important intracellular messenger, and Ca^{2+} influx could have several effects on aqueous humour dynamics including hydrostatic component, ciliary perfusion and osmotic component.[4] Calcium channel blockers (CCBs) which are commonly used for the treatment of hypertension and coronary vascular disease, reduce the tone of blood vessels by inhibiting Ca^{2+} influx, causing vasodilation and increasing regional blood flow in several organs including the optic nerve head. [5-10]

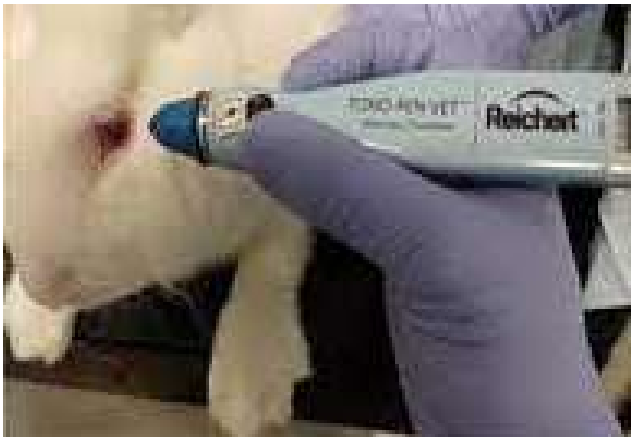
CCBs may also inhibit the synthesis of extracellular matrix collagen protein, suggesting beneficial effect in glaucoma[11] CCBs cause relaxation of trabecular meshwork cells by inhibition of L-type channels which increases outflow facility of aqueous humuor. The perfusion studies in dissected human eyes showed dose related increase in outflow facility after verapamil administration.[11,12]

In the present study we investigated the ocular hypotensive role of CCBs in rabbit eyes.

Methods

The holding and experimental protocols were conducted in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. The study protocol was approved by the institutional ethics committee. Eighteen albino rabbits (aged 3-4 months) of either sex weighing 1.5-2.5 kg were used in this study. The rabbits were inbred in the central animal house under suitable conditions of housing, temperature, ventilation and nutrition. All IOP

measurements were obtained with Tonopen XL (Reichert Technologies) after anesthetizing the rabbits with 5 mg/ml intravenous midazolam given in dose of 0.5-1 mg/kg through marginal ear vein. In addition, topical anesthesia in the form of lignocaine hydrochloride was used before each IOP measurement. An average of three IOP readings was used.



Ocular hypertension was induced by bilateral instillation 1% predisolone acetate eye drops twice a day for a period of 40 days.IOP measurements were obtained before and after treatment with topical corticosteroid eye drops. Subsequently, the rabbits were divided into three groups and all right eyes in each group received twice daily ditiazem 0.5% eye drops (group A; n=6) or verapamil 0.125% eye drops (group B; n=6) or timolol maleate 0.5% eye drops (group C; n=6) twice daily for twelve days. Sterile distilled water was used twice daily in all left eyes. Diltiazem 0.5% eye drops were prepared by diluting injection diltiazem 25 mg/ml with distilled water upto a concentration of 5mg/ml. Verapamil 0.125% eye drops were prepared by diluting injection verapamil 2.5 mg/ml with distilled water to a concentration of 1.25mg/ml.

IOP was measured in both eyes before instilling these drugs and on every 4th day till the end of 12 days of treatment period.

Statistical Analysis

Results were expressed as mean± SD and percentage changes wherever required. Intra-group comparisons were performed using the t-test. One way ANOVA was used for multiple group comparisons followed by post- hoc Tukey's test for group wise comparisons. A 'p' value of 0.05 or less was considered for statistical significance.

Results

Mean basal IOP increased in all three groups after 40 days of twice-daily treatment with 1% prednisolone acetate eye drops (Table 1,2& 3).All groups were comparable in terms of pre- and post-corticosteriod treatment (p>0.05). Group A (diltiazem 0.5%) eyes did not show any statistically significant reduction in the IOP in the left eyes (controls) up to day 12. However, the IOP reduced in the right eyes (treatment) starting from day 4 as shown in figure 1. There was a statistically significant difference in the mean IOP treatment and control eyes in group A (p=0.0153). The control eyes in group B did not show a significant reduction in the IOP over the study period. The treatment eyes showed a significant reduction in the mean IOP level on days 4, 8 and 12 (p=0.0171) (Figure 2). Similar results were obtained in the treatment and control eyes of group C (p=0.0192) (Figure 3).Further, there was no statically significant difference in the IOP lowering effect of all three drugs (post-hoc Tukey's test) (figure 4).During the study period, no ocular surface toxicity or systemic side effects were noted in any of the rabbits.

Table 1: Mean basal, post-topical corticosteroid and post-topical diltiazem treatment intraocular pressure in group A rabbits

	Baseline	*After corticosteroid*	*Day 4*	*Day 8*	*Day 12*
OD diltiazem	16.4 ± 1.4	25.5 ± 1.6	22.9 ± 1.7	17.9 ± 1.3	16.9 ± 1.1
OS control	18.0 ± 2.3	25.9 ± 1.9	25.9 ± 1.9	25.2 ± 1.7	24.8 ± 1.7

Table 2: Mean basal, post-topical corticosteroid and post-topical verapamil treatment intraocular pressure in group B rabbits

	Baseline	*After corticosteroid*	*Day 4*	*Day 8*	*Day 12*
OD verapamil	16.4 ± 1.4	24.5 ± 1.0	22.7 ± 1.3	18.0 ± 2.3	15.5 ± 1.4
OS control	15.5 ± 1.4	25.9 ± 1.9	25.9 ± 1.9	25.5 ± 1.6	25.5 ± 1.6

Table 3: Mean basal, post-topical corticosteroid and post-topical timolol treatment intraocular pressure in group C rabbits

	Baseline	*After corticosteroid*	*Day 4*	*Day 8*	*Day 12*
OD timolol	16.0 ± 1.5	22.4 ± 1.9	22.4 ± 1.9	19.0 ± 1.8	16.4 ± 1.4
OS control	16.4 ± 1.4	26.2 ± 2.1	26.2 ± 2.1	25.5 ± 1.6	25.5 ± 1.6

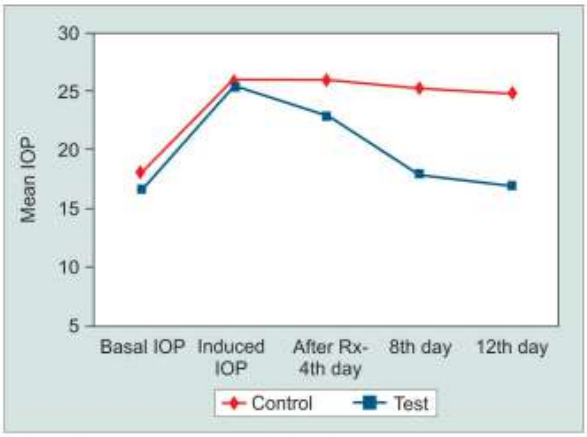


Fig. 1: Intraocular pressure changes in treatment and control eyes during study period in 0.5% diltiazem treated rabbits (group A)

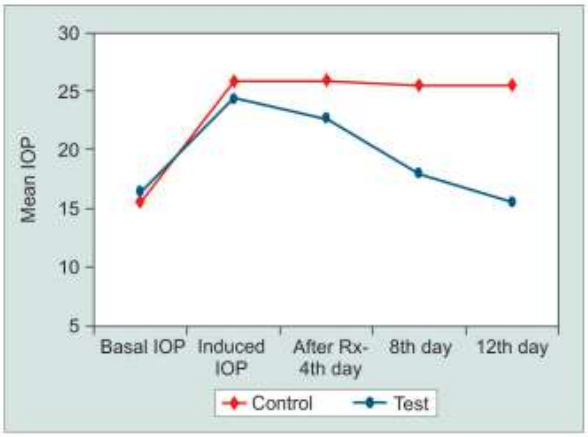


Fig. 2: Intraocular pressure changes in treatment and control eyes during study period in 0.125% verapamil treated rabbits (group B)

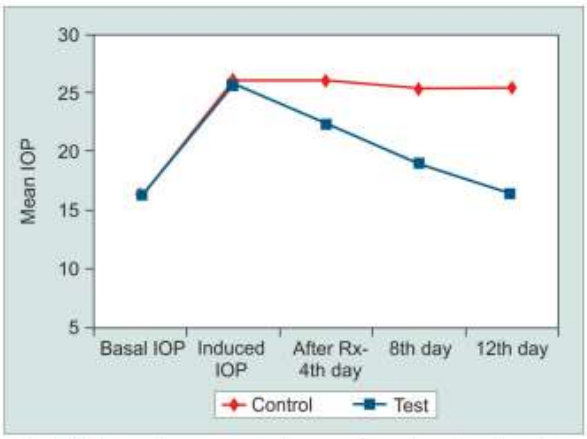


Fig. 3: Intraocular pressure changes in treatment and control eyes during study period in 0.5% timolol treated rabbits

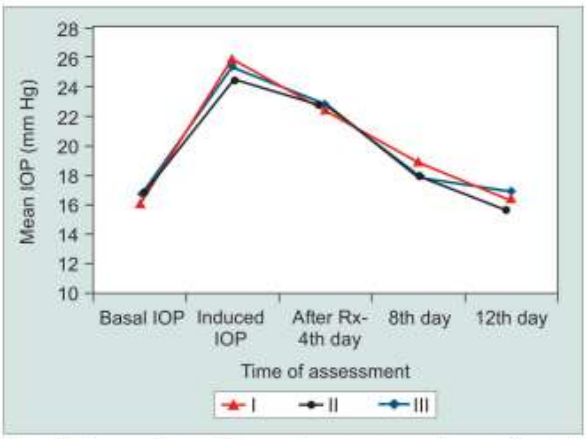


Fig. 4: Comparison of intraocular pressure changes in right (treatment) eyes in I-0.5% diltiazem, II-0.125% verapamil and III-0.5% timolol-treated rabbits during study period

Discussion

Most of the previous studies have employed normal/ low tension glaucoma animal models to demonstrate the effects of topical CCBs on intraocular pressure (IOP). In the present study, we demonstrated a reduction in corticosteroid-induced ocular hypertension with topical calcium channel blocking drugs. The hypotensive effect was comparable to that of topical timolol eye drops.[13]

Calcium channel blockers alter the intracellular calcium concentration by modifying calcium flux across cell membranes and affect various intracellular signaling processes.[14,15] Lipid soluble CCBs act at the central nervous system level whereas water soluble CCBs act mainly on the cornea and optic nerve.[16] It is also known that calcium influx is the terminal step in axonal death in the glutamate pathway. The ability to block calcium influx can therefore produce a neuroprotective benefit. [17] Furthermore, CCBs can improve ocular blood flow through inhibition of endothelin-1. [18-21] Despite this, the effect of calcium channel blockers on IOP remains controversial. [22-27]

Calcium influx could have several effects on aqueous humor dynamics, including a hydrostatic component caused by an effect on arterial blood pressure and ciliary body perfusion, and an osmotic component caused by an effect on the active secretion of sodium, calcium and other ions by ciliary epithelium.[28]Recent reports have addressed the effect of calcium channel blockers on ocular blood flow. Using laser Doppler velocimetry and flowmetry in cats, Harino et al demonstrated increased optic nerve head blood flow following administration of intravenous nicardipine.[29] Netland and associates utilized color Doppler ultrasound analysis and found that topical verapamil may decrease the vascular resistance in ocular blood vesselss.[26]

Favorable effects of calcium channel blockers on visual field defects as well as contrast sensitivity have also been reported.[30-32] Verapamil tends to block both activated and inactivated L-type calcium channels. It has also been shown to improve the blood supply in rabbit eyes with experimental glaucoma acting as vasodilator and improving the outflow facility.[33] Diltiazem, on the other hand, has been shown to produce relaxation of serotonin-induced contraction of bovine ophthalmic artery primarily by inhibiting the Ca^{2+} influx.[34] It was shown to exhibit a long lasting and dose-related effect on intraocular pressure.[35]

CCBs may therefore play a potential role in relaxing the retinal, long posterior ciliary, and ophthalmociliary arteries to improve the ocular circulation in vascular diseases in which considerable vascular tone is present.[36]Santafe et al reported that CCBs decrease aqueous humor secretion in addition to causing a slight but significant reduction in tonographic outflow facility.[35] Also, the outflow of aqueous humour influenced by episcleral venous pressure may be directly affected by calcium inhibition. Verapamil may interfere with gap junctions between nonpigmented and pigmented ciliary epithelial cells altering cellular permeability of the ciliary epithelium and thus inhibiting normal aqueous humour formation.[35, 37]It may also alter the cyclic adenosine monophosphate content in ciliary epithelial cells, thereby affecting IOP through a decrease in aqueous humour formation, or an increase in outflow facility.[38]

Lowering of IOP by verapamil and diltiazem may be due to inhibition of the intracellular uptake of calcium by inactivating the inner phosphorylation dependent calcium gate of the cellular membrane .[10] It is known that trabecular meshwork cells have contractile properties, which may be influenced by Ca2+ influx through voltage dependent L-type Ca2+ channels. These agents cause relaxation of trabecular meshwork cells and increase the outflow facility. The perfusion studies in dissected human eyes showed dose-related increase in outflow facility after verapamil administration.[39]

Calcium-channel blockers cause vasodilatation and reduce vascular resistance, increase the capillary blood speed in the optic nerve head, this make them to be possible drugs useful in the treatment of low-tension glaucoma.[10]The results of our study match the earlier reports that showed that topical application of verapamil and diltiazem effectively lowered IOP in a dose-related fashion.[24,35]

Topical verapamil has also been shown to reduce IOP in humans.[7,26,40] A single topical application of 0.125% verapamil prompted a 3 to 4 mm Hg IOP decrease in 12 ocular hypertensive patients that lasted up to 10 hours [7] whereas a slight reduction (≈1.5 mm Hg) was noted in normal volunteers.[26] After topical application of 0.125% verapamil for 2 weeks, a 7.0 ± 2.9 mm Hg decrease in IOP has been measured in ocular hypertensive subjects.[8]

Our study highlights the potential role of calcium channel blockers in management of corticosteroid-induced glaucoma in rabbit eyes. CCBs were comparable with commonly used beta blocker drug. Nevertheless, further studies are needed to replicate the ocular effects of CCBs in humans and determine their potential clinical use in glaucoma patients.

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SMILE, LASEK and LASEK Combined with CXL for High Myopia

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Abstract

Purpose: To compare the visual and refractive outcomes of small-incision lenticule extraction (SMILE), laser-assisted subepithelial keratomileusis (LASEK), and LASEK combined with corneal collagen cross-linking (LASEK-CXL) surgery for high-degree myopia. **Methods**: Medical records of patients with spherical equivalent (SE) greater than -6.00 diopters (D) treated with SMILE, LASEK, and LASEK-CXL were reviewed. Uncorrected distance visual acuity (UCVA), SE, and corneal haze were followed up in the 3 groups for 6 months. **Results**: The SMILE group included 69 eyes, the LASEK group included 61 eyes, and the LASEK-CXL group included 40 eyes. At 6 months postoperatively, there were no statistically significant differences in UCVA between the SMILE, LASEK, and LASEK-CXL groups (logMAR 0.00 +/- 0.00, 0.01 +/- 0.08, and 0.01 +/- 0.08, respectively, *P* = 0.69). The averages of the absolute value of SE were 0.34 +/- 0.25 D, 0.50 +/- 0.36 D, and 0.42 +/- 0.34 D in the SMILE, LASEK, and LASEK-CXL groups, respectively (*P* = 0.04). The percentages of the patients with a postoperative residual refractive error within +/-0.50 D were 84% in the SMILE group, 65% in the LASEK group, and 76% in the LASEK-CXL group. The percentages of the patients with greater than 20/25 postoperative UCVA were 100%, 91%, and 95%, respectively. SMILE produced no postoperative corneal haze. However, 18% of patients treated with LASEK and 25% of those treated with LASEK-CXL had corneal haze at 6 months postoperatively.

Conclusions: SMILE, LASEK, and LASEK-CXL surgery appear to be safe and effective for high-degree myopic correction. However, the SMILE group had no haze and fewer induction of some higher-order aberrations compared with the LASEK and LASEK-CXL groups.

Key Words: SMILE; high myopia; LASEK; collagen cross-linking

Laser-assisted in situ keratomileusis (LASIK) is the most common refractive surgical procedure.[1,2] It has excellent refractive correction ability and offers predictable and stable refractive results. However, LASIK sometimes causes flap-associated complications and long-term myopic regression, especially in cases of correction of moderate to high myopia when there are concerns about the risk of corneal ectasia.[3-5] As alternative procedures, femtosecond laser small-incision lenticule extraction (SMILE) and laser-assisted subepithelial keratomileusis (LASEK) can be performed, which are flapless and avoid flap-related complications.[6-8] SMILE creates an intrastromal lenticule using a femtosecond laser and extracts it through a small side incision. This procedure was believed to be stable because the anterior stroma and Bowman layer remain largely intact.[9] Another recently introduced procedure, LASEK with prophylactic collagen cross-linking (LASEK-CXL), which is performed on the stromal bed in highly myopic eyes with thin residual stroma, aims to enhance corneal rigidity and thus reduce the possibility of long-term myopic shift and corneal ectasia disease.[10,11] Therefore, this study aimed to investigate and compare the predictability, efficacy, safety, and complications of SMILE, LASEK, and LASEK-CXL.

Materials and methods

This retrospective study included all patients who underwent SMILE, LASEK, or LASEK-CXL between December 2016 and December 2020 at Prasad Netralaya. This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board/ethics committee. Inclusion criteria for the study were 18 years of age or older and no other previous ocular surgery. Before surgery, a complete preoperative ophthalmologic

examination was performed to ensure that there was no present or past ocular pathology other than refractive errors. Patients had spherical myopia equal to or greater than -6.00 diopters (D) and myopic astigmatism less than -4.50 D cylinder, and minimum corneal thickness over 480 [mu]m.

Exclusion criteria were the presence of residual, recurrent, or active ocular disease such as uveitis, retinal disorder, severe dry eye, or significant cataract. Patients with a history of ocular surgery or systemic collagen vascular disease were excluded. The advantages and disadvantages of each surgical procedure were explained. Especially, the patients who were expected to have residual corneal thickness under 320 [mu]m were recommended to undergo a concurrent collagen CXL procedure.

Surgical Procedures

All patients received topical anesthesia, standard sterile draping, and insertion of a speculum. SMILE surgery was done using a VisuMax 500-kHz laser system (Carl Zeiss Meditec AG, Jena, Germany) with a repetition rate of 500 kHz and pulse energy of 140 nJ, spot spacing 4.50 [mu]m and followed a previously published surgical procedure.[12] The intended diameter was 7.5 mm, whereas the diameter of the refractive lenticule was 6.5 mm. A single side cut 2 mm in length was made in the superior position. After the cutting procedure, the lenticule was dissected and separated through the side cut and manually removed. LASEK began with 20% alcohol-assisted epithelial removal, then continued with excimer laser ablation (6.0-6.8 mm optical zone) with a Mel-90 excimer laser (Carl Zeiss Meditec, Jena, Germany). After laser ablation, a bandage soft contact lens was applied. LASEK-CXL began with the same protocol as LASEK until laser ablation, but after ablation, one drop of 0.22% riboflavin (isotonic solution, mixed with saline), was applied and the eye was soaked for 90 seconds. After stromal soaking, a UV-A fluence of 30 mW/cm^2 was applied for 90 seconds (total energy, 2.7 J/cm^2) using the KXL CXL system. All 3 groups aimed to gain postoperative emmetropia, and there were no personal nomograms.

To avoid cyclotorsion, all eyes of the 3 groups were marked preoperatively along the horizontal meridian at the limbus (3 o'clock and 9 o'clock) under the slit lamp with measured data using the Pentacam (Oculus Optikgerate GmbH, Germany) preoperatively. All patients were treated with Moxifloxacin and loteprednol 4 times a day for 1 month.

Postoperative Visual Outcomes and Parameters

Patients were examined preoperatively, and at 1 month, 3 months, and 6 months postoperatively. When patients visited the clinic, objective and subjective refraction tests were performed and uncorrected distance visual acuity (UCVA) and best-corrected distance visual acuity (BCVA) were recorded. Topographic imaging (Optikon 2000, Rome, Italy) was performed for all patients at the 6-month visit. In addition, evaluation of corneal haze was performed by slit-lamp microscopy examination and Fantes grading.[13]

Three parameters were calculated using data obtained at postoperative 6 months. The efficacy index was calculated by dividing postoperative 6-month UCVA by preoperative BCVA. The safety index was calculated by dividing postoperative 6-month UCVA by preoperative UCVA. Predictability represents the proportion of postoperative spherical equivalent (SE) within 0.5 or 1.0 D. Statistical analysis was performed using SPSS software (version 22, SPSS, Inc.). The analysis of variance 1-way test and [chi]^2 test were used for preoperative and postoperative comparisons. $P < 0.05$ was considered to indicate statistically significant results.

Results

A total of 86 patients were enrolled in the study.SMILE group consisted of 69 eyes, LASEK, 61 eyes, and LASEK-CXL, 40 eyes. Table 1 shows patient demographics and preoperative data. There were no significant differences among the 3 groups in mean astigmatism or sex. The lasek group was younger on average than the SMILE group or LASEK-CXL group. The SMILE group had a lower preoperative mean SE than did the lasek group, but there were no significant differences between the SMILE group and LASEK-CXL group or the LASEK group and LASEK-CXL group.

	SMILE (n = 69)	LASEK (n = 61)	LASEK-CXL (n = 40)	*P*
Age, yrs	26.4 ± 6.1	22.8 ± 6.8	25.4 ± 7.4	<0.01*
Male:female	34:35	31:30	18:22	0.21†
SE	−7.14 ± 0.98	−7.82 ± 1.29	−7.53 ± 1.52	<0.01*
BCVA, logMAR	−0.01 ± 0.03	−0.01 ± 0.04	−0.02 ± 0.09	0.793
Astigmatism, D	1.55 ± 0.85	1.83 ± 0.85	1.91 ± 0.76	0.62
Central corneal thickness, µm	540.0 ± 23.4	527.4 ± 22.7	510.5 ± 19.4	<0.01*

*Analysis of variance 1-way test $P < 0.05$.
†χ^2 test.

TABLE 1. Characteristics of Patients

Postoperative Visual Outcomes

The SE (Table 2) indicates that the SMILE group (0.34 +/- 0.25 D) had a lower SE than did the LASEK group (0.50 +/- 0.36 D) at 6 months (P = 0.04), but there were no statistically significant differences between the SMILE group and the LASEK-CXL group or the LASEK group and the LASEK-CXL group. Also, tests for astigmatism indicated that the SMILE group (0.35 +/- 0.21) had a lower cylinder than did the LASEK group (0.70 +/- 0.33) and the LASEK-CXL group (0.56 +/- 0.26), but there was no significant difference between the LASEK and LASEK-CXL groups.

	SMILE	LASEK	LASEK-CXL	P
1 mo				
SE	0.42 ± 0.33	0.52 ± 0.42	0.65 ± 0.47	0.02*
Cyl	0.55 ± 0.37	0.81 ± 0.52	0.73 ± 0.57	0.02*
3 mo				
SE	0.38 ± 0.31	0.43 ± 0.32	0.49 ± 0.45	0.99
Cyl	0.47 ± 0.25	0.82 ± 0.42	0.62 ± 0.34	<0.01*
6 mo				
SE	0.34 ± 0.25	0.50 ± 0.36	0.42 ± 0.34	0.04*
Cyl	0.35 ± 0.21	0.70 ± 0.33	0.56 ± 0.26	<0.01*

*Analysis of variance 1-way test $P < 0.05$.
Cyl, cylinder.

Table 2. Postoperative Refractive Errors (Average of Absolute Values)

Uncorrected visual acuity (UCVA) was recorded at 6 months postoperatively; 97.1% of eyes in the SMILE group had a postoperative UCVA of 20/20 or better, and 100% had 20/25 or better. In the LASEK group, 72.1% of eyes had a postoperative UCVA of 20/20 or better, and 91.8% had 20/25 or better. In the LASEK-CXL group, 72.5% of eyes had a postoperative UCVA of 20/20 or better, and 92.5% had 20/25 or better. The BCVA at postoperative 6 months was 20/20 in the following percentage of eyes: SMILE, 97.1%; LASEK, 80.3%; and LASEK-CXL, 75%. Furthermore, 100% of SMILE, 100% of LASEK; and 75% of LASEK-CXL eyes were 20/25 or better, which is similar to the results of UCVA analysis (Fig. 1).

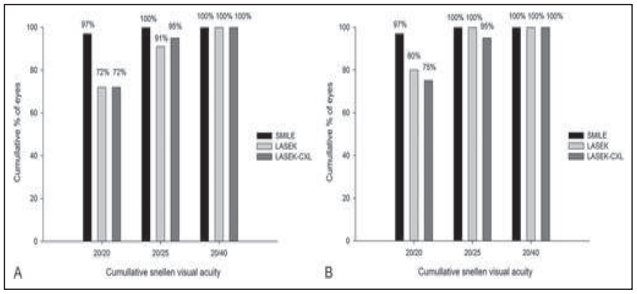

Figure 1. Postoperative distance visual acuity in the 3 (SMILE, LASEK, and LASEK-CXL) groups at 6 months postoperatively. A, UCVA. B, Best-corrected visual acuity.

The corrections in SE are presented in the form of a scatter plot (Fig. 2), in which the vertical axis corresponds to the achieved SE and the horizontal axis corresponds to the attempted SE. Predictability was within +/-1.00 D in 99%, 95%, and 92% of eyes (SMILE group, LASEK group, and LASEK-CXL group, respectively) and within +/-0.50 D in 84%, 65%, and 76% of eyes, respectively.

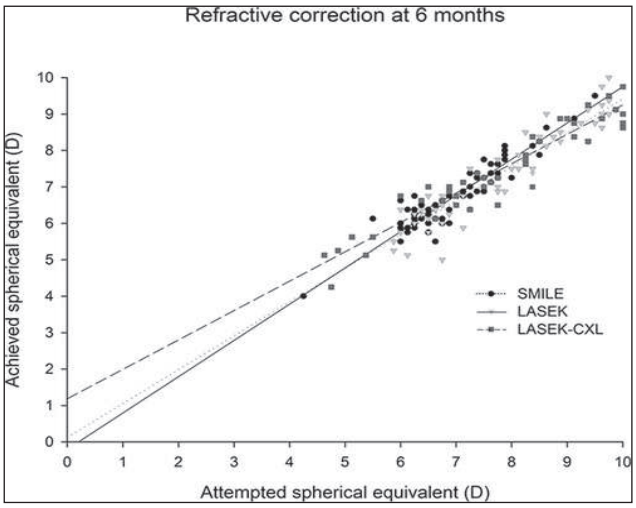

Figure 2. Predictability of SE correction, measured at 6 months postoperatively, showing achieved SE versus attempted SE in the SMILE, LASEK, and LASEK-CXL groups.

Changes in SE from 1 month to 3 months were -0.08 +/- 0.31 D, -0.01 +/- 0.38 D, and -0.06 +/- 0.67 D in the SMILE, LASEK, and LASEK-CXL groups, respectively. There were no differences among the 3 groups. Changes in SE from 1 month to 6 months were -0.05 +/- 0.32 D, -0.17 +/- 0.58 D, and -0.00 +/- 0.62 in the SMILE, LASEK, and LASEK-CXL groups, respectively (Fig. 3). The LASEK group had the highest SE change; however, there were no statistically significant differences among the 3 groups (Table 2).

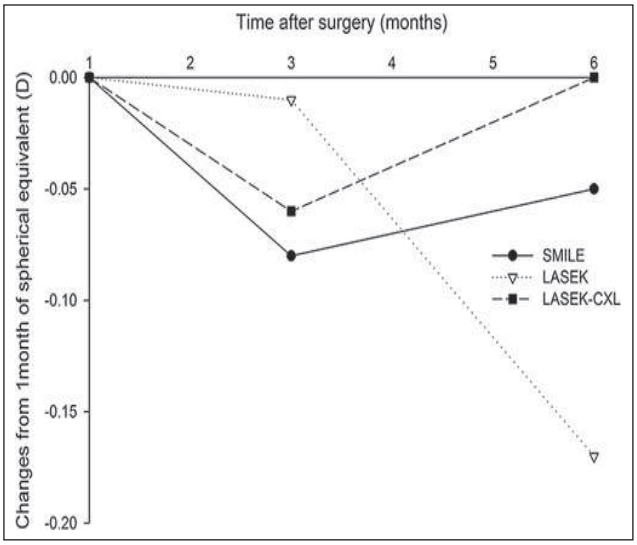

Figure 3. Changes from 1 month of manifest SE refraction for the 3 groups, expressed in diopters (D), up to 6 months postoperatively.

Postoperative Visual Parameters

The efficacy index was 0.98 +/- 0.08, 0.96 +/- 0.15, and 0.99 +/- 0.21 in the SMILE, LASEK, and LASEK-CXL groups, respectively. There were no significant differences among the 3 groups (P = 0.4). Comparison of preoperative BCVA with 6-month postoperative BCVA revealed that the SMILE group had 0% visual acuity loss, but 18% of the LASEK group and 15% of the LASEK-CXL group had lower postoperative BCVA than preoperative BCVA (Fig. 4). The safety index ratings were 0.98 +/- 0.08, 0.97 +/- 0.11, and 1.01 +/- 0.20 in the SMILE, LASEK, and LASEK-CXL groups, respectively. There were no significant differences among the 3 groups (P = 0.296).

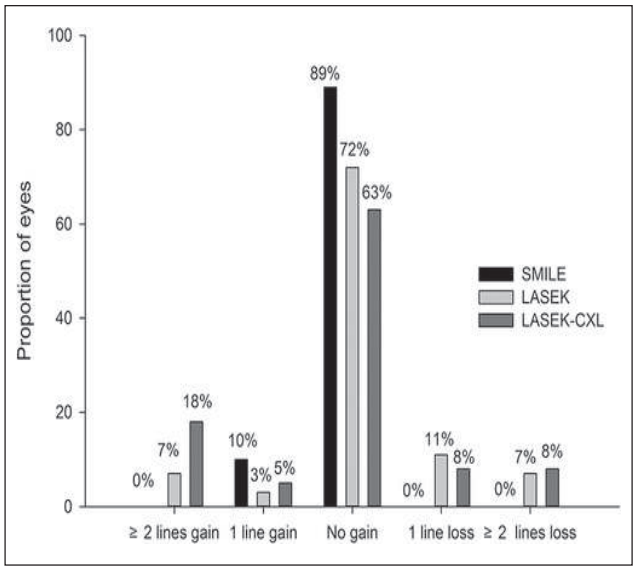

Figure 4. Difference between preoperative and postoperative BCVA.

Complications

Table 3 indicates that corneal haze developed in 18% of LASEK patients and 25% of LASEK-CXL patients, which were significantly higher than 0% in the SMILE group (P < 0.01). Higher-order aberration at postoperative 6 months was similar in the 3 groups, but higher-order aberration (HOA) root mean square in the SMILE group (0.73 +/- 0.30) was lower than in the LASEK-CXL group (1.05 +/- 0.24), whereas there were no differences between the SMILE group and the LASEK group (0.86 +/- 0.02) or the LASEK group and the LASEK-CXL group. The SMILE group had lower total fourth-order and spherical aberration than did the LASEK group and LASEK-CXL group (Table 4).

Haze Grade	SMILE (n = 69)	LASEK (n = 61)	LASEK-CXL (n = 40)	P
0	69 (100%)	50 (81%)	30 (75%)	<0.01*
Over 0.5	0	11 (18%)	25 (25%)	

*Person χ^2 test $P < 0.05$.

Table 3. Corneal Haze Score at 6 Months Postoperatively

	SMILE (n = 18)	LASEK (n = 35)	LASEK-CXL (n = 12)	P
HOA-RMS	0.73 ± 0.30	0.86 ± 0.22	1.05 ± 0.24	<0.01*
Total third order	0.51 ± 0.21	0.53 ± 0.27	0.49 ± 0.28	0.88
Coma	0.43 ± 0.17	0.47 ± 0.28	0.44 ± 0.28	0.86
Total fourth order	0.48 ± 0.20	0.63 ± 0.11	0.69 ± 0.27	<0.01*
Trefoil	0.21 ± 0.20	0.21 ± 0.12	0.22 ± 0.15	0.96
Spherical aberration	0.38 ± 0.19	0.59 ± 0.11	0.72 ± 0.27	<0.01*
Secondary astigmatism	0.19 ± 0.10	0.16 ± 0.11	0.23 ± 0.15	0.21
Quadra foil	0.12 ± 0.18	0.08 ± 0.05	0.14 ± 0.13	0.27

*Analysis of variance 1-way test $P < 0.05$.
HOA-RMS, root mean square of higher-order aberration.

Table 4. Higher-Order Aberrations at 6 Months Postoperatively

Discussion

Improved ablation profiles and laser beam-tracking technology have contributed to excellent results of LASIK procedures in the correction of myopia. Thus, currently, LASIK surgery is most often performed to correct myopia. However, LASIK may be associated with myopic regression in eyes with a high degree of myopia, mechanical flap loss, creation of a button hole, epithelial ingrowth, etc.[14-17] However, SMILE and LASEK created no flap or flap-related disadvantages of the LASIK procedure.

SMILE uses a femtosecond laser to cut a refractive lenticule within the corneal stroma, which is then removed through a small epithelial incision, minimizing trauma to the corneal surface. Theoretically, this should reduce corneal denervation as compared with LASIK, thus reducing postoperative dry eye and epithelial ingrowth. He et al.[18] SMILE decreases lower central corneal sensitivity and provides faster recovery compared with LASIK during the first 3 postoperative months. Li M et al [19] reported that the loss of subbasal nerve fiber density was less in the SMILE group than in the FS-LASIK group at the first 3 months after surgeries. Reinstein et al [20] also demonstrated that SMILE improved the postoperative dry eye compared with LASIK given that the anterior cornea was left untouched other than the small incision. In particular, this procedure may enhance biomechanical stability as compared with LASEK surgery because it preserves the Bowman layer.

Kim et al [21] reported the results of SMILE surgery in a group with mild to moderate myopia and a group with high myopia; predictability, efficacy, and safety were not significantly different between both groups. That report found that SE 6 months postoperatively was within +/- 1.00 D in 96.9% of cases of high myopia, which is similar to the results of the present study. The efficacy index at postoperative 6 months was 0.99 +/- 0.18, and the safety index was 1.14 +/- 0.16 in high myopia. The efficacy index and safety index in our study 6 months after SMILE surgery is 0.98 +/- 0.08 and 0.98 +/- 0.08, respectively, which is similar to the results of the previous study.

Lin et al [22] reported the results of SMILE surgery and femtosecond laser-assistant LASIK (FS-LASIK) surgery

for myopia correction 3 months postoperatively. SMILE surgery and FS-LASIK showed no differences in correction of SE and final visual acuity. However, the SMILE group had fewer higher-order aberrations and spherical aberrations at postoperative 1 month and 3 months. This could be explained by previous study that SMILE was likely to minimize the change in the shape of the cornea, maintaining biomechanical stability to the largest extent.[21] Our results were similar to those of previous studies; however, at 6 months postoperatively, SE, astigmatism, and some of the HOA (root mean square of HOA, total fourth order, spherical aberrations) were less prevalent in the SMILE group.

Another procedure is LASEK, which produces less pain, a shorter rehabilitation time, and a lower rate of corneal haze than does photorefractive keratectomy,[23,24] although previous literature comparing LASIK and LASEK is controversial. Scerrati et al [23] reported that LASEK produces superior results in postoperative corneal topography, BCVA, and contrast sensitivity than does LASIK. Also, Kim and Chung [24] found that LASIK and LASEK are similar regarding 6-month postoperative UCVA, SE, and corneal haze. In that study, SE in the LASEK group was 0.01 +/- 0.14 D, SE was within +/-0.50 D in 100% of eyes in the LASEK group, and the efficacy index was 1.39 6 months postoperatively. In our study, SE was 0.50 +/- 0.36 D, SE was within +/-0.50 D in 65% of LASEK eyes, and the efficacy index was 0.96 +/- 0.15. The difference may result from baseline differences. Kim and Chung restricted their subjects to only those with moderate myopia (-3.00 D ~ -6.00 D), and the average preoperative SE was -4.02 +/- 1.29 D, whereas our study restricted the study subjects to those with high myopia (-6.00 D or over), and average preoperative SE was -7.82 +/- 1.29 D.

Another available treatment to decrease myopic progression and corneal ectasia is prophylactic CXL with corneal ablation surgery. Kanellopoulos et al [25] found that prophylactic CXL with corneal ablation surgery prevented postoperative epithelial thickening, leading to a reduction in myopic progression. Although another, later, study by their group [26] compared LASIK and LASIK with CXL surgery and showed no differences in the degree of myopic correction and postoperative visual acuity, CXL contributed to improved refractive and keratometric stability. A previous report [27] on LASIK with CXL compared with LASIK only 2 years after surgery reported that LASIK with CXL was associated with an SE within +/-0.50 D in 81.3% of cases, 20/20 vision or better in 93.8% of cases, and no eyes that lost a line. In our study, LASEK with CXL resulted in an SE within +/-0.50 D in 76% of cases, 20/20 vision or better in 75% of cases, and 16% of eyes that lost a line at 6 months postoperatively. These differences may be attributable to the more severe myopic SE in our study population (-7.53 +/- 1.52 D) as compared with the previous study (-6.67 +/- 2.14 D), and also differences in surgical techniques (LASIK vs. LASEK).

The study by Kanellopoulos indicated that prophylactic CXL concurrent with LASIK improves refractive and keratometric stability. Also, in our study, LASEK-CXL showed the lowest myopic progression at 6 months, but there were no statistically significant differences between the 3 groups. Changes in SE at 3 months and 6 months as compared with 1 month revealed no differences among the 3 groups. However, the difference at 6 months compared with 1 month were lower than that at 3 months compared with 1 month in the SMILE group and the LASEK-CXL group, whereas the LASEK group had a greater change of SE at 6 months compared with 1 month than at 3 months compared with 1 month (Figure 3). A long-term follow-up study may reveal slight myopic regression. It was presumed that 2 possible causes led to this difference. The first was corneal protrusion due to biomechanical unstability of the postoperative cornea after ablation. Pan et al [28] found that refractive regression after LASIK was mainly caused by corneal protrusion. CXL increased the mechanical and biomechanical stability of the stormal tissue through the induced formation of new covalent bonds between the amino acids among the neighboring collagen molecules and among proteoglycan core proteins, which would prevent corneal protrusion.[29] The other cause was the thickening of epithelium after epithelial healing. Kanellopoulos et al [30] compared LASIK combined with prophylactic high-fluence CXL and LASEK only in high myopia and reported that there was a statistically significant reduction of the epithelial increase in the LASIK-CXL cases compared with the LASIK-only case. CXL affected epithelial thickness remodeling, leading to reduced overall thickness [25]

Previous studies reported the development of postoperative corneal haze after SMILE, LASEK, and LASIK with CXL at a rate of 0 to 9%.[21-34], There is currently no consensus as to which refractive surgery has a lower risk of corneal haze. Our study results indicate that SMILE is associated with a lower incidence of corneal haze. Nakamura et al [35] reported that an intact corneal epithelium is essential to prevent stromal haze after LASIK. The SMILE group may have the lowest rate of corneal haze in this study because SMILE surgery affects the corneal epithelium less than do LASEK and LASEK-CXL.

This study had some limitations such as its retrospective design and relatively short period of observation. Another limitation of this study was that corneal centration data were not obtained. Further studies were needed to measure decentration of the optical zone that could lead to irregular astigmatism and reduced optical quality. Another limit was that the average of preoperative central cornea thickness of the LASEK-CXL group was lower than that of the LASEK group. Therefore, this result should be interpreted with caution, and further prospective, randomized clinical trials evaluating effects of SMILE, LASEK stand alone, and LASEK with CXL are needed. Recently, the early clinical outcomes of combined SMILE and CXL (SMILE xtra) were reported. SMILE xtra had a good overall safety profile and was effective in correcting myopia.[31] Further studies with SMILE xtra as another treatment option for individuals with high myopia who have high risk of corneal ectasia or

postoperative regression should be considered.

In conclusion, all 3 methods provided appropriate predictability, stability, and apparent safety during the 6 months immediately after surgery. Also, visual outcomes showed no statistically significant differences at postoperative 6 months between the 3 groups. However, the SMILE group had no haze and fewer induction of some HOA compared with the LASEK and the LASEK-CXL group.

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Original article

Prevalence of Monocular Childhood Blindness in Rural Population of Southern India

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Abstract

Purpose- To determine the prevalence and etiology of childhood monocular blindness in a rural population in southern India through a population based study.**Methods** - All children aged ≤ 15 years having monocular blindness (Visual acuity of < 3/60 in one eye) were screened. Surveyed villages had 8,222 households with a total population of 40,336 of which 14,423 (35.7%) were children aged ≤15 years. Screening was carried out in two stages, at first stage all children with a visual acuity <6/18 in at least one eye referred to the second stage. All children with visual acuity <3/60 in the better eye were referred to the tertiary care hospital for further management. **Results-** Age range of affected children was 1-15 years with a median age of 12. Fifteen children had monocular visual impairment giving a prevalence rate of 1.13/1000 children including those screened by examination and those screened by history (15/13241, 95% CI, 0.58-1.77). Nutritional deficiencies due to Vitamin A and infective causes accounted for 20.0% (3/15) of the monocular visual impairment**.** Refractive error leading to Amblyopia was the most common cause of monocular visual impairment followed by Trauma and congenital disorders.**Conclusion-** Monocular blindness is often neglected and is avoidable .Almost 70% of cases are due to preventable and treatable causes. Improved screening methods especially for refractive errors, genetic counseling and therapeutic interventions will reduce the burden of childhood blindness. Prevalence studies should be the first priority in control of childhood blindness within the purview of WHO's VISION 2020.

Introduction

India has an estimated 320,000 blind children, more than any other country in the world.[1] Even though this represents a small fraction of the total blindness, the control of blindness in children is one of the priority areas of the World Health Organization's (WHO) "Vision 2020: the right to sight" program. This is a global initiative, which was launched by WHO in 1999 to eliminate avoidable blindness worldwide by the year 2020.[2] Nearly 500,000 children become blind each year; consequently the fight against childhood blindness has become a priority for the Vision 2020 Global Initiative.[3] The prevalence of blindness in children ranges from approximately 0.3/1000 children in affluent regions to 1.5/1000 in the poorest communities. Globally there are estimated to be 1.4 million blind children, almost three-quarters of them live in developing countries.[4]

The population of India in 2001 was estimated to be 1.03 billion, approximately 420 million were children under 16 years of age (40.8%).[5] Many causes of childhood blindness can be prevented or treated.[6] Preventable causes include vitamin A deficiency (VAD), opthalmia neonatorum and use of harmful traditional eye medicines.[7] Treatable causes include cataract, retinopathy of prematurity and glaucoma.

Monocular blindness is a common ocular problem which affects all ages and gender.[8] It leads to loss of binocular single vision with all its advantages including stereopsis, field overlap, exteroception of form and colour, and enhanced performance of visuomotor tasks.[9,10] A monocular blind person is at risk of developing bilateral visual impairment and therefore needs special care to prevent or treat visual disabilities in the fellow eye.[11]

Pediatric age group is also considered a priority as severe visual loss in children can affect their development, mobility, education, and employment opportunities. This has far- reaching implications on their quality of life and their affected families. In terms of the 'blind person years' they form the maximum burden of blindness on the

community, next only to cataract, the commonest cause of avoidable blindness.[4]

Information on the major causes of blindness in children is required to design effective prevention of blindness programs.[12] Reliable, population-based data on the causes of blindness in children are difficult to obtain in developing countries as registers of the blind do not exist, and very large sample sizes would be required for formal cross-sectional surveys. Alternative sources include the use of key informants, and examination of children identified as blind in community-based rehabilitation programs. Examination of children in special institution has increasingly been used to provide data on the causes of blindness in children, but possible sources of bias need to be borne in mind. Population based surveys are the gold standard for accurate prevalence data as they can provide cross-sectional and community based data and are less subject to bias. The advantages of population based surveys are the presence of both parents and siblings but they fail to take onto account of children who are in the residential schools for blindness, which will be mostly located in urban areas and those children tends to have poor vision compared to children in the mainstream schools. Owing to financial constraints; it is likely that children with severe visual impairment in remote rural areas of developing countries stay at home instead of attending school .Unlike adult blindness surveys because of low prevalence of childhood blindness, a large sample size is needed to get more precise data and tends to be expensive.

Monocular blindness often under-reported and neglected as a significant source of morbidity. There is a lack of published information on the causes of monocular childhood blindness in India. This study is designed to enumerate the proportions of ocular conditions contributing to monocular childhood blindness in a rural population in Southern India. The causes amenable to prevention and treatment, receive attention, not only because there are interventions available for these conditions, but also devastating consequences if not addressed.

Material and Methods

The study design was cross sectional and carried out in the vacation period of schools, so as to include as many children aged ≤15 years as possible .In order to get a good response community leaders, health administrators and peripheral health assistants were involved in a meetings prior to survey. Quality control and a decreased non sampling error was ensured by pilot testing the survey procedure, validating and field-testing the proforma's used and training the interns regarding proper administration of the survey. The method adopted was to complete the survey in a village and then proceed to the next. Study protocol adhered to the guidelines of the Declaration of Helsinki; Approval was obtained from Institutional Ethics Committee of Nayana superspecialty eye hospital and research center. Two stage screening was done in each village; a house to house survey was done by the screening teams consisting of two medical interns. A group of two such two teams was supervised by a postgraduate or resident. Secondary screening team included post graduates or residents and an optometrist , final confirmation of the data was done by a consultant .All children with a visual acuity <6/18 in at least one eye referred to the second stage. Study area included all 127 villages associated to the tertiary care center of the Regional Institute of Ophthalmology, Bangalore. Surveyed villages had 8,222 households with a total population of 40,336 of which 14,423 (35.7%) were children aged ≤15 years. All children from birth to 15 years, whose parents had resided in the study area for at least 6 months, were screened.

Monocular blindness was defined as presenting visual acuity < 3/60 in worse eye.[13] In all children recordings included: relevant ophthalmic history, general and ophthalmic examination, visual acuity assessment, category of visual impairment, presence of any abnormalities, anatomical and etiological cause of visual impairment, need for optical, medical or surgical interventions and the visual prognosis was assessed. Anterior segments of the eye were examined using a light and loupe magnifier, Posterior segment was examined either with direct or indirect ophthalmoscope after dilatation in relevant cases.

Visual acuity was assessed in each eye using a Snellen tumbling "E" visual acuity test chart. The child who did not cooperate with the "E" chart, were assessed for the ability to fix and follow light. Near vision was assessed using figures (Table 1).

Table 1-Methods of visual assessment

Age	Measurement of visual acuity [13],[14]
5-15 years	Snellen's Tumbling E chart at 6 meters
3-4 years	Snellen's equivalent picture chart at 6m
< 3 years	Examination with a flash light and assessment of the ability to fix and follow the light

To categorize a child under low visual category, simple tests of functional vision were used. They were, the ability to navigate around two chairs set two meters apart unaided with a visual acuity of <20/60 to light perception; to recognize faces at a distance of three meters, and to recognize the shape of symbols at any near distance. The children who failed to cooperate with these tests due to additional handicaps were judged on their visual behavior.

The causes of visual impairment were classified based on the WHO.[15,16] The anatomical classification of causes of visual loss defined that part of the eye which had been

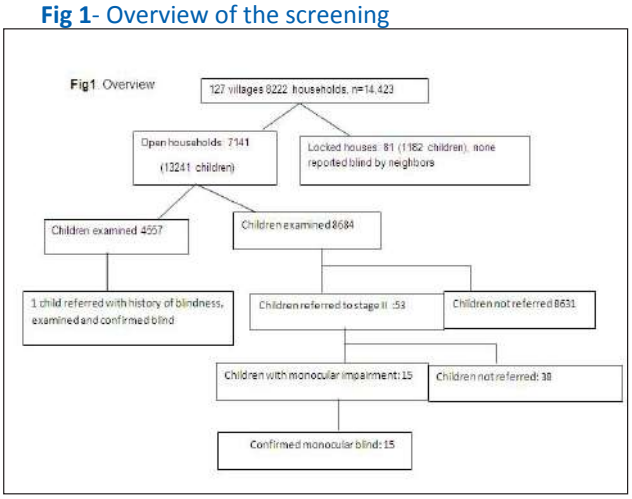
damaged leading to visual loss (such as cornea, lens, retina, optic nerve, whole globe). Where two or more anatomical sites were involved the major site was selected, or where two sites contributed equally, the most treatable condition was selected.

The etiological classification was divided into congenital (hereditary, intrauterine, perinatal), traumatic, Infective, nutritional and refractive error. All children with visual acuity <3/60 in the better eye, requiring further investigations and treatment procedures were referred to the tertiary care hospital. The data were entered into a database and analyzed using SPSS for Windows.

Results

Flow chart depicts the overview of the screening process which was carried out (Fig 1).

Fig 1- Overview of the screening



Fifteen children had monocular visual impairment giving a prevalence rate of 1.13/1000 children including those screened by examination and those screened by history (15/13241, 95% CI, 0.58-1.77). Age range of affected children was 1-15 years with a median age of 12. Examination rate was higher in younger children as they were more likely to be at home compared to older children. Similarly, 68.7% of the female children were available while only 63.3% of the male children could be examined. Males constituted 48.1% of the examined children however majority of the monocularly impaired children were male (10/15, 66.6%). The total number of children whose parent's marriage was consanguineous 4010 (30.06%).The proportion of first degree consanguinity was 46.4%,second degree was 37.5% and third degree consanguinity was seen in 16.1%. In children with monocular visual impairment, the worse eye improved with refraction in two male and female children.

Anatomical cause in children with monocular visual impairment showed globe anomalies are common in children ≤ 5 years and corneal abnormality was common in children between 5-15 years age group. Etiological causes for monocular blindness are shown in Table 2 and Fig 2A-2D.

Table 2-Etiological causes for monocular blindness

Etiology	No of affected %	Prevalence(95% CI)
Refractive error (amblyopia)	6 (40.0%)	0.45(0.17-0.99)
Nutritional (Vitamin A deficiency)	2 (13.3%)	0.38(0.08-0.77)
Trauma	3 (20.0%)	0.15(0-0.42)
Congenital (Globe anomaly)	3 (20.0%)	0.08(0-0.42)
Infective (Toxoplasmosis)	1 (6.7%)	0.08(0.12-0.88)
Total	15 (100%)	1.13(0.58-1.77)

Data presented as number of persons (%)

Values are expresses as prevalence per 1000; Values in percentages are 95% CI.

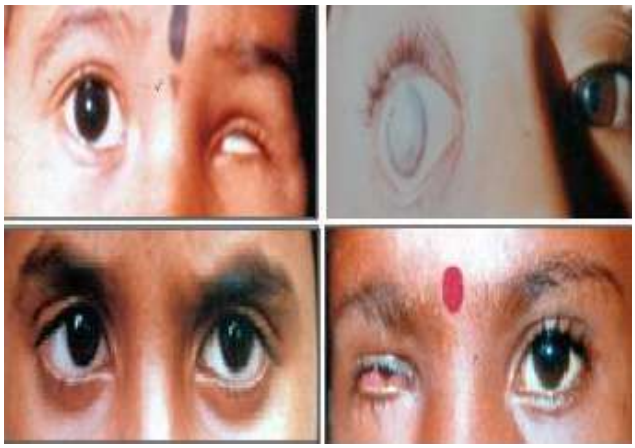


Fig 2A -Congenital anophthalmos, **Fig 2B**- Corneal opacity, **Fig 2C**-Right convergent squint with amblyopia, **Fig 2D**- Phthisis bulbi

Refractive error leading to Amblyopia was the most common cause of monocular visual impairment followed by Trauma and congenital disorders. Nutritional deficiencies due to Vitamin A and infective causes accounted for 20.0% (3/15) of the monocular visual impairment.

Discussion and conclusion

In the absence of a registration system for blind in India, this study of a well-defined community, conducted systematically using trained medical interns and ophthalmology residents for initial screening, provides valuable insight into the causes and magnitude of childhood blindness

In a study conducted among urban population in the state of Andhra Pradesh in southern India, 20.2% of unilateral visual impairment was seen in children ≤15 years underscoring its importance in this age-group. [17] Strabismus with amblyopia accounted for 40% of the cases. Refractive errors were responsible for 67% of unilateral

visual impairment in age group ≤16 years in the Andhra Pradesh study.[17] In Los Angles Latino Eye study, 10.6% of adults with monocular blindness had amblyopia.[18] Similar statistics were found in the Blue Mountains study (13.3%) [19], the SEE study (10.9%) [20], and the Beaver Dam study (9.4%)[21].

These statistics reflect the importance of developing screening programs to prevent unilateral amblyogenic conditions and access to low vision services to diagnose, assess and prescribe the appropriate optical devices in children with severe visual loss. Trauma often the most important cause of unilateral loss of vision was seen in 20% of the affected children.[22] However post-traumatic corneal ulceration is preventable and highlights the need for effective safety measures and education on eye injuries. The use of traditional eye medicines (TEM) is an important risk factor as they are often contaminated and provide a vehicle for the spread of pathogenic organisms.[7] Microphthalmos and Anophthalmos, an important cause of bilateral childhood blindness in India accounted for 20% of unilateral blindness.[23] Increase in consanguineous marriages could be one of the reasons.

It is likely that hereditary factors are responsible for some cases, but it is also possible that various teratogenic factors (toxins or maternal deficiencies) could be harmful to the developing fetus. [23] More definitive data on the etiologies is needed to effectively preempt these causes. Vitamin A deficiency continues to be of significance though our primary screening data showed low prevalence of signs of Vitamin A deficiency (0.46% conjunctival and corneal xerosis).Vitamin A deficiency can be prevented through widespread measles immunizations, regular distribution of high-dose Vit A capsules to children at risk, nutritional education and dietary fortification.

Almost 70% of the monocular blindness seen was due to preventable and treatable causes. Improved primary care with appropriate prevention measures, genetic counseling, early identification and therapeutic interventions will reduce the burden of childhood blindness. Prevalence studies should be the first priority in control of childhood blindness within the purview of WHO's VISION 2020-The Right to Sight program.

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Original article

Early Postoperative Outcomes after Pterygium Surgery: Sutures vs Serum Fixation of Conjunctival Autograft

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Abstract

Purpose: To compare early outcomes of pterygium surgery and conjunctival autograft secured with sutures or autologous serum. **Methods**: In this prospective study, 60 eyes of 60 patients underwent pterygium excision with conjunctival autograft. The graft was secured with autologous serum (group 1) or sutures (group 2). Main outcome measures included pain score, foreign body sensation, tearing, hyperemia, subconjunctival hemorrhage, graft edema, and graft displacement. **Results:** The duration of surgery was significantly shorter in group 1 (average 18 minutes) than in group 2 (average 26.87 minutes). On the first postoperative day, foreign body sensation and graft edema were significantly higher in group 2 than group 1. At 1, 3, and 6 weeks follow-up, pain, foreign body sensation, tearing, and hyperemia were significantly higher in group 2 than group 1. There were no intraoperative complications. The conjunctival graft was irretrievably displaced in two cases in group 1 on the first postoperative day. **Conclusions:** Our study showed that both autologous serum and sutures are effective methods for securing the graft during pterygium surgery. The use of autologous blood significantly shortens the operating time. It is accompanied by less postoperative pain, foreign body sensation, and hyperemia in the early postoperative period. Graft displacement is a potential complication.

Introduction

Pterygium is a triangular encroachment of the bulbar conjunctiva on to the cornea.[1] The prevalence rate varies from 0.3 to 29% and is high in hot and dusty regions of the world, mostly between the latitudes of 37 degrees North and South of the equator.[1] Surgical removal is the treatment of choice. The indications for surgery include reduced vision due to encroachment of the visual axis and irregular astigmatism, chronic irritation and recurrent inflammation, restriction of ocular motility, and cosmesis. The main challenge of pterygium surgery is prevention of recurrence. A multitude of different operative techniques are described to reduce the recurrence rate, including pterygium excision with or without the use of adjuncts like beta irradiation, thiotepa eye drops, intraoperative, or postoperative mitomycin-c, amniotic membrane transplantation, and conjunctival autograft (CAG) with or without limbal stem cells.[2] The current method of conjunctival autografting involves fixation of the graft by means of suturing, which is associated with several disadvantages like prolonged operating time, postoperative discomfort, and potential for suture related complications.[3]

Use of fibrin glue to attach the graft reduces operating time and postoperative discomfort, but as it is a plasma-derived product, it has the potential risk of prion disease transmission and anaphylaxis in susceptible individuals.[4,5,6] In this study, we compared the outcomes of pterygium excision during the early postoperative period using sutures and autologous serum to fix the CAG.

Methods

A total of 60 eyes of 60 patients of primary pterygium who attended the outpatients department at Chigateri General Hospital and Bapuji Hospital attached to J.J.M. Medical College, Davangere between November 2018 and September 2020, were included. Patients with pseudopterygium, associated ocular surface problems, previous pterygium surgery, and history of any bleeding abnormalities were excluded. An informed consent was obtained from all participants. Visual acuity was tested using Snellen's acuity chart. Grading of pterygia was performed based on its size (extent of encroachment on to cornea and span of pterygium at limbus), thickness, and vascularity. Systemic evaluation of all patients was done in consultation with a physician along with relevant investigations like blood sugar, clotting

time, and bleeding time. Patients were randomized to receive pterygium excision and CAG with autologous serum (group 1) or sutures (group 2).

Surgical Technique

All surgeries were performed under peribulbar anesthesia. After disinfecting the ocular surface and surrounding area with 5% povidone-iodine, the surgical area was covered with a sterile drape. After insertion of a lid speculum, the pterygium was incised along the limbus down to the bare sclera. The pterygium head was removed by blunt dissection from the base to the apex.The head of the pterygium was then avulsed from its corneal attachment by reverse stripping using slow, firm, and deliberate traction holding at its base parallel to the cornea. The conjunctiva was reflected backward and fibrovascular tissue underneath the cut end of the conjunctiva was dissected as far as possible on the canthal side and excised, leaving the sclera and the muscle free from episcleral tissue. Tenon's tissue was carefully removed from the region of the conjunctival defect and from under the surrounding conjunctiva. Electrocautery was not used. The dimensions of the resulting conjunctival defect were measured using calipers. The donor tissue was harvested from the same eye. The area of conjunctiva in the superotemporal quadrant (1-2 mm larger than the size of bare sclera) was measured with calipers and marked. Sharp dissection was used to make two parallel radial incisions along the marked lines. Conjunctival scissors were used to undermine the conjunctiva from the lateral borders taking care to avoid inclusion of Tenon's tissue beneath it. Non-toothed forceps were used to handle the graft tissue to avoid injury to the edges and buttonholing. When the posterior and lateral ends of the graft were free, conjunctiva was cut along the posterior border. The free conjunctiva that was still attached anteriorly was reflected upon the cornea and blunt dissection was continued anteriorly until the limbus. Westcott scissors and crescent knife were used to dissect towards the peripheral cornea for about 1 mm beyond the vascular arcade with the goal of including limbal stem cells in the graft. The conjunctival graft was then excised using sharp Vannas scissors. The graft was placed on the bare sclera, with the epithelial side up in such a way as to maintain the original orientation of the juxtalimbal border towards the cornea.

In the autologous serum group, hemostasis was allowed to occur spontaneously. Host-graft borders were dried with a cotton-tipped applicator, squeezing out excess fluid from the interface. The scleral bed was viewed through the transparent conjunctiva to ensure that residual bleeding did not lift the graft. Small central hemorrhages were tamponaded with direct compression. The free graft was allowed to dry in position for 10 minutes. In the group with sutures, the graft was secured to the host bed with four 10-0 nylon sutures. Each suture bite included episcleral tissue near the limbus.

All eyes received 0.5 ml subconjunctival injection of dexamethasone and amikacin at the end of the procedure away from the site of the graft. The eye was bandaged for 24 hours. The donor site was left bare to allow it to heal. The operating time was measured starting from the placement of the lid speculum to its removal at the end of the surgery.

Postoperatively, a combination of corticosteroid and antibiotic eye drops was used 4 times a day for one month. Follow-up visits were at postoperative week 1, 3, and 6. During each follow-up visit patients were evaluated for degree of discomfort, inflammation, subconjunctival hemorrhage, graft stability (graft displacement and graft retraction), chemosis, recurrence, and any other complications. Pterygium recurrence was defined as any fibrovascular growth that crossed the limbus by more than 1 mm. Graft success was defined as an intact graft 6 weeks after surgery. Subjective sensations of pain, foreign body sensation, tearing, and discomfort were analyzed using a 5-point scale[7]: (0) none, no pain; (1) very mild, presence of pain, but easily tolerated; (2) mild, pain causing some discomfort; (3) moderate, pain that partially interferes with usual activity or sleep; (4) severe, pain that completely interferes with usual activity or sleep. Postoperative grading of inflammation was performed as follows: grade 0 - No dilated corkscrew vessel in graft; grade 1 - 1 bright red, dilated corkscrew vessel crossing the graft bed margin; grade 2 - 2 bright red dilated corkscrew vessels crossing the graft bed margin; grade 3 - 3 bright red dilated corkscrew vessels crossing the graft bed margin; grade 4 - ≥3 bright red dilated corkscrew vessels crossing the graft bed margin.[8] Graft edema was graded as 0 (nil): graft tightly attached to the sclera and no graft edema; 1 (mild): graft attached to the limbus with mild graft edema; 2 (moderate): graft moderately edematous at the level of limbus; 3 (serious): heavy graft edema.[9] Subconjunctival hemorrhage was graded as grade 0 - none; grade 1 - ≤25% of size of the graft; grade 2 - ≤50% of size of the graft; grade 3 - ≤75% of size of graft; grade 4 - hemorrhage involving the entire graft.[8] Assessment for retraction of graft edge and graft displacement was graded as grade 0: all four sides of the graft margin well apposed; grade 1: gaping/displacement of one side of the graft-bed junction; grade 2: gaping/displacement of two sides of the graft-bed junction; grade 3: gaping/displacement of three sides of the graft-bed junction; grade 4: graft completely displaced from the bed.[8]

Statistical Analysis

The statistical analysis was performed using SPSS version 20. Continuous data was presented as mean and standard deviation, whereas categorical measurements were presented as percentages. Student t test (independent, two tailed) was used to find out the significance of study parameters on a continuous scale between two groups. Chi-square test was used to find out the significance of study parameters on a categorical scale between two groups. A p value <0.05 was considered to be statistically significant.

Results

The age distribution in both groups is shown in table 1. There were 18 and 19 females in group 1 and group 2, respectively. There was no significant difference in the demographic characteristics of patients (Table 1). The total number of patients with grade T1 (4 vs 7), T2 (15 vs 15), and T3 (11 vs 8) was comparable in both groups.

Table 1: Distribution of age in patients who underwent fixation of conjunctival autograft using autologous serum (Group I) and sutures (Group II)

Age (years)	Number of patients	%	Group I	%	Group II	%
21-30	7	11.67	3	10	4	13.34
31-40	14	23.33	7	23.33	7	23.33
41-50	18	30	10	33.33	8	26.66
51-60	13	21.67	6	20	7	23.33
61-70	6	10	3	10	3	10
71 and above	2	3.33	1	3.34	1	3.34
Total	60	100	30	100	30	100

Mean graft size was 24.80 sq mm in Group 1 and 25.65 sq mm in Group 2 with no significant difference between both groups. The average duration of surgery in Group 1 and Group 2 was 18 minutes and 26.87 minutes, respectively ($p<0.05$).

On postoperative day 1, there was no difference in the pain score ($p=0.094$), tearing ($p=0.344$), subconjunctival hemorrhage ($p=0.065$), and hyperemia ($p=0.157$) in both groups (Figure 1). However, foreign body sensation ($p<0.001$) and graft edema were significantly higher in group 2 than group 1 ($p=0.041$) (Figure 2).

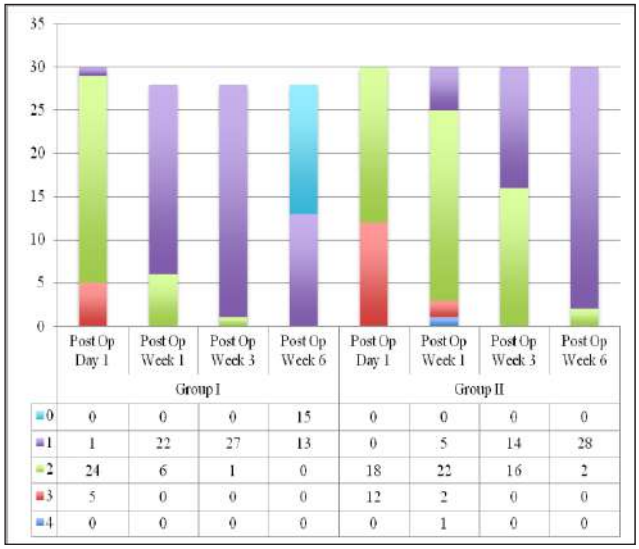

Figure 1: Comparison of pain score in both groups from postoperative day 1 to the end of postoperative week 6

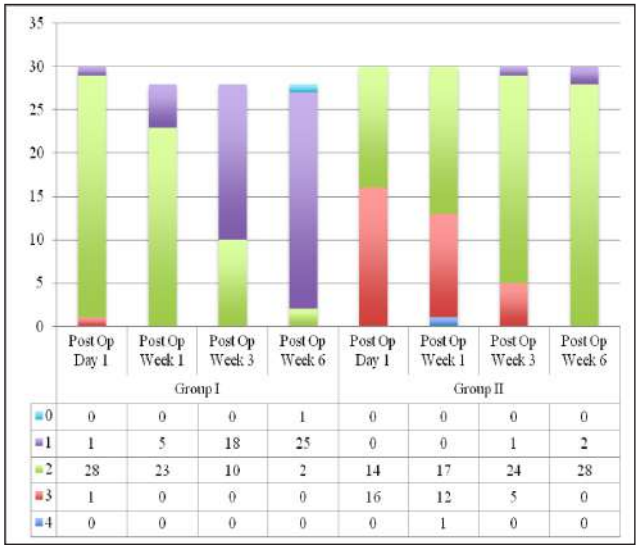

Figure 2: Comparison of foreign body sensation score in both groups from postoperative day 1 to the end of postoperative week 6

At the postoperative week 1 follow-up, pain score ($p<0.001$), foreign body sensation ($p<0.001$), tearing ($p<0.001$), subconjunctival hemorrhage ($p=0.024$), hyperemia ($p=0.013$), and graft edema ($p=0.001$) were significantly higher in group 2 as compared to group 1. Graft retraction occurred more in group 2, but the difference was not statistically significant ($p=0.086$).

At the postoperative week 3 follow-up, pain ($p<0.001$), foreign body sensation ($p<0.001$), tearing ($p<0.001$) (Figure 3), and hyperemia ($p<0.001$) were significantly higher in group 2 compared to group 1. Subconjunctival hemorrhage ($p=0.127$) (Figure 4), graft edema ($p=0.051$), and graft retraction ($p=0.086$) were noted more frequently in group 2; however, the difference between both groups was not statistically significant.

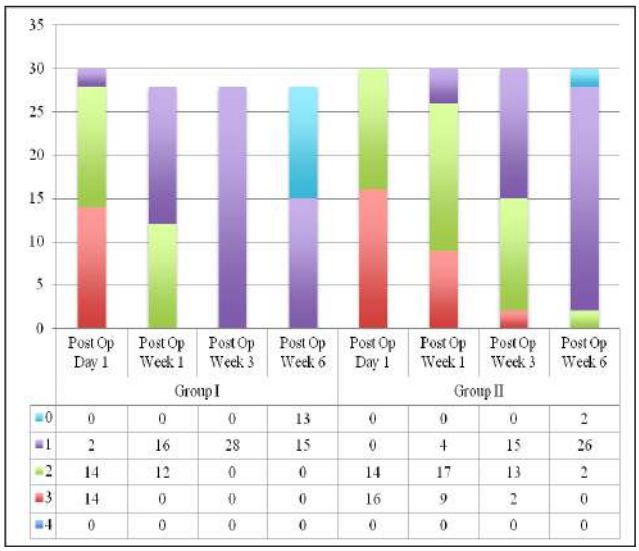

Figure 3: Comparison of tearing in both groups from postoperative day 1 to the end of postoperative week 6

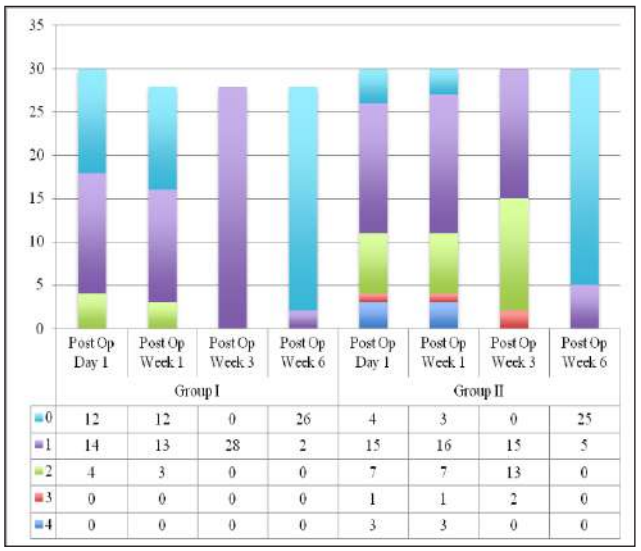

Figure 4: Comparison of subconjunctival hemorrhage in both groups from postoperative day 1 to the end of postoperative week 6

Likewise, at the postoperative week 6 follow-up, pain ($p<0.001$), foreign body sensation ($p<0.001$), tearing ($p=0.002$), and hyperemia ($p<0.001$) (Figure 5) were significantly higher in group 2 compared to group 1. Subconjunctival hemorrhage ($p=0.266$), graft edema ($p=0.164$) (Figure 6), and graft retraction ($p=0.086$) were comparable between both groups.

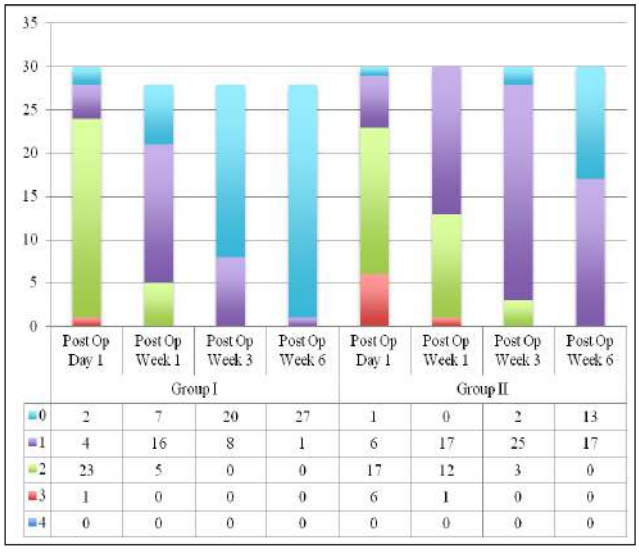

Figure 5: Comparison of hyperemia in both groups from postoperative day 1 to the end of postoperative week 6

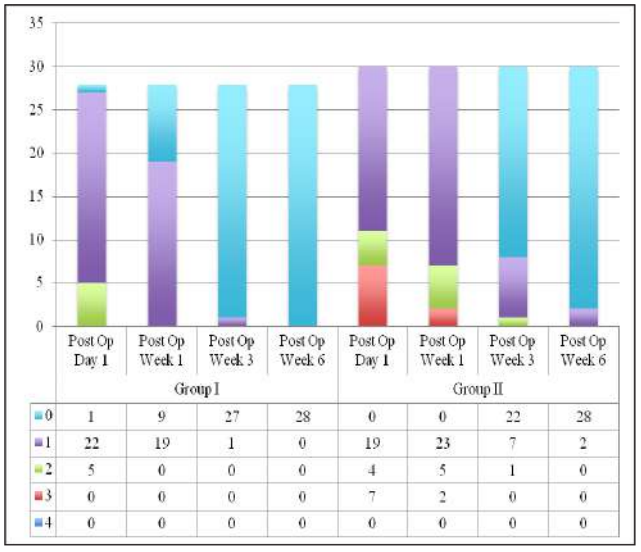

Figure 6: Comparison of graft edema in both groups from postoperative day 1 to the end of postoperative week 6

Complications

On postoperative day 1, the conjunctival graft was irretrievably displaced in two cases in Group 1. These cases were excluded from further study analysis. In addition, 1 case had grade 2 and 1 case had grade 4 graft displacement. In group 2, 3 cases had grade 1 graft displacement due to loose sutures. The difference between the two groups was not found to be statistically significant ($p=0.071$).

Discussion

Pterygium is a commonly seen external eye condition. Nevertheless, it remains an ophthalmic enigma, as the actual pathogenic mechanisms of this condition remain unknown.[10] Pterygium excision with conjunctival autografting is by far the most commonly used surgical technique for management of pterygium.[2] The conjunctival graft, which is harvested from the superior or superotemporal quadrant of the patient's own eye, can be fixated to the bare sclera with or without sutures. Sutureless fixation of conjunctival autograft using fibrin glue during pterygium surgery was popularized in 2004.[11] One of the major issues with the use of fibrin glue is the risk of potential transmission of infectious agents.[12] The fibrin used commercially for gluing can be substituted by the patients' own blood. Graft adhesion can be achieved if adequate time is given for the blood to collect and the graft to adhere to the bare area. The apposition of the lids to the graft bed further enables fast wound healing. In addition to being cost effective, the use of the patient's own serum would avoid any risk of disease transmission.

We analyzed the outcomes of pterygium surgery and conjunctival autografting in the early postoperative period. The conjunctival autograft was fixed with sutures or with autologous serum. The average duration of surgery was shorter in cases where autologous serum was used compared to the cases where sutures were used to fix the graft. This was similar to earlier reports in the literature .[13,14,15] Postoperatively, some amount of graft edema and hemorrhage was present in nearly all of the eyes of both groups, which gradually subsided over time. Significant differences were noted in pain score, tearing, foreign body sensation, and conjunctival hyperemia between both groups in early postoperative period. Subjective symptoms of pain, foreign body sensation, and tearing were fewer and disappeared more rapidly in patients without sutures. The intensity of these symptoms was also lower without the use of sutures on all follow-up visits.

We did not encounter cases of severe graft retraction in any of our cases. It has been suggested that the risk of graft retraction appears to be no greater without suturing as long as meticulous dissection of sub-epithelial graft tissue is respected.[16] Rangu et al, postulated that even tension across the whole of the graft interface without any direct tension on free graft edges reduces the stimulus for subconjunctival scar tissue formation in sutureless and glue-free graft.[17] In our study, two grafts could not be retrieved and one was grossly displaced (grade 4) in cases where autologous serum was used. Although no obvious risk factors could be determined for graft-related complications in these cases, in general, excessive accumulation of blood and eye rubbing have been associated with graft displacement in cases with serum-assisted fixation of conjunctival autograft.[15]

Although we did not encounter any recurrences by the end of the 6-week observation period in both the treatment groups, no definite conclusions could be made from our data regarding long-term recurrence rates since this was not the main aim of our study.

In summary, both autologous serum and sutures are effective methods for fixation of conjunctival grafts during pterygium surgery. The use of autologous serum can significantly shorten the operating time without any added surgical risks. Our study showed that conjunctival autograft fixation with autologous serum is associated with less postoperative signs and symptoms in the immediate postoperative period.

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Case report

Fuch's uveitis with birefringent crystals in the anterior chamber

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Abstract

Crystalline deposits in iris and anterior chamber (AC) are seen in chronic uveitis and rarely reported. They are seen as very tiny refractile bodies within the iris stroma on slit lamp examination. We report a 38 year old female in Fuch's uveitis syndrome (FUS) with minute refractile crystals studded on the iris. Other features of FUS were present in this case with posterior sub-capsular cataract in the left eye (OS). Phacoemulsification with intraocular lens implantation was carried out in the OS. AC fluid aspiration revealed numerous birefringent crystals under polarizer. Free crystals in AC without plasma cells were not reported in the literature previously.

Key Words: Anterior chamber, crystals, Fuch's, phacoemulsification, uveitis

Introduction

Introduction: Crystals on iris and anterior chamber (AC) are seen in chronic uveitis.[1, 2, 3, 4, 5] Majority of the anterior uveitis (AU) were found to be idiopathic inspite of extensive investigations. [1,3,4,5,6] Fuch's uveitis syndrome (FUS) is one of the conditions which is seen in the practice with diffuse stellate keratic precipitates (KP) with absence of posterior synechiae, occasional iris nodules, posterior sub-capsular cataract, vitreous cells, occasional posterior vitreous detachment and secondary open angle glaucoma. [1,5,6,7,8,9,10] Heterochromia in iris is less seen in brownish eyes. [1,7,8,9,10] Gonioscopy is important investigation to find filiform blood vessels in the angle of anterior chamber which can bleed. [8], [9], [10] There were previous report of raised immunoglobulin levels associated with oligoclonal immunological (Ig) bands which had been reported in aqueous samples of Fuch's uveitis.[5] Crystals on iris surface in chronic uveitis is a uncommon clinical sign which can be picked-up in higher magnification of the slit lamp biomicroscopy. [2,3,4,5] These crystals were thought to be present within the plasma cells representing as Russell bodies [5] We present a case of a middle age woman with clinical features of Fuch's uveitis and posterior sub-capsular cataract (PSC). During cataract surgery, aqueous aspiration was done which revealed multiple refractile particles in the fluid without the evidence of plasma and other inflammatory cells.

Case: A 38-year-old female presented with chief complaint of gradually progressing painless diminution of vision in both the eyes (OU) which was more in the left eye (OS) than the right eye (OD) for the last one year. Her family history was unremarkable. She had no history of ocular trauma or surgery. She complained of occasional cough and joint paint. On ophthalmic examination, her best-corrected visual acuity (BCVA) was 20/20, N6 OD and 20/30, N6 OS. The anterior segment examination OS revealed an absence of conjunctival congestion and the presence of diffuse stellate shaped greyish-white small keratic precipitates (KPs) over the corneal endothelium [Figure 1]. There was presence of very small sand like refractile specks on the iris with posterior subcapsular cataract in the OS. The anterior segment findings in the OD were within normal limit. Intraocular pressure measured with Goldman's applanation tonometer was 14 mm of Hg in the OD and 11 mm of Hg in the OS respectively. On gonioscopy with Posner's 4 mirror goniolens, sand like refractile particles were noted over the angles in the OS and the angles were open up to scleral spur in both the eyes (OU). No blood vessels were seen in the angles. Dilated fundus examination with an indirect ophthalmoscope; +20Dioptre (D) and slit lamp biomicroscope; +90D lens showed presence vitreous cells+, vitreous haze+ OS. The optical coherence tomography and fundus fluorescein angiography OU were normal. The Mantoux test was negative and serology of syphilis was non-reactive. The blood investigations revealed a normal complete blood cell count with a slightly raised ESR (30mm at the end of first hour, Westergren). The patient was diagnosed as having FUS with PSC in the OS and phacoemulsification with foldable intraocular lens implantation under topical

anesthesia was carried out in that eye. The surgery was uneventful and the patient achieved a BCVA of 20/20 N6 post-operatively. During the phacoemulsification procedure, after making the side port, AC fluid aspiration was done and sent to ocular pathology laboratory for compound microscopic examination which revealed the presence of crystalline bodies under polarizing microscope (Zeiss Axioskop 40, AxioCam MRc, Germany) [Figure 2].

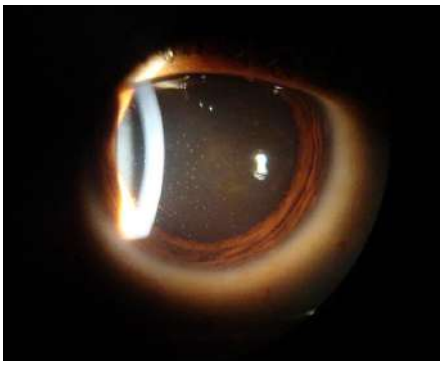

Figure 1: Slit lamp (Swiss, HAAG-STREIT, BP 900; 10 X) view in diffuse illumination showed diffuse stellate shaped keratic precipitates without posterior synechie in the left eye. Please note same eye had posterior sub-capsular cataract.

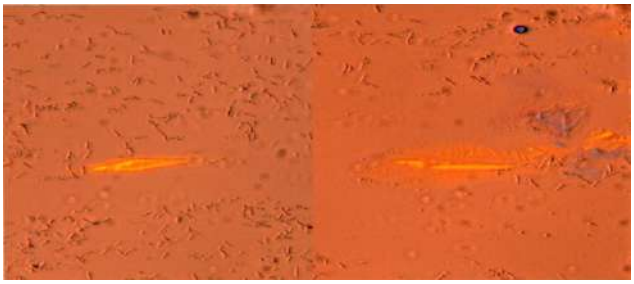

Figure 2: Refractile birefringent bodies were seen under polarizer of compound microscope (Zeiss, Germany, Axioskop 40, AxioCam MRc, 5 X)

Discussion:

Anterior uveitis is the inflammation of iris and anterior part of the ciliary body[1 -10] The reaction is manifested as flare and cells in the anterior chamber.[4,5] The clinical signs include KP's which are usually located in the Arlt's tringle. [1,2,3] There are few conditions in uveitis where we get diffuse KP's. Diffuse white stellate KP's are the features of FUS uveitis. [1,2,3] In FUS, there is absence of posterior synechie of iris and can have iris nodules. [1,2,3] Small iris crystals in FUS were reported in literature previously. [1,2,3,4,5] Oligoclonal Ig band due to plasma cell proliferation can give rise to crystal formations. [5] These dichroic bodies under the objective of microscopy were observed under cross polarizer. On rotation in polarized light using polarizer, the change of colour and intensity in those bodies could be seen in retaining 90 degree. The original colours returned after further 90 degree rotation. This is due to differential absorption of two rays in those unusual birefringent substances depending on the direction of polarizer. Some of the crystals showed pleochroic by absorbing all colours equally. These crystals are found in the cytoplasm of transformed plasma cells which were better known as Russells bodies.[5] This cascade of inflammation is B-cell type and we know that the prototype of AU is Juvenile idiopathic arthritis associated anterior uveitis which is also B-cell type. [5] In most of the previous studies of AC tap and iris biopsy, refractile bodies in chronic uveitis were seen within the plasma cells.[5] Our case had refractile structures in the iris surface and on anterior chamber fluid during cataract surgery aspiration showed free floating crystals in the aqueous fluid which were documented under polarizer of the compound microscope as birefringent bodies. This case can open up to study aqueous fluid for those unusual bodies during cataract surgery in FUS.

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Case series

"Beyond the Shadows : Unraveling CHRRPE-Clinical Insights, OCT Secrets and Management option"

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Abstract

Combined Hamartoma of Retina and Retinal Pigment Epithelium (CHR-RPE) is a rare benign intraocular tumor characterized by disorganized glial, vascular, and melanocytic tissue involving the neurosensory retina, retinal pigment epithelium (RPE), and vitreo-retinal interface. CHR-RPE typically presents as a unilateral, focal, charcoal grey lesion near the macula, leading to decreased visual acuity due to retinal traction and dragging. The diagnosis usually is established through indirect ophthalmoscopy and optical coherence tomography (OCT), but the recentadvanced imaging modalities like multicolor imaging and OCT angiographycan aid in precise localization and evaluation.Tailored management strategies, depend on patient age and lesion location, with some cases benefiting from pars plana vitrectomy with membrane peeling. CHRRPE remains an intriguing ocular entity, necessitating ongoing research and meticulous patient care to ensure the best possible outcome.

Keywords: Hamartoma, Combined hamartoma, CHRRPE

Introduction

Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) is a congenital malformation involving the neurosensory retina, retinal pigment epithelium (RPE), and the vitreo-retinal interface, as originally described by Gass.[1] This rare benign intraocular finding presents as a unilateral, focal, and charcoal grey lesion, commonly located at or near the macula. Histopathologically, CHRRPE is characterized by conglomerations of disorganized retinal, glial, and vascular tissue intertwined with tubules of retinal pigment epithelium, showing reduplication of the normally singular RPE layer.[2,3,4] Patients with CHRRPE often experience decreased visual acuity due to retinal traction in both vertical and horizontal directions, leading to retinal dragging and eventual vision loss.[5]To facilitate clinical categorization, Gass classified combined hamartoma into four anatomically based groups: papillary, peripapillary, macular and peripheral.[6] In this article, we present a case series encompassing the diverse clinical spectrum of CHRRPE, featuring varied presentations encountered in our outpatient department (OPD). We aim to explore the management approaches for these cases, which depend on factors such as patient age and the specific location of the lesion thereby optimizing visual outcomes in patients with CHRRPE.

Case 1: A 14-year-old female presented to our OPD with chief complaints of gradual and progressive blurring of vision. Her best-corrected visual acuity (BCVA) in the right eye (OD) was 6/24, and in the left eye (OS) was 6/6. The anterior segment of both eyes were unremarkable. Funduscopy of OD revealed a slightly elevated grey membrane on the macula, suggestive of an epiretinal membrane (ERM) with retinal thickening extending towards the peri-papillary area. Furthermore, tortuosity was observed along the inferior arcuate with radial retinal folds(Fig 1).

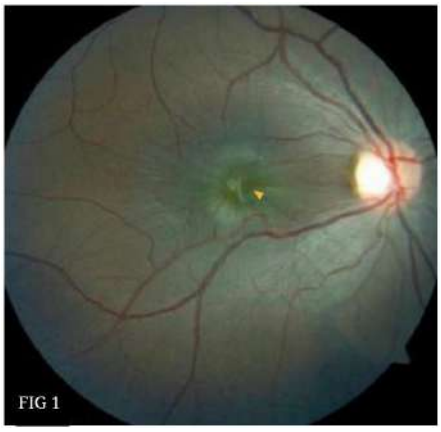


Fig 1: Epiretinal membrane on the macular area (asterix) with radial folds and vascular tortuosity.

Spectral-domain optical coherence tomography (SD-OCT) confirmed the presence of an ERM in OD with thickening and disorganization of the inner retina, particularly marked posteriorly by the outer plexiform layer (OPL), exhibiting saw-tooth-like corrugations along the vitreo-retinal interface. To gain more insights, multicolor imaging was conducted, which depicted epiretinal gliosis, retinal dragging, and striations localising the different layers of retina involved (Figures 2a-c).

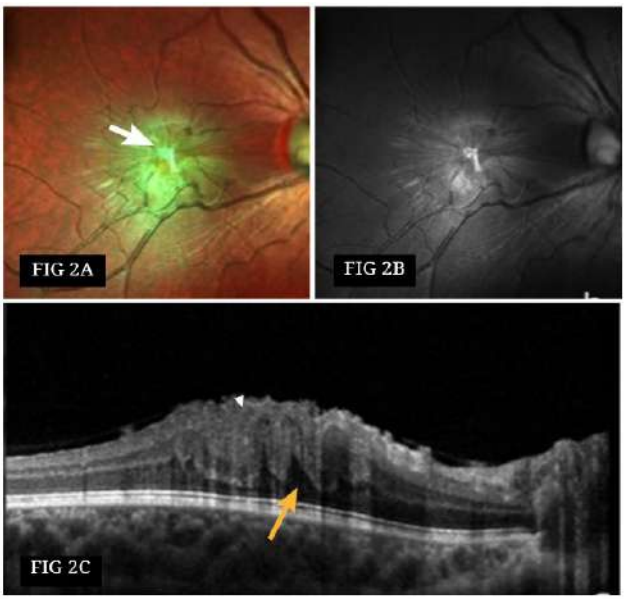


Fig 2a: Multicolor imaging showing prominent epiretinal pigment migration on the posterior fundus marked by greenish hue(asterix).**2b**: On Green Reflectance (GR), the extent of epiretinal folds and retinal dragging canbe clearly seen.**2c**: Spectral Domain Optical Coherence Tomography (SD-OCT) showing inner retinal disorganization (mini peaks shown by short arrow) limited by outer plexiform layer (Omega sign shown by long arrow) with relatively preserved outer retinal layers.

Optical coherence tomography angiography (OCTA) revealed significant distortion of the retinal microcirculation within the lesion, displaying tortuous vessels in both the superficial and deep vasculature (Figures 2 d).

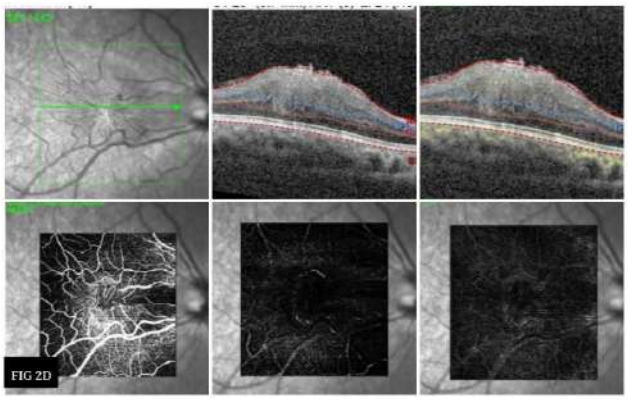
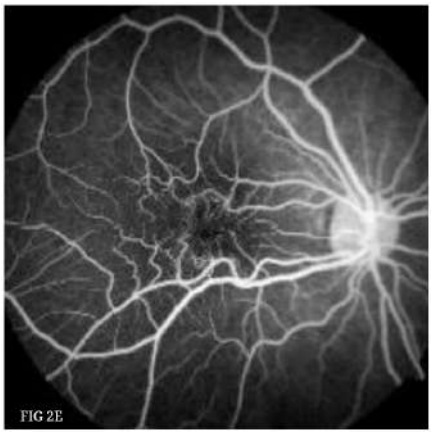


Fig 2d: Showing retinal vessels distortion in the superficial and deep capillary plexus.

Fluorescein angiography (FA) showed dilated and tortuous retinal vessels, although no active leakage was evident (Figure 2e).



The fundus of OS appeared normal. Subsequently, the patient underwent vitrectomy with membrane peeling in OD. Postoperatively, there was a decrease in retinal thickness with marginal visual improvement (6/18); however, in spite of some symptomatic improvement , there was no significant structural changes observed. (Figures 3a-c).

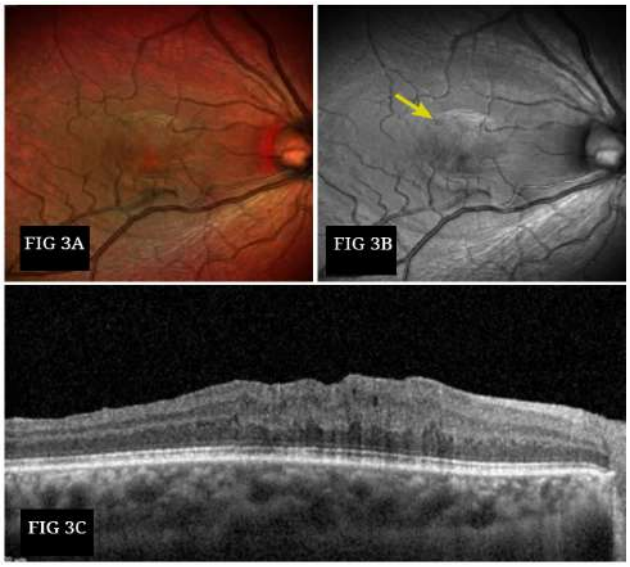


Fig 3**a:** Post operative multicolor imaging of right eye showing complete resolution of the epiretinal membrane visible with a reddish hue.**3b:** On GR, the extent of the membrane peeled area (arrow) is clearly highlighted.**3c:** SD-OCT showing decrease in the retinal thickness but persistence of structural abnormality of inner retinal layers is still seen.

Case 2: A 50-year-old male came with chief complaints of irritation in OD since one year. His BCVA in OD was found to be counting fingers close to face (CFCF), and in the OS was 6/6. The anterior segment of both eyes appeared unremarkable, and the intraocular pressure (IOP) was measured to be 13 mmHg in OD and 15 mmHg in OS. Fundus examination of OD revealed a superior peripapillary grey membrane, and no involvement of the macula was observed (Figure 4a). On SD-OCT, it displayed the presence of an ERM and marked disorganization of inner retinal layers with disruption of the ellipsoid zone and irregularities in the retinal pigment epithelium (Figure 4b).

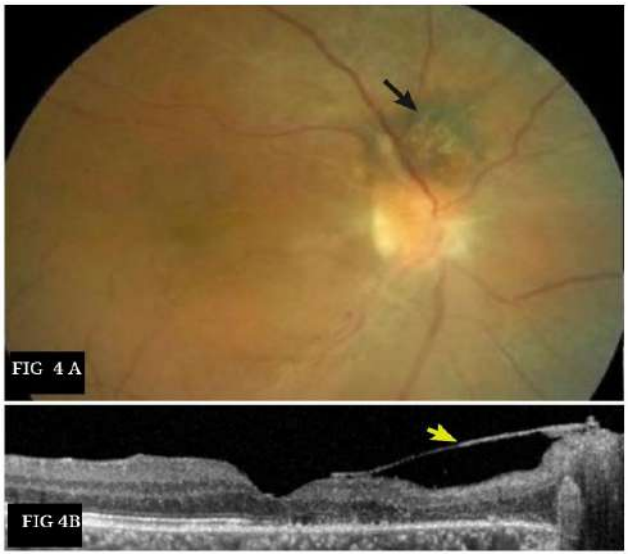


Fig 4a: Right eye showing superior peripapillary grey membrane not involving macula (asterix), 4b: showing epiretinal membrane (long arrow) with marked disorganization of inner retinal layers and disruptionof ellipsoid zone and retinal pigment epithelium.

On further diagnostic evaluation by Humphrey visual field testing, OD demonstrated an inferior altitudinal visual field defect (Figure 4c) while full-field flash visual evoked potential testing revealed normal latency and amplitude (Figure 4d).

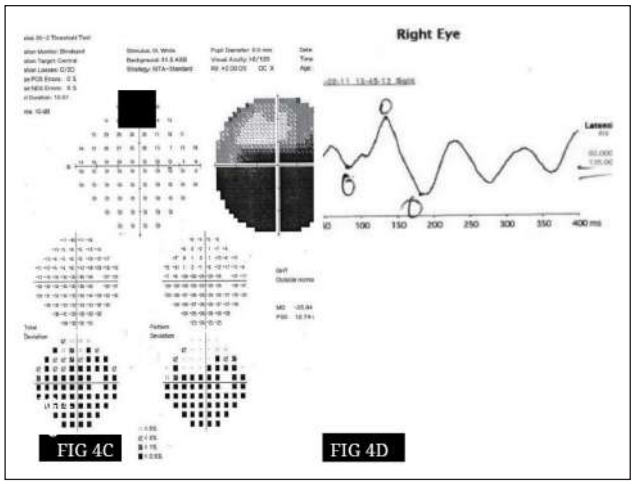


Fig 4 c: showing inferior arcuate visual field defect; 4d : showing normal latency and amplitude in visual evoked potential.

Case 3: A 29-year-old female presented with chief complaints of diminished vision in the OD persisting for the last 2 years. Her BCVA in OD was hand movements (HM), and in OS was 6/6. The anterior segment of both eyes appeared unremarkable, and IOP was measured to be 11 mmHg in OD and 13 mmHg in OS. Fundus examination of OD revealed a prominent greyish peripapillary membrane with distortion of the superficial retinal vasculature and tortuosity of blood vessels. The membrane also involved the macula, and intraretinal hard exudates were noted, particularly in the temporal parafoveal region and the inferior quadrant (Figure 5a). On Humphrey visual field testing of OD, it demonstrated a superior altitudinal visual field defect (Figure 5b). Ocular USG revealed a raised area over the optic nerve head with moderate to high surface reflectivity and mild to moderate internal reflectivity, with no shadowing observed (Figure 5c).

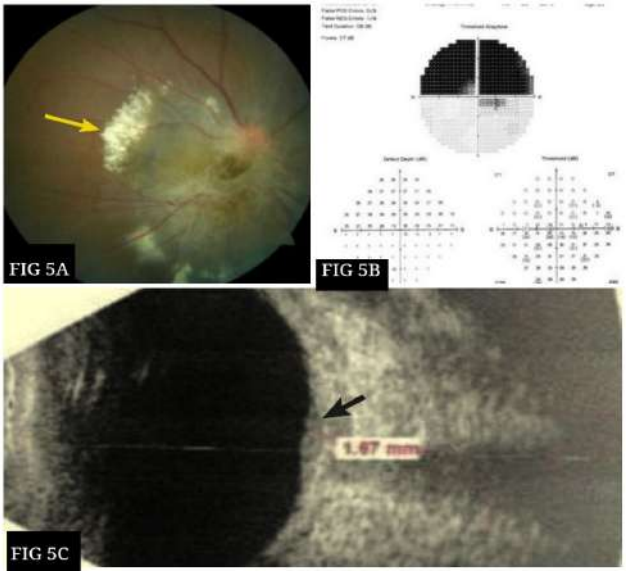


Fig 5 a: showing peripapillary membrane with intraretinal hard exudates (short arrow), 5b: showing superior altitudinal visual field defect ;5c: showing raised area over the optic nerve head (long arrow) with moderate to high surface reflectivity,mild tomoderate internal reflectivity with no shadowing .

Discussion:

Combined hamartoma of the retina and retinal pigment epithelium (CHR-RPE) is a rare presumed congenital benign intraocular tumor, characterized by a disorganized mound of glial, vascular, and melanocytic tissue originating from the retina and the RPE. [5] This uncommon tumor alters the retinal architecture, affecting the inner retinal layers and sometimes the deeper retinal layers and RPE, leading to hyperpigmentation, macular and papillary distortion, epiretinal membranes, and tortuous vessels. CHRRPE has been observed to occur more frequently in patients with neurofibromatosis type 2. Less common associations include neurofibromatosis type 1, Poland syndrome, Gorlin syndrome, and branchio-oculo-facial syndrome.Generally, CHRRPE lesions do not undergo malignant transformation but choroidal neovascularization may cause complications such as vitreous hemorrhage, retinoschisis, and macular holes. Diagnosis of combined hamartoma is typically made through indirect ophthalmoscopy and OCT, supported by other ancillary tests. Ultrasonographic examination reveals slightly raised, acoustically solid lesions with moderate to high surface reflectivity. In OCT findings, CHR-RPE exhibits thickened retinal tissue along with a distinct ERM and vitreo-retinal interface disturbances, as described by Shields et al.[7] Determining the size and extent of the tumor is crucial, especially if it encroaches upon the macula, as the degree of macular involvement significantly impacts

visual function. While OCT provides detailed structural analysis, it may not precisely determine the tumor's exact location.[1]ERMs are a prominent feature of combined hamartomas and are associated with "mini-peaks" of minor vertical vitreo-retinal traction and "maxi-peaks" involving the retinal folding of inner layers, along with distortion of OPL in a saw tooth configuration or omega sign.[8,9] FA shows hyperfluorescence in the lesion despite increased pigmentation in the RPE, as a result of RPE atrophy and cell migration. Microaneurysms and telangiectatic vessels may be observed, with minimal leakage from the tortuous vessels in the late phase. OCTA reveals filigree pattern of vascular network owing to the perivascular distribution of RPE cells around the tiny vessels with retinal vascular tortuosity and disorganized vascular networks in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) . Clinically, differentiating the boundaries of combined hamartomas can be challenging. However, multicolor imaging in Case 1 proved useful in precisely locating the tumor and surrounding retina by utilizing three different wavelengths. Green reflectance helped characterize epiretinal gliosis, illustrating retina dragging and defining the extent of inner retinal distortion. Hence, multicolor imaging and OCTA can be a valuable adjunct to OCT, aiding in establishing morphological features of the vitreo-retinal interface and inner retina, and influencing surgical management decisions.[1]Treatment and prognosis for CHRRPE involve periodic monitoring, and the role of epiretinal membrane peeling surgery remains controversial as visual improvement has been reported in younger patients but not in older patients.[10,11,12] Case reports demonstrate various surgical management approaches for ERM on CHR-RPE. In a case series by Zhang et al., visual improvement was reported in 60% of cases following ERM removal in CHR-RPE with a mean age of 12 years. Based on this, we decided to perform pars plana vitrectomy in Case 1, considering the patient's age and the extent of the lesion, which favored a positive outcome. However, in Cases 2 and 3, the age and structural loss of retinal layers were determining factors against surgery, as visual improvement would have been unlikely. Postoperatively in Case 1, there was only mild visual improvement, but there was a reduction in retinal thickness and vascular tortuosity.[13-17]Intravitreal anti-vascular endothelial growth factor (VEGF) injection can be administered in eyes with secondary choroidal neovascularization.Amblyopia treatment may be provided, but visual improvement is rarely achieved, and vision loss occurs in most cases.

In conclusion, selected patients with CHR-RPE can potentially benefit from pars plana vitrectomy with membrane peeling at an appropriate time, resulting in improved retinal architecture and visual acuity. OCT, OCTA and Multicolor imaging plays a significant role in understanding the anatomical characteristics of combined hamartomas, aiding in diagnosis, guiding management decisions, and providing valuable prognostic information.

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JOURNAL OF
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Case series

Tenon Cyst Patch Graft for Ahmed Glaucoma Valve Tube Exposure

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Purpose

To report our experience using a Tenon cyst autograft in the management of tube exposure post Ahmed glaucoma valve (AGV) implantation. **Methods**: This is a retrospective case series. **Results**: Four patients who underwent tube exposure repair using Tenon cyst autograft were identified in our tertiary care center. The duration between initial AGV implantation and tube exposure ranged between 3 and 36 months with a mean of 16 months (± 14.35 mo). All patients were followed postoperatively for a range of 4 to 24 months with a mean of 11.75 months (± 9.03 o) and all remain exposure free at last follow-up. **Conclusion:** The use of a Tenon cyst autograft for the surgical repair of a tube exposure is valuable, as it involves using autologous scar tissue that is available in eyes that have undergone AGV implantation. The patch autograft is technically easy to harvest, and represents a significantly lower cost when compared with other available options.

Key Words: glaucoma drainage device, erosion, wound repair, autograft, Tenon cyst

Glaucoma drainage device (GDD) implantation is one of the most frequent surgeries performed in glaucomatous eyes that require significant intraocular pressure (IOP) lowering.[1–3] As with any surgical intervention, a variety of complications may occur after implanting GDDs including prolonged hypotony, choroidal detachment, tube or plate migration, and corneal decompensation, among others. Another major complication of GDD implantation include failure due to encapsulation as well as tube exposure which has been reported in multiple published studies.[4–9] Exposure of the tube and/or plate is associated with melting or erosion of tissues overlying the device hardware. Depending on the location of the erosion, tissues involved can include sclera, patch graft materials, Tenon capsule and and conjunctiva. It has been suggested that micro-movements of the device secondary to ocular pulsation and blinking is a major cause of tissue erosion post GDD surgery. Compromised tissue due to prolonged glaucoma medication exposure is also likely an associated factor. Tube and plate exposure can lead to hypotony, endophthalmitis, and phthisis bulbi.[10-12]

Removal or relocation of the GDD, along with replacement of the patch graft, has been proposed as an effective repair method with different success rates, depending on the technique reported.[13] Several patch graft materials such as human sclera, cornea, *dura mater*, fascia *lata*, buccal mucosa, and acellular dermis, bovine pericardium, and synthetic materials like collagen matrix and polyetrafluoroethylene have all been used to repair exposed drainage devices.[14] Commercial patch graft materials are not available in all operating rooms and are costly, especially when compared with autografts, which are available at virtually no cost. Device encapsulation with Tenon cyst formation post GDD surgery is not uncommon and can lead to failure of IOP control along with other complications such as double vision and discomfort. Excision of the Tenon cyst or capsule over the plate is often needed to control IOP.[1,15-18] Even though the formation of scar tissue around the plate in the form of a Tenon cyst is usually considered a complication, it can be useful in the setting of GDD tube exposure, as surgeons can use it as an autograft to cover the exposed area when both encapsulation and tube erosion co-exist. In this case series, we report on the use of Tenon cyst tissue to repair coexisting tube erosion in eyes post Ahmed glaucoma valve implantation.

Methods

This is a retrospective case series which was approved by the institutional review board and Ethics Committee. All patients consented to the publication of their cases and photographs. We examined the clinical data of 4 patients who attended the glaucoma clinic with a diagnosis of coexisting Tenon cyst and tube erosion. Data obtained from medical records included demographics, medical/ ophthalmological history, intraoperative, and postoperative information.

The surgical technique is detailed with accompanying photographs

Surgical Technique

Under peribulbar or retrobulbar anesthesia, subconjunctival lidocaine (1 mL) is injected using a 31-G needle far from the conjunctival defect. A weck-cel spear or cotton swab is used to gently spread open the conjunctiva and Tenon capsule while distributing the anesthetic to assist with dissection.The conjunctiva is incised at the limbus to create a fornix-based peritomy and conjunctival dissection around the exposed area, the tube, and over the Tenon cyst covering the GDD plate is performed (Figs. 1A, A1). Once the tube and plate are exposed, it must be assured that the conjunctiva is well dissected posteriorly to allow traction and mobilization. A 15-degree blade is used to make a full-thickness incision of the Tenon cyst at the base of the plate (Fig. 1As, A1). The incision is extended posteriorly and laterally by holding the Tenon cyst with micro forceps, and unroofing the plate with Wescott or corneal scissors (Figs. 1B, B1).

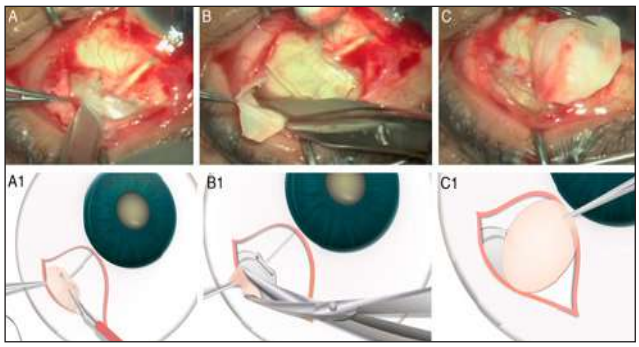

Figure 1. A and A1, The tube and plate are exposed after conjunctival dissection, and a 15 blade is used to perform a full-thickness incision in the cyst. B and B1, The cyst is held with micro forceps and cut with Westcott or corneal scissors to unroof the plate posteriorly. C and C1, The excised cyst covers the complete length and width of the plate.

Once the excision is complete and the plate is exposed, the position of the tube and the conjunctiva are evaluated. If the position of the tube has an increased risk of re-erosion due to bending or kinking, the tube is relocated to an entry point distant from the initial tube course. Once the tube is in an acceptable position, the Tenon patch graft is sutured over the tube using 10-0 nylon suture (Fig. 2).

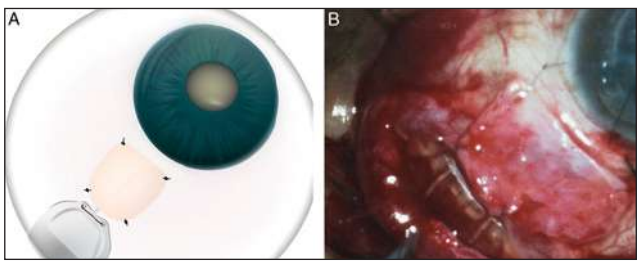

Figure 2. A and B, The tube is covered with the graft and secured with 10-0 nylon suture.

The conjunctiva should be closed at the limbus and not over the tube or plate to prevent re-exposure. The conjunctival closure at the limbus avoids conjunctival damage secondary to rubbing of eyelid against the tissue. Postoperative management includes topical antibiotic 4 times per day for 1 week as well as prednisolone 1% or fluorometholone (depending on surgeon preference) 4 times per day tapered over 6 to 8 weeks.

Results

Case 1

A 57-year-old female with diagnosis of Sjogren dyndrome secondary to rheumatoid arthritis and previous penetrating keratoplasty due to corneal perforation in the left eye developed secondary glaucoma that required a supero-temporal AGV implantation. Sixteen months after AGV surgery, the patient presented with hand motion vision and conjunctival erosion with tube exposure. The patient was also noted to have Tenon cyst formation which was stable from past exams. Tenon cyst autograft technique was utilized for repair of the exposure and the patient remained stable after 4 months of follow-up with hand motion vision and IOP at 10 mm Hg off all IOP lowering medications (Fig. 3).

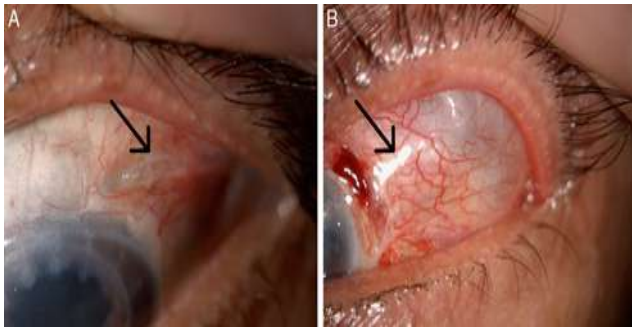

Figure 3. A, Ahmed glaucoma valve (AGV) tube exposure in the supero-temporal quadrant. Arrow shows the exposed tube. B, Early postoperative photograph shows the AGV tube covered by the autograft and overlying conjunctiva. Arrow shows the previously exposed area covered with conjunctiva.

Case 2

A 73-year-old male with diagnosis of neovascular glaucoma secondary to proliferative diabetic retinopathy in the left eye underwent supero-temporal AGV implantation. At postoperative month 3 the patient presented with VA at count fingers and exposure of the tube without signs of infection. A co-existant Tenon cyst was also noted. The patient underwent surgical repair of the exposure using the Tenon cyst patch graft technique. At postoperative month 6, the patient presented with best-corrected visual acuity (BCVA) of 20/800 and IOP of 16 mm HG on 3 IOP lowering medications. The tube and plate were fully covered at this last follow-up (Fig. 4).

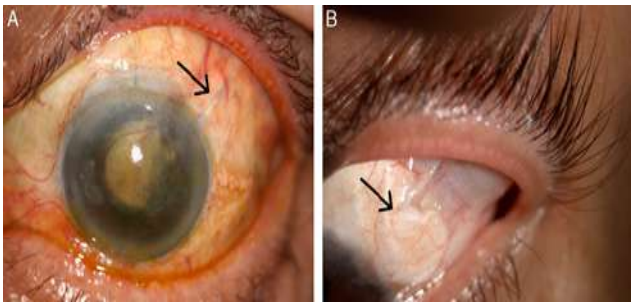

Figure 4. A, Ahmed glaucoma valve tube exposure quadrant near the limbus, neovascular glaucoma and diabetic cataract are evident, with no signs of superficial or intraocular infection. B, Postoperative image show the healed graft and conjunctiva after erosion repair.

Case 3

A 72-year-old female with diagnosis of right eye steroid-induced glaucoma underwent AGV implant supero-temporally and subsequently presented 3 years later with coexisting Tenon cyst and eroded conjunctiva and sclera resulting in tube exposure. At postoperative month 12 after tube exposure repair with Tenon cyst autograft, the patient had a BCVA of 20/200 and IOP of 14 mm Hg on 3 IOP lowering medications and with no signs of recurrence of conjunctival erosion.

Case 4

A 58-year-old female with history of right eye secondary glaucoma after a penetrating keratoplasty was treated with an AGV implantation 9 months before presenting with eroded conjunctiva and tube exposure, Tenon cyst formation and no signs of infection.

The patient underwent tube exposure repair with Tenon cyst autograft. At postoperative year 2, the patient presented with BCVA of 20/200, IOP at 20 mm Hg on 1 IOP lowering medication, and without signs of recurrence of tube exposure (Fig. 5).

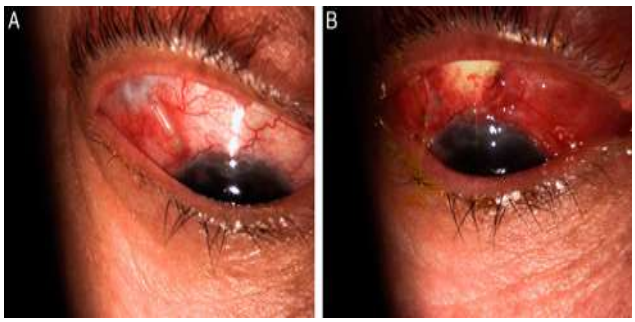

Figure 5. A, Supero-temporal Ahmed glaucoma valve tube exposure. B, Early postoperative aspect of supero-temporal area with no signs of erosion or exposure.

In the 4 cases, the Tenon cyst autograft technique performed well in the different clinical scenarios throughout the different follow-ups. All patients ended their follow-up with no re-erosion, with a lower IOP and a reduction of glaucoma medications (Table 1).

Case	Diagnosis		BCVA	IOP (mm Hg)	Glaucoma medications	FUP (Months)
1	PKP associated glaucoma	Baseline	HM	40	3	4
2	NVG	Post op	HM	10	0	6
		Baseline	CF	20	4	
3	Steroid induced glaucoma	Post op	20/200	16	3	13
		Baseline	20/800	14	3	
4	PKP associated glaucoma	Post op	20/200	14	3	24
		Baseline	20/200	26	4	

BCVA- Best corrected visual acuity, IOP- Intraocular pressure, NVG- Neovascular glaucoma, PKP- Penetrating keratoplasty, HM- Hand motion, CF- Counting fingers

Discussion

GDD implantation has been widely recommended for patients that require significant IOP lowering, especially for those with refractory glaucoma and high risk of surgical failure with other surgical interventions. However, tube or plate exposure is not uncommon and has been described in 2% to 7% of patients undergoing this intervention. Tube and plate erosion can lead to sight-threatening complications such as endophthalmitis and phthisis bulbi.[4-9]

The implementation of a patch graft to cover the tube when a primary GDD is implanted, reduces the rate of exposure in the long-term from 30% to 5% as reported by Ainsworth et al.[19] Different materials such as autologous and donor ocular and extraocular tissues, synthetic materials (scaffold collagen matrix, polytetrafluoroethylene),[20] and other techniques like the partial-thickness flap or long scleral tunnel have been described when implanting a GDD.[18-20]

Even though the use of graft material is helpful to decrease the re-erosion rate in cases in which a previous tube exposure is reported, there is no strict evidence-based recommendation for the use of a specific graft material as it relates to safety or success. Commonly reported patch grafts used to repair exposed GDDs include human sclera and cornea, autologous Tenon capsule and conjunctiva, fascia lata, buccal mucosa, acellular dermis, amniotic membrane, dura mater, pericardium (bovine), and synthetic materials like expanded polytetrafluoroethylene and collagen matrix.[20]

Even though success rates are similar between patch grafts, using an autograft instead of an allograft allows for some advantages. Autografts are readily available, do not require special handling or storage and are stronger in structure than tissues that have been sterilized and processed. A case report on the use of autologous scar tissue as a patch graft to cover an exposed tube was published by Puustjarvi and colleagues in 2007. They also reported the microscopic findings of the encapsulated membrane scar tissue (collagen I, III, and IV), supporting the idea that Tenon cyst could be a good option to use as a patch graft.[18]

The process of obtaining autograft tissues from extraocular sites or from the contralateral eye involves a "secondary" surgical procedure that can introduce added surgical risk and complications. Using autologous tissue from the same eye has the added benefit of reducing invasiveness and limiting risk in other areas of the body. Also, the technique to obtain the Tenon cyst graft is straightforward and does not involve the use of special instrumentation. In most cases it is feasible to obtain a 3x3 mm graft or larger, which is adequate to cover the tract of the tube (Figs. 1C, C1). It is important to consider that after incising and removing the cyst, the anterior chamber may collapse due to lack of resistance to egress of aqueous humor out of the eye. The surgery may then become more complex due eye wall instability, and can also increase the risk of malignant glaucoma, choroidal detachment and expulsive hemorrhage. This can be managed by reforming the anterior chamber with air, balanced salt solution, or viscoelastic.

In the Tenon cyst patch graft technique we describe, the autograft is obtained from the same eye without invading healthy tissue. Also, there is an additional decrease in IOP and glaucoma medication use when the excision of the cyst is performed, since it enhances outflow of aqueous humor and overall functionality of the GDD procedure.[14] A Tenon cyst will develop after 6 to 8 weeks in most of the patients that have undergone a primary AGV implantation. Even though there is no high-quality evidence regarding the incidence of Tenon cyst after a GDD implantation, encapsulation is one of the most common complications of AGV.[21,22]

There are some notable limitations for this report including a small sample size and retrospective nature of data collection. Still, the utility of the described approach to repairing ocular tissue erosion and evidence of success may be of particular relevance to resource poor areas where the economics of using expensive patch graft material or the added cost of a second procedure to harvest autograft material from a distant site are prohibitive. In this case series we describe 4 cases that underwent Tenon cyst autograft technique for surgical repair of tube exposure. The 4 cases have varied clinical scenarios and different follow-up times. In all the cases, this technique performed well at repairing the exposure without re-exposure in both short and long-term follow-up. IOP and the number of IOP lowering medications also decreased after the Tenon cyst was excised.

Conclusion

The use of a Tenon cyst autograft for surgical repair of a tube exposure is a viable option to address tube exposure in eyes post AGV implantation. The patch autograft is technically easy to harvest, and represents a significantly lower cost when compared with other grafts.

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Case report

SMLT for refractory exudative Perifoveal vascular anomalous complex(ePVAC)

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Abstract

Purpose : To report a case of exudative perifoveal vascular anomalous complex treated with a 532-nm subthreshold micropulse laser unresponsive to intravitreal injections. Methods: A case report. Results: A 56-year-old man presented with blurred vision in the left eye for 1 month. An isolated perifoveal aneurysm surrounded by retinal hemorrhages and hard exudates was revealed in fundus examination, and optical coherent tomography showed a round lesion with a hyperreflective wall, subretinal fluid, and an intraretinal cyst. He was diagnosed with exudative perifoveal vascular anomalous complex and received four intravitreal injections. However, his best-corrected visual acuity decreased, and an aneurysmal lesion with macular edema persisted for approximately 6 months. Three sessions of 532-nm subthreshold micropulse laser therapy around the aneurysm were applied because the intravitreal injection treatment was ineffective. Since the last session, macular edema disappeared, the involuted lesion remained substantially stable without recurrence, and his best-corrected visual acuity improved without visual field defect. Conclusion: subthreshold micropulse laser treatment could be a safe and effective method for the patient unresponsive to intravitreal injections.

Key words: exudative perifoveal vascular anomalous complex; subthreshold micropulse laser

Perifoveal vascular anomalous complex (PVAC) has been described as an uncommon macular disorder defined by a unilateral, isolated, perifoveal aneurysm in otherwise healthy patients and recently renamed with exudative stage (ePVAC) and the nonexudative stage (nePVAC).[1,2] It is assumed to be the result of a focal and progressive, retinal, vascular, endothelial cell injury in the absence of retinal ischemia or inflammation. Therefore, this could explain the reason for the unresponsiveness of PVAC to intravitreal anti-vascular endothelial growth factor (VEGF) injection.[2-4] Mrejen et al [4] reported on a PVAC treated with focal thermal laser photocoagulation, but there is currently no standard treatment protocol for PVAC.

Rather than conventional laser photocoagulation, nondamaging retinal laser therapy with a subthreshold micropulse laser (SMPL) has been demonstrated as a promising treatment option for macular diseases because of the safety of SMPL treatment without detectable damage in retinal pigment epithelium or photoreceptors.[5] In this report, we describe an unusual case of ePVAC treated with multiple sessions of SMPL that was previously unresponsive to intravitreal injection treatment.

Case Report

A 56-year-old man presented to our clinic with blurred vision in the left eye lasting 1 month. He had no other relevant medical or surgical history. His best-corrected visual acuity was 6/6 in the right eye and 6/12 in the left eye. Intraocular pressure was normal, and anterior segment examination was unremarkable in both eyes except mild nuclear cataracts. Fundus examination of the right eye showed normal reuslts. However, fundus examination and photography of the left eye showed an isolated perifoveal aneurysm surrounded by small retinal hemorrhages and hard exudates. The bulb-like aneurysm was located at one of the terminal arteriolar ends in the superior perifoveal area (within 500 *[micro]*m). Multimodal imaging was performed using a fundus camera (Visucam 224; ZEISS, Oberkochen, Germany), spectral-domain optical coherence tomography, and optical coherent tomography angiography (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography revealed a well-defined hyperfluorescent lesion in the early phase but with leakage in the late phase. Optical coherence tomography showed macular edema with 542 *[micro]*m of central macular thickness and a round lesion (diameter, 314 *[micro]*m) with a hyperreflective wall, subretinal fluid, and an intraretinal cyst. Optical coherent tomography angiography

revealed blood flow of the isolated large aneurismal lesion in the deep capillary plexus corresponding to the leaking point on the fluorescein angiography (Figure 1).

tomography examination. Optical coherent tomography angiography continued to show the blood flow of the lesion in the deep capillary plexus (Figure 2).

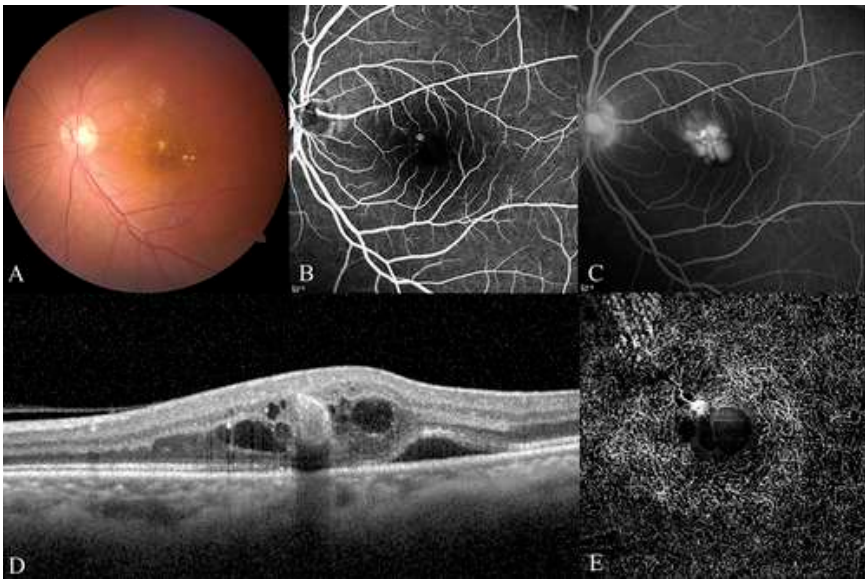

Fig. 1. Multimodal imaging of the left eye at the initial visit. A. **Fundus photography showed a large aneurysm, retinal** hemorrhage, and hard exudates. B. **Fluorescein angiography revealed a well-defined hyperfluorescent lesion in the early phase but with leakage in the late phase(**C). D. **Optical coherence tomography showed a round lesion with a hyperreflective** wall, subretinal fluid, and intraretinal cyst. E. **Cross-sectional optical coherence tomography angiography visualized blood flow of the isolated aneurysmal lesion in the deep capillary plexus.**

lesion except for the fovea directly, and three or four shots were applied repeatedly on the aneurysmal point, which was considered the main leakage point (Figure 3). However, macular edema with an intraretinal cyst remained 2 weeks after the first SMPL. We applied the second session with modified settings: 100-millisecond duration, 10% duty cycle, and 300 mW power. An optical coherence tomography examination 1 month after the second session showed that the macular edema with intraretinal cyst decreased (central macular thickness, 462 *[micro]*m). We applied the third session according to the modified settings. Three month after the third session, the patient's best-corrected visual acuity had improved to 20/50, and the retinal hemorrhage and hard exudates had decreased. Optical coherence tomography showed the shrinkage of the round lesion (diameter, 125 *[micro]*m) compared with the previous image and resolution of macular edema (central macular thickness, 222 *[micro]*m); however, focal disruption of ellipsoid zone around the round lesion was

Based on these characteristics, the patient was diagnosed with ePVAC. Initially, intravitreal injection of anti-VEGF was considered, although this method has been reported to be less effective. The patient received three monthly intravitreal injections of two bevacizumab (Avastin; Genetech Inc, San Francisco, CA) and one aflibercept (Eylea; Regeneron Pharmaceuticals Inc, Tarrytown, NY), but there was no distinct treatment effect. We performed additional injection of triamcinolone acetonide. The subretinal fluid and hard exudates decreased slightly, but the intraretinal cyst remained, then gradually increased for 3 months (central macular thickness, 511 *[micro]*m). The patient's best-corrected visual acuity decreased from 6/12 to 6/60 in the left eye over the 6 months during which she received 4 intravitreal injections. Moreover, a round lesion with a hyperreflective wall persisted. The intraretinal cyst and hard exudates also remained in fundus photography and optical coherence

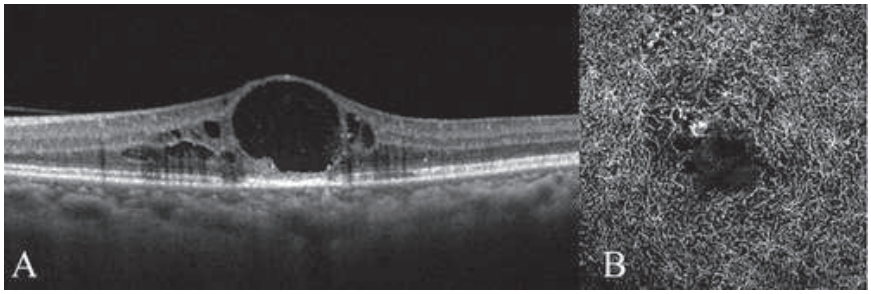

Fig. 2. A. Even after four intravitreal injections, the intraretinal cyst in the fovea remained upon optical coherence tomography examination. B. Optical coherence tomography angiography still showed the aneurysmal lesion in deep capillary plexus.

We performed multiple sessions of 532 nm SMPL around the aneurysm (IQ 532; Iridex, Mountain View, CA) using an Ocular Mainster focal/grid (x1.05) lens (Ocular Instruments Inc, Bellevue, WA) with following setting: 100-*[micro]*m spot diameter, 2 x 2 matrix pattern mode (0.25 width), and low power ranging from 300 to 400 mW, which was increased in 50-mW increments every 3 to 4 weeks. In the first session, we used a 50-millisecond duration, 5% duty cycle, and 300 mW power. Subthreshold micropulse laser was applied only around the ePVAC

remained. The aneurysmal lesion was no longer visible on optical coherent tomography angiography slabs, and fluorescein angiography did not show leakage from the lesion in the early and late phases (Figure 4). Humphrey 10-2 visual field examination (HFA 720i; Carl Zeiss, Dublin, CA) demonstrated that there was no scotoma around the lesion. The patient's best-corrected visual acuity had improved to 6/9 in the left eye at 6 months after the last SMPL treatment.

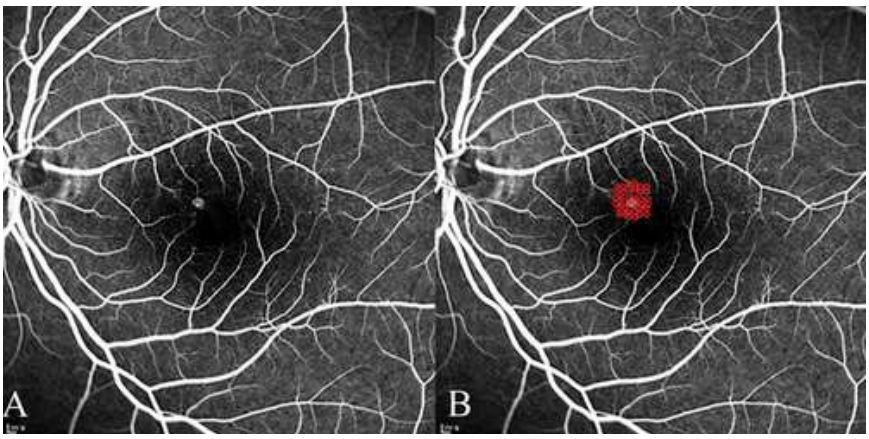

Fig. 3. A. Fluorescein angiography of the early phase showed a hyperfluorescent lesion. B. Simulated image of the subthreshold micropulse laser mode. The red dots represent the area where the laser was applied.

Discussion

Perifoveal vascular anomalous complex, which was first reported in 2011 by Querques et al,[2] is described as an isolated aneurysmal lesion, occurring unilaterally with no systemic or ocular conditions associated with the aneurysmal lesion and recently characterized with exudative and nonexudative type.[1] However, its prevalence, pathogenesis, course, and treatment had remained unclear. Sacconi et al [3] reported that approximately half of the eyes with PVAC had concomitant retinal disorders, such as concomitant age-related macular degeneration or myopia. Kim et al [6] also reported that the majority of patients were healthy and that two patients also had age-related macular degeneration.

Unlike other macular diseases, PVAC is known to be unresponsive to intravitreal injection of anti-VEGF.[2-4] In addition, in this case, intravitreal injection of triamcinolone acetonide was also ineffective. Perifoveal vascular anomalous complex is assumed to be the result of a focal and progressive retinal vascular endothelial cell injury in the absence of retinal ischemia or inflammation.[2-4,6] It is postulated that PVAC is a response to an anatomical variation and is not associated with VEGF levels. Spaide and Barquet [7] reported cases of retinal capillary macroaneurysms treated with the focal laser photocoagulation, which we presumed had the same pathogenesis as PVAC. They proposed

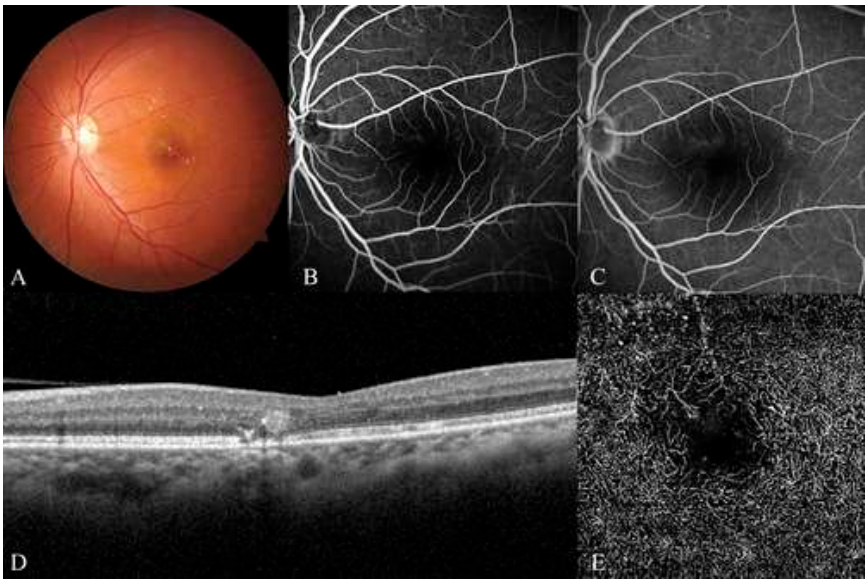

Fig. 4. Multimodal imaging of the left eye after subthreshold micropulse laser applications. A. Fundus photography showed decreased aneurysm, retinal hemorrhage, and hard exudates. B. Fluorescein angiography did not show a hyperfluorescent lesion in the early phase (C) and leakage in the late phase. D. Optical coherence tomography showed the resolution of macular edema, but focal disruption of ellipsoid zone around the lesion remained. E. The aneurysmal lesion was no longer visible in deep capillary plexus upon optical coherence tomography angiography examination.

that retinal capillary macroaneurysms were caused by the presence of matrix metalloproteinase-9, which may work to decrease the structural integrity of the basement membrane, potentially decreasing the wall strength and inducing the aneurysmal expansion. These expansionary factors are not necessarily VEGF dependent, and anti-VEGF agents may not have much of a beneficial effect. The coagulation effect of the laser was suggested as the treatment leading to the involution of the aneurysmal lesion and resolution of leakage.

The treatment of ePVAC has not been established. Recently, there was a single case report that described successful treatment with focal laser photocoagulation after the failure of intravitreal anti-VEGF injections.[4] Laser photocoagulation has been used for many years as an effective treatment of retinal disease as a means to improve oxygenation of the retina and production of heat shock protein, which triggers the repair process of the retinal tissue. However, laser photocoagulation can also involve the destruction of retinal tissue, including visible retinal tissue scar, laser scar enlargement, secondary hemorrhage, or secondary choroidal neovascularization. It can lead to functional impairment such as scotoma or visual field loss and should not be considered in macular disease because of the risk of permanent paracentral scotoma.[5]

Subthreshold micropulse laser has emerged as a new noninvasive and effective treatment for retinal disease.

The laser impact is delivered in a train of short impulses between which there are some intervals to allow the retinal tissue to cooldown, so the laser impact does not have any track on the retina. Consequently, SMPL has been used in the treatment of retinal diseases that involve the fovea, such as central serous chorioretinopathy, diabetic macular edema, or edema secondary to retinal vein occlusion.[5]

We had experiences with treating idiopathic macular telangiectasia (MacTel) Type 1 and central serous chorioretinopathy without retinal damage using SMPL therapy. We also applied SMPL to the patient reported herein, who was diagnosed with ePVAC that did not respond to intravitreal injection therapies. We followed a similar SMPL protocol as that described in previous reports.[8,9] We increased the duty cycle and duration after the first session of SMPL on the aneurysmal lesion more repeatedly to expect closure of aneurysm. After treatment, the involution of aneurysm was achieved; however, it was not clear whether it means preclinical nonexudative stage PVAC stage or complete resolution.

In summary, this patient with ePVAC showed improved visual acuity and resolution of macular edema after SMPL treatment. According to these results, SMPL treatment could be a safe and effective method for treating patients with ePVAC that is unresponsive to intravitreal injection therapies. In the short-term follow-up, there has been remained focal ellipsoid zone disruption around the lesion after the resolution of macular edema. It seems necessary to observe the restoration of ellipsoid zone disruption after SMPL application in long-term follow-up.

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Case series

Descemetopexy for Descemet's Membrane Detachment

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Abstract

Descemet's membrane detachment (DMD) is an uncommon, vision-threatening, ocular surface complication of cataract surgery. Among several treatment strategies, sulfur hexafluoride (SF_6) descemetopexy is the standard of care. Herein, we report three cases of DMD after cataract surgery managed with SF_6 descemetopexy, showing different outcomes. Anatomical success was achieved in cases 1 and 2 while intraocular pressure (IOP) was elevated in case 2. In case 3, despite SF_6 descemetopexy, recurrent DMD was observed. Due to persistent corneal edema and possible corneal decompensation in case 3, Descemet's stripping automated endothelial keratoplasty was performed and a clear graft was found at the final visit. In conclusion, descemetopexy with 20 % SF_6 is an effective and safe procedure for repairing DMD in most cases. Pupillary block with elevated IOP is another concern and prophylactic peripheral iridectomy is recommended. For recurrent DMDs, repeat descemetopexy could be considered. However, close monitoring is advocated since secondary management, such as endothelial keratoplasty, may be required.

Keywords: ocular surface; treatment; descemet's membrane detachment; sulfur hexafluoride descemetopexy

Introduction

Descemet's membrane (DM) detachment (DMD), first reported in the late 1920s, is an uncommon but vision-threatening complication of cataract surgery.[1] The most common cause of DMD is cataract surgery.[1] but other surgeries, such as iridectomy or penetrating keratoplasty, can cause DMD.[2] In cases of less severity, DMD may resolve spontaneously without treatment. [3,4] However, in cases of extensive DMD spreading to the corneal center, early surgical intervention is advocated to prevent corneal edema and decline in visual acuity.[5,6]

There are several surgical interventions to manage DMD, including the injection of air, viscoelastic materials or expandable gases into the anterior chamber (AC) and suturing DM to the stroma.[7] Descemetopexy with air was first applied by Spark et al. in 1967 for extensive DMD and showed a good anatomical outcome.[8] However, AC tamponade with non-expansile and expansile gases such as sulfur hexafluoride (SF_6) or perfluoropropane (C_3F_8) has recently gained popularity as a method to avoid fast absorption of air.[9] Zusman first reported SF_6 descemetopexy of an intractable DMD in 1987 [10] Since then, both air and SF_6 have been used widely but no strong evidence supports what is the more appropriated gas to deal with DMD. Chaurasia et al. and Singh et al. have suggested air descemetopexy as a safe treatment option for DMD in most patients.[11,12]; however, some researchers prefer the long-lasting effect of SF_6 descemetopexy.[1,13] Air resolution occurs within 3–4 days and might not be long enough for reattachment of the DM. Repeat descemetopexy to reach fair visual and anatomical outcomes in some cases may indicate the need for longer tamponade.[14] Although SF_6 descemetopexy had been proposed as initial management, it has different outcomes. For cases of failed SF_6 descemetopexy, further treatment remains controversial and is decided on a case-to-case basis.

Here, we report a case series of three cases of DMD that occurred after cataract surgery and managed with descemetopexy using a single injection of 20% SF_6. We analyzed the different conditions of the three patients, including the possible causes of the poor visual outcome with anatomical success in case 1, increased intraocular pressure (IOP) in case 2 and failed descemetopexy that resulted in corneal transplantation in case 3.

Material and Methods

This case series included three eyes of three patients who were diagnosed with DMD after phacoemulsification surgery. Further, the outcomes after descemetopexy with 20% SF_6 were evaluated. We received signed informed consent forms from all patients.The study was approved by institutional review board. Best-corrected visual acuity (BCVA) was obtained by correcting the refractive error with suitable glasses. All the patients underwent a comprehensive eye examination with a slit-lamp biomicroscopy (Topcon, Japan), which consists of an intense light source that can narrow light into a slit and biomicroscope. Both the anterior and posterior eye segments were examined. In the case of DMD, the slit lamp can reveal the extent (large area or not), location (peripheral or central) and distance of the DM separation from stromal side and the severity of the corneal edema. The volume of the degraded bubble in AC after descemetopexy was also documented.

High-speed anterior segment optical coherence tomography (AS-OCT; Optovue, CA, USA) is a noncontact method using a 1310-nm wavelength to provide objective and high-resolution images. The structure of the anterior segment, such as the corneal thickness, DM, anterior chamber depth, lens thickness and chamber angle, can be assessed and quantified. AS-OCT is particularly useful in the detection of early and minimal DMD when the corneal is edematous with poor visualization by slit-lamp biomicroscopy. The area of DMD delineated by slit-lamp biomicroscopy can be confirmed further by AS-OCT before and after intervention.

The descemetopexy procedure was performed under retrobulbar anesthesia and 5% betaiodine disinfection. A 0.2-mL 20% SF_6 injection was administered through a paracentesis via a bevel-up 30-gauge needle with a 1-mL syringe. The entry site was the site where the DM was still attached and filled with 70% of the AC volume. The patient was advised to remain in the supine position. Peripheral iridectomy (PI) was performed using Westcott scissors. The entry wound for the PI was sutured with 10-0 nylon. The procedures were all performed by the same operator in the operating room.

Results

The patients' demographic characteristics, including age, sex and clinical characteristics, including the operated eye, BCVA of the pre-cataract surgery, DMD diagnosis, post-descemetopexy 20% SF_6 injection, DMD features and time from surgery to descemetopexy are summarized in Table 1. We described DMD as a either a planar or nonplanar type,[15] depending on whether the DM and stroma separation was greater than 1 mm or not and as peripheral or central DMD,[16] depending on whether the detachment area involved a visual axis or not, in our cases, on slit-lamp biomicroscopy and AS-OCT. The BCVA at DMD diagnosis of case 2 was not available and the DMD features were evaluated by an experienced operator only because the descemetopexy with 20% SF_6 was performed intraoperatively.

Table 1. Demographics and clinical characteristics of patients with Descemet's membrane detachment after cataract surgery.

Case	Age/Sex	Eye	Surgery	Pre-Cataract Surgery BCVA	BCVA at DMD Diagnosis	DMD Features	Time from Surgery to D-Pexy (D)	Surgical Procedure	Final BCVA
1	81/M	R	Phaco/IOL	20/200	20/800	Central, nonplanar	21	SF_6 + PI	20/200
2	81/F	L	Phaco/IOL	20/60	NA	Central, nonplanar	intraoperative	SF_6 and then PI	20/30
3	82/F	L	Phaco/IOL	20/100	20/200	Central, nonplanar	22	SF_6+ PI and then DSAEK	20/50

BCVA = best-corrected visual acuity; DMD = Descemet membrane detachment; D-pexy = Descemetopexy; DSAEK = Descemet's stripping automated endothelial keratoplasty; NA = not available; Phaco/IOL = phacoemulsification and intraocular lens implantation; PI = peripheral iridectomy; SF6 = sulfur hexafluoride.

Case 1

An 81-year-old man, who had undergone a cataract surgery in the right eye 2 weeks before, presented with persistent corneal edema. The BCVA was 20/800 in the right eye. Examination revealed DMD in the central-lower portion with bullous formation (Figure 1A) and AS-OCT showed the same finding (Figure 1B). Descemetopexy with 0.2 mL of 20 % SF_6 and PI were performed. One day later, silt-lamp revealed corneal edema regression and AS-OCT showed DM reattachment (Figure 1C,D). Nine days later, the bubbles in AC had disappeared (Figure 1E) and the cystic edema had subsided (Figure 1F). Six months later, BCVA was 20/200 without obvious corneal edema (Figure 1G). The patient was lost to follow-up afterwards.

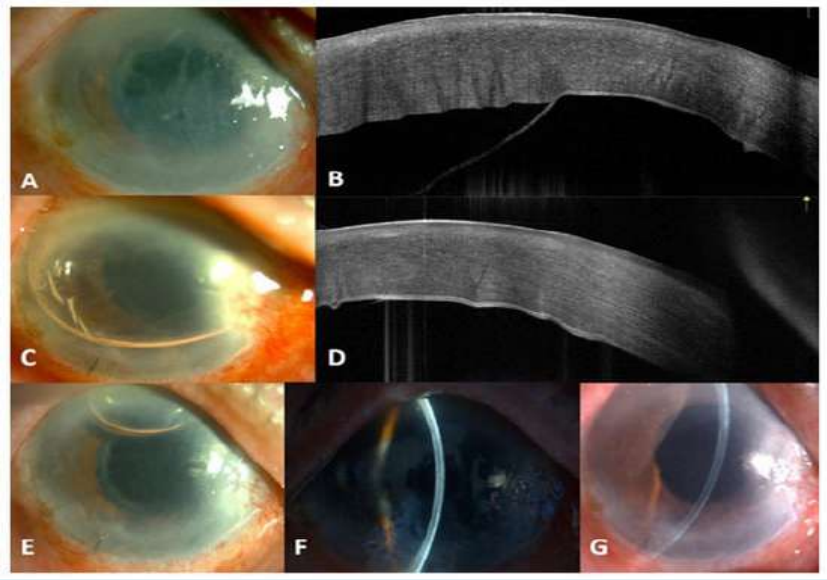

Figure 1. Clinical appearance of the first patient (case 1). (**A**) The detached Descemet's membrane on silt-lamp biomicro scopy. (**B**) The detached Descemet's membrane on anterior segment optical coherence tomography. (**C**) The anterior chamber after descemetopexy on silt-lamp biomicroscopy. (**D**) The anterior chamber after descemetopexy on anterior segment optical coherence tomography. (**E**) A degraded bubble in the anterior chamber. (**F**) Decreased cystic edema. (**G**) The final appearance of the attached Descemet's membrane on silt-lamp biomicroscopy.

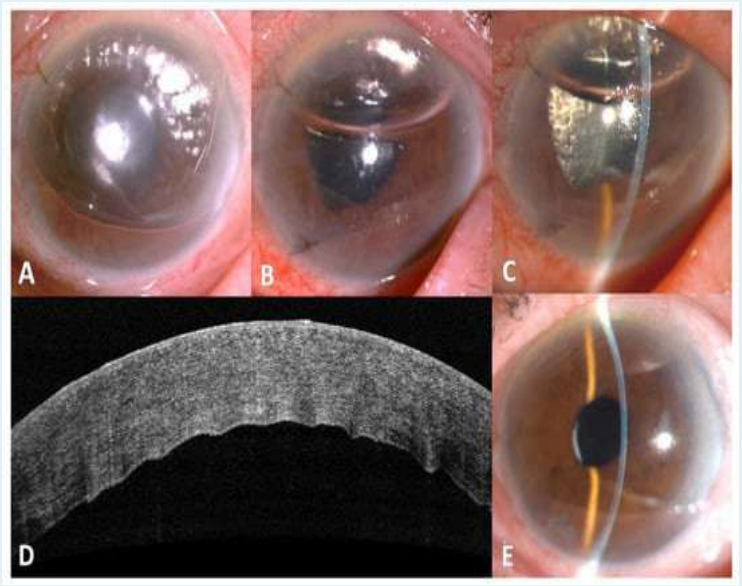

Figure 2. Clinical appearance of the second patient (case 2). (**A**) The anterior chamber one day after descemetopexy on silt-lamp biomicroscopy. (**B**,**C**) A degraded bubble in the anterior chamber. (**D**) The attached Descemet's membrane on anterior segment optical coherence tomography. (**E**) The attached Descemet's membrane on silt-lamp biomicroscopy five months after descemetopexy.

Case 2

An 81-year-old woman underwent cataract surgery in the left eye with a preoperative BCVA of 20/60. During the surgery, large and central DMD was noted and descemetopexy with 0.2 mL of 20 % SF_6 was performed immediately (Figure 2A). However, the IOP increased to 61 mmHg on the following day despite mannitol infusion and carteolol and brimonidine instillations. Three days after the initial cataract surgery, due to persistent ocular hypertension and suspected pupillary block, PI was performed and AC was partially filled with SF_6 to approximately 70 % in volume. The ocular hypertension subsided immediately after the intervention. Ten days later, the gas bubbles had decreased with a well-attached DM (Figure 2B,C) and AS-OCT also showed an attached DM (Figure 2D). Five months later, BCVA improved to 20/30 (Figure 2E) and persisted for 31 postoperative months.

Case 3

An 82-year-old woman underwent cataract surgery in the left eye with a preoperative BCVA of 20/100. One day later, persistent corneal edema was noted. Three weeks later, BCVA had deteriorated to 20/200 and DMD was found in the nasal portion on AS-OCT (Figure 3A). Descemetopexy with 0.2 mL of 20 % SF_6 and PI were performed. Four days later, DM had re-attached and BCVA had improved to 20/50 (Figure 3B,C). One week later, recurrent DMD on the nasal side had developed following gas resolution and BCVA had decreased to 20/100 (Figure 3D,E). Six months after the initial cataract surgery, due to persistent corneal edema and possible loss of DM on the nasal side, Descemet's stripping automated endothelial keratoplasty (DSAEK) was performed. Five months later, the corneal edema had resolved (Figure 3F) and BCVA had improved to 20/50 (Figure 3G,H). The patient was lost to follow-up afterwards.

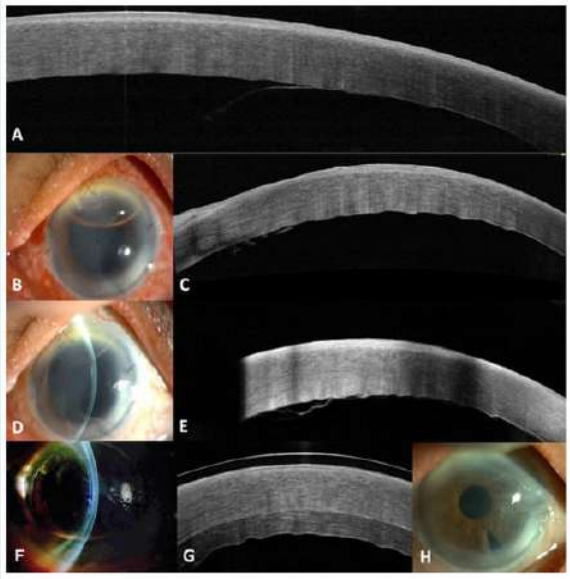

Figure 3. Clinical appearance of the third patient (case 3). (**A**) The detached Descemet's membrane on anterior segment optical coherence tomography. (**B**) The anterior chamber after descemetopexy on silt-lamp biomicroscopy. (**C**) The anterior chamber after descemetopexy on anterior segment optical coherence tomography. (**D**) The re-detached Descemet's membrane on silt-lamp biomicroscopy. (**E**) The re-detached Descemet's membrane on anterior segment optical coherence tomography. (**F**) The re-attached Descemet's membrane after Descemet's stripping automated endothelial keratoplasty on silt-lamp biomicroscopy. (**G**) The re-attached Descemet's membrane after Descemet's stripping automated endothelial keratoplasty on anterior segment optical coherence tomography. (**H**) The final appearance of the attached Descemet's membrane on silt-lamp biomicroscopy.

Discussion

DMD occurs during several ocular surgeries, characterized by a demarcation line and detached DM on slit-lamp biomicroscopy.[6,9] Tamponade with the injection of air, SF_6 or C_3F_8 in AC is effective and considered as the standard of care for DMD.[1,9,17] A previous study showed that air descemetopexy was comparable with SF_6 descemetopexy [18] but the SF_6 tamponade showed a better outcome than the air tamponade in endothelial keratoplasty and DMD refractory to air descemetopexy [19,20]. C_3F_8 descemetopexy illustrated an excellent reattachment rate in DMD [7] but the injection of C_3F_8 was less favorable because of its greater effect on IOP elevation compared to the injection of SF_6. [21] In this case series, we chose 20 % SF_6 descemetopexy for an immediate intervention in patients with DMD.

In 2016, Samarawickrama et al. proposed the classification of DMD into two categories—peripheral and central DMD.[16] The central type was defined as DMD involving the visual axis, whereas the peripheral type was defined as DMD not involving the visual axis. The classification aims to provide clinicians guidance on whether surgical intervention is to be indicated. Peripheral DMD is often treated conservatively, while central DMD is indicated for early surgical intervention. Mackool and Holtz defined planar or nonplanar DMD according to the DM separated from the corneal stroma by less than or greater than 1 mm.[15] They assumed that planar DMD has the possibility of spontaneous reattachment and better prognosis. The nonplanar type should receive early surgical treatment. In our report, cases 1 and 3 had central and nonplanar DMDs. Thus, 20% SF_6 descemetopexy was performed. In case 2, DMD occurred intraoperatively and a large area with central detachment was observed. Although case 2 was not examined under slit-lamp biomicroscopy and AS-OCT at diagnosis, a nonplanar type was highly suspected. Immediate SF_6 descemetopexy was performed during operation.

In case 1, although DM reattached successfully and corneal edema and macular disease resolved, the BCVA was only 20/400. The poor visual improvement in case 1 may be caused by large, corneal center-involved and nonplanar DMD, which is defined as > 1 mm of detachment with a worse prognosis than the planar type.[15] The degree of endothelial cell trauma resulting from DMD was an indicator of persistent poor visual acuity. [16] A previous study suggested that early surgical intervention may benefit the anatomical success of DMD and prevent scarring of the cornea.[22] The surgical intervention in this case was

performed in postoperative week 3 and prolonged surgical intervention is the possible reason for poor vision recovery.

Case 2 had elevated IOP one day after 20% SF_6descemetopexy possibly caused by pupillary block and expansible gas. The incidence of postoperative pupillary block was 7.7% in a previous study. [14] To prevent pupillary block and IOP elevation, cycloplegics, prophylactic PI, anti-glaucoma agents or partial filling of gas in AC can be used. Partial air–fluid exchange in AC could be performed to avoid fullness of expansible gases associated with IOP elevation. However, quick absorption of gas bubbles can reduce the efficacy of the tamponade and lead to a failed reattachment. Ocular hypertension and pupillary block in case 2 were possibly caused by no PI and AC filled with gas. PI and AC partially filled with SF_6 to approximately 70% in volume could reduce IOP and retain the efficacy of the tamponade in case 2. Due to prompt surgical management, IOP elevation did not compromise the final BCVA. The better prognosis of case 2 may be attributed to its misidentification as nonplanar DMD because of the unavailability of AS-OCT during surgery. However, immediate SF_6 descemetopexy in the same operation may play the most important role in the superior visual acuity in case 2.

The initial treatment for DMD was 20% SF_6 descemetopexy in the present cases. Case 3 was of recurrent DMD. There is no consensus on steps for the management of recurrent DMD after failed descemetopexy. Repeat injections of gases has been performed for recurrent DMD after the initial descemetopexy.[14,23,24] Jain and Mohan reported that attached DM was achieved with repeat descemetopexy in 12 of 13 cases of recurrent DMD (92.3%).[14] In a study, 15% of patients developed recurrent DMD, with no significant correlation with age, cataract score, severity of DMD or preoperative visual acuity, which resolved with repeat descemetopxy.[23] In another study, three eyes that required repeat expandable gas injections had more than 50% of corneal involvement and marked separation of DM from the stroma or curling or folding of DM.[24] Case 3 was of large DMD and partial DM loss during cataract surgery was suspected. Therefore, DSAEK was performed instead of repeat descemetopexy.

Conclusions

Our case series analyzed the diversity and different outcomes of 20% SF_6 descemetopexy in three patients with DMD. Cases with poor visual outcome but attached DM eventually, avoidance of the pupillary block with elevated IOP and management of recurrent DMD were discussed in this study. Application of a new imaging technique for AS-OCT could precisely diagnose, classify and monitor the anatomical outcome, thereby providing guidance in the treatment decision making.

In conclusion, prompt intervention with descemetopexy using 20% SF_6 is often effective and safe in repairing DMD, including a large and central DMD. Pupillary block with elevated IOP is a concern, so prophylactic PI is recommended and proper treatment should be timely initiated. Repeat descemetopexy could be considered in cases of recurrent DMD. However, close monitoring is advocated since secondary management, such as endothelial keratoplasty, may be required.

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Case Report

Clinicopathological correlation-Tuberculous chorioretinitis

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Abstract

Purpose: To report a challenging case of tuberculous chorioretinitis. Methods: Case report of a 46-year-old male, who was referred with a suspicious retinal lesion in his right eye. Results: Clinical examination showed multifocal, pale, elevated lesions temporal to the right macula with no vasculitis or hemorrhages. Infective and inflammatory workup showed unremarkable results. B-scan ultrasound confirmed an 8 mm x 3 mm x 10 mm right focal chorioretinal thickening. CT scan showed calcified lung hilar nodes supporting a prior granulomatous process, along with an enhancing nodule in the right globe. MRI brain and obits showed retinal thickening of the temporal surface of the right globe with subtle enhancement without retrobulbar extension or evidence for cerebral vasculitis. Subretinal lesion biopsy showed mononuclear inflammatory cells with granulomatous inflammation, including multinucleated giant cells but no neoplastic features. Interferon-gamma release assay testing for tuberculosis showed negative result, but a high index of suspicion lead to tuberculin skin testing and subsequent treatment for tuberculous chorioretinitis. Conclusion: Ocular tuberculosis presents in a variety of ways, making it a challenging diagnosis. Herein, we describe such case of tuberculous chorioretinitis

Pulmonary tuberculosis (TB) is the most common manifestation of *Mycobacterium tuberculosis* infection. Nevertheless, this acid-fast bacillus can affect any tissue, including the eye. Ocular manifestations of TB range from anterior and intermediate uveitis to choroiditis, vasculitis, and endophthalmitis.[1] It is this immense variability in clinical presentations that make TB one of the greatest ophthalmic mimics. Herein, a case of tuberculous chorioretinitis that posed a significant diagnostic and management challenge was described.

Case Report

A 46-year-old male patient was referred with a suspicious retinal lesion in his right eye. He had 4-month-history of headache. On presentation, the patient denied having any visual changes, eye pain, or loss of sight. He reported to be well, apart from chronic headache. The systems review was unremarkable, and there were no features to suggest giant cell arteritis as a cause for his ongoing headaches. His medical history included hypertension and hypercholesterolemia, with the recent introduction of 25 mg of oral prednisolone daily by his family physician for the headaches and possible rhinosinusitis.The patient denied ever having or receiving treatment for TB, nor was he aware of any potential contacts with TB. He did, however, receive Bacillus Calmette-Guerin vaccine in the past.

On examination, the best-corrected visual acuity was 6/9 in both eyes, with normal intraocular pressures. The anterior segment of both eyes was unremarkable, with no cells in the anterior chambers. There was 1+ vitreous cells noted in the right eye only. The posterior segment of the right eye showed multifocal, pale, elevated lesions temporal to the macula (Figure 1); the left eye was unremarkable. Fundus autofluorescence showed hyperautofluorescence of the lesion in question with patchy internal areas hypoautofluorescence and surrounded by smaller areas of hypoautofluorescence (Figure 2). No vasculitis or hemorrhages were seen. Optical coherence tomography taken through the lesion showed a contact zone between neurosensory retina and RPE-choriocapillaris layers, with an area of district subretinal hyperreflectivity (Figure 3). The findings on optical coherence tomography closely resembled not only those previously described in tuberculous granuloma [2-4] but also those of vitreoretinal lymphoma.[5] Given the diagnostic ambiguity, further investigations followed.

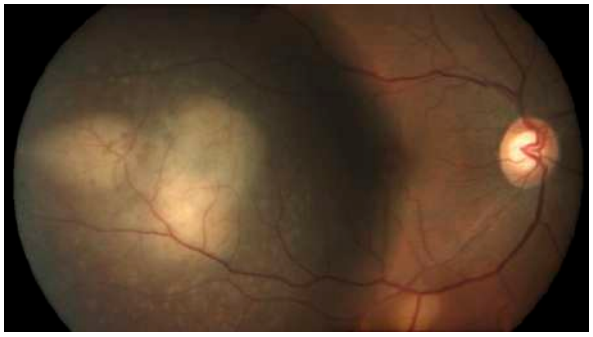

Fig. 1. Color fundus photograph of the right eye showing multifocal, pale, and elevated retinal lesions temporal to the macula.

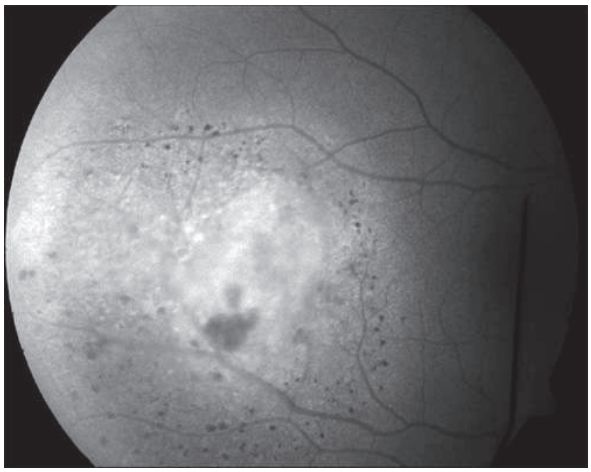

Fig. 2. Fundus autofluorescence showing hyperautofluorescence of the lesion with patchy internal hypoautofluorescence areas and surrounding smaller areas of hypoautofluorescence.

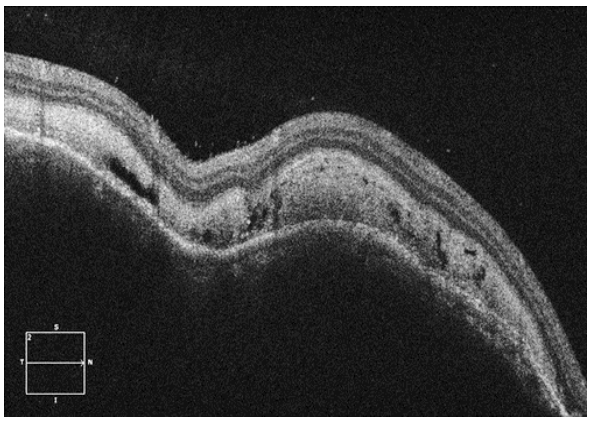

Fig. 3. Spectral-domain optical coherence tomography image of the right eye taken through the retinal lesion observed clinically. An elevation of choroid can be appreciated. A contact zone exists between the RPE-choriocapillaris layer and the neurosensory retina. Also note, intervening subretinal hyperreflective infiltrate appearing as a confluent band above RPE.

Ultrasound scan confirmed an 8 mm x 3 mm x 10 mm focal chorioretinal thickening. Bloodwork showed a normal full blood count with normal electrolytes and renal and liver function. Toxoplasma, hepatitis B, syphilis, antinuclear antibody, and extractable nuclear antigen antibodies showed negative results. Angiotensin-converting enzyme was within normal limits. Interferon-gamma release assay testing for TB also showed negative result. Given our high index of suspicion for possible malignant or infective processes, the patient underwent computed tomography scanning. The scan showed calcified hilar nodes supporting a prior granulomatous process, along with an enhancing nodule in the right globe. No other evidence of chronic or acute infection, malignancy, or lymphadenopathy was identified. Computed tomography head angiography showed no acute cerebrovascular abnormality. Further magnetic resonance imaging brain and obits showed retinal thickening of the temporal surface of the right globe with subtle enhancement without retrobulbar extension or evidence for cerebral vasculitis or lymphoma.

Although metastatic disease now seemed unlikely, the exact etiology of the retinal lesions was still unknown. Accepting this uncertainly was challenging for the patient, and ruling out a malignant process was of primary importance to the patient and their family. In discussion with patient and her family, we proceeded to right vitrectomy with subretinal biopsy of the lesion, 6 weeks after cessation of prednisolone. Using, 19-g forceps, 2 pieces of tissue 2.0 mm and 2.5 mm, with 2 mL of vitreous fluid were obtained. The tissue underwent acid-fast staining, with no positive results yielded. Retinal tissue histopathology (Figure 4) revealed necrotic retinal elements, infiltrated by mononuclear inflammatory cells with granulomatous inflammation, including multinucleated giant cells. No convincing features of neoplasia or any well-formed granulomas of sarcoidosis were identified. No lymphoid populations were detected on immunophenotyping, nor did the sample grow any bacteria, including acid-fast bacilli.

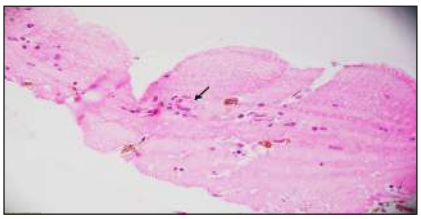

Fig. 4. Histopathological image of the sampled retina. Bruch membrane oriented inferiorly with giant cell indicated by an arrow.

Concurrent to above investigations, the patient was reviewed by the infectious diseases team. Tuberculin skin test showed positive result with 19-mm induration. Taken together, the investigations strongly supported the underlying diagnosis of TB, and the patient was started on a 9-month course of isoniazid and pyridoxine for latent TB as per current protocols, along with tapering dose of prednisolone. The final ophthalmic diagnosis of tuberculous chorioretinitis was thus reached.

On regular follow-up, the retina remained flat (Figure 5) and no vitritis was noted. However, shortly after completion of isoniazid and pyridoxine, reactivation of the inflammatory chorioretinal lesion was noted, necessitating escalation of prednisolone dose to achieve quiescence. Repeat magnetic resonance imaging brain and spine showed no evidence of central lymphoma, optic nerve enhancement, demyelinating lesions, or vasculitis. The previous noted right chorioretinal lesion was now markedly reduced. In months to follow, the patient developed glucose impairment secondary to steroid therapy. He maintains a best-corrected visual acuity of 6/18 in her right eye with no further activity at retina.

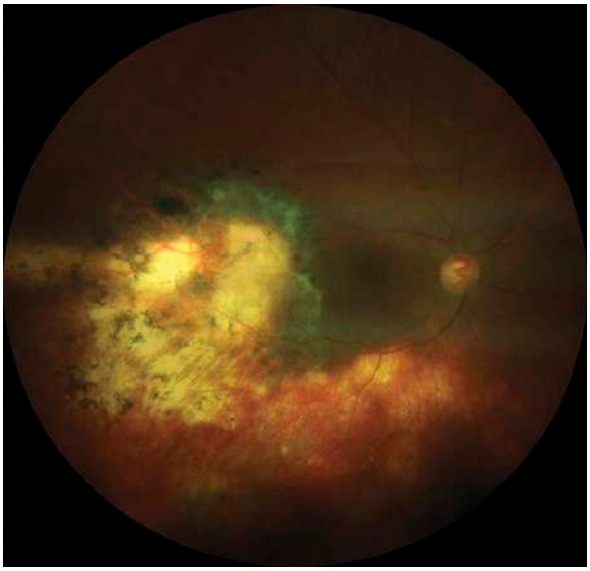

Fig. 5. Color fundus photograph of the right eye taken on follow-up postsubretinal biopsy and completion of tuberculosis treatment. Retina remained flat and media was clear.

Discussion

Ocular TB presents in a variety of ways. Posterior uveitis is estimated to account for 35% to 42% of all ocular presentations.[1,6,7] Retinitis is thought to accompany choroiditis, rather than being a sole clinical finding.[1] Overall, the most common posterior segment finding is multifocal choroiditis[6,8,9]

Intraocular TB is a challenging diagnosis, and delays in treatment can lead to devastating patient outcomes.[1,7] Maintaining a high index of suspicion is essential because obtaining a definitive microbiological confirmation is often not possible.[1,8] The response to anti-TB treatment supports the diagnosis of intraocular TB,[6,10] but it is essential to exclude other important differentials, such as toxoplasmosis and syphilis, which may present similarly. Moreover, it is important to remember that isoniazid and ethambutol can cause optic neuropathy,[1,11] which should be monitored and not confused with recurrence of ocular TB.

It is important to mention that lymphoma, another significant ophthalmic mimic, can present similar to the case illustrated above. Recently, Barry et al [3] identified a range of spectral-domain optical coherence tomography findings, which may aid diagnosis of primary vitreoretinal lymphoma. These included hyperreflective subretinal and inner retinal infiltrates, sub-retinal pigment epithelium (RPE) deposits, clumps of vitreous cells, and RPE undulation. Interestingly, similar features can be observed in TB choroidal granulomas.[3,4] This in itself further underscores the importance of histopathological sampling as was undertaken in our case.

Herein, we described a unique case of tuberculous chorioretinitis serving as a pertinent reminder of this great mimic, and the diagnostic challenge it poses in clinical practice.

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