Volume 6

ADVANCES IN OPHTHALMOLOGY AND OPTOMETRY

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Advances in Ophthalmology and Optometry

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Table of Contents

Pediatric

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Preface

Myron Yanoff, MD, *Editor*

In Volume 6 of *Advances in Ophthalmology and Optometry*, we again have asked experts in each of the pertinent fields to sift through the current literature to give us insights on the latest developments, such as: Optical Coherence Technology in Glaucoma Diagnosis; Prenatal Diagnosis of Retinoblastoma; Systemic Immunomodulatory Therapy in Pediatric Uveitis; Update on Intravitreal Chemotherapy for Retinoblastoma; Microinvasive Glaucoma Surgery; Artificial Intelligence in Retina; Artificial Intelligence in Neuroophthalmology Review; Retina in the Age of COVID-19; Neuroophthalmologic Manifestations of Novel Coronavirus; Advances in Endothelial Keratoplasty Surgery; Adenoid Cystic Carcinoma of the Lacrimal Gland; Refractive Error Changes Associated with Eyelid Weight Placement; Optical Coherence Tomography Angiography in White Dot Syndromes; and much more.

We continue to explore the new ideas, new treatments, and new ways of doing things to give us a fresh frame of reference to sort through the crush of data and to make sense in a real way of how to proceed.

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In Memoriam

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In Memory of Dr Alan Crandall

We were extremely saddened to hear about the passing of Dr Alan Crandall, renown ophthalmologist and internationally known humanitarian, this past October. Dr Crandall was a founding

member of *Advances in Ophthalmology and Optometry* and has served as our Cataracts Section Editor for the last five consecutive issues of publication. Dr Crandall's boundless expertise and commitment to the publication have, without a doubt, helped us grow the series into a true and trusted resource for our readers, clinicians around the world. We wanted to acknowledge his passing with some words of tribute from our Editor-in-Chief, Dr Myron Yanoff, as well as from Dr Crandall's son, Dr David A. Crandall.

> Even as a resident, Alan stood out as being a very special person. So special that at the end of his residency, I asked him to stay on staff. He accepted. Whatever he did, he did it well with a sparkle in his eyes. Whether patient care, surgical prowess, or my tennis partner, he was a joy to be with. After a few years on staff, we decided that it was time to perform intraocular lens implantation at the Scheie Eye Institute (only intracapsular cataract extraction was done by the full-time staff). We operated together and taught ourselves first to do extracapsular surgery and then entered into the world of lens implants (all under an air bubble, as Healon had not yet been invented). Alan was a brilliant surgeon, a gifted clinician, and a personality that made one wish to work with him. One of my saddest days was when Alan decided that it would be best for his family for him to leave and go back to where he grew up in Salt Lake City.
>
> We remained fast friends until the end. In fact, a year before he left us, he removed my cataracts (I would have no other cataract surgeon anywhere do the surgery), of course, with perfect results. Each year at the American Academy of Ophthalmology meeting, we would have dinner together the night before the meeting started. I cherished our friendship. I also marveled at his other endeavors. He trained hundreds of surgeons around the world and performed countless free surgeries to restore sight in Utah, on the Navajo Nation, and in more than 20 countries, including Ghana, Nepal, and South Sudan. Among many awards, he received the AAO

Humanitarian Award, the American Society of Cataract and Refractive Surgery (ASCRS) Humanitarian Award, and the inaugural ASCRS Foundation Chang Humanitarian Award. Alan has left a legacy that few other ophthalmologists even come close to. He left this world a better place than he found it. He certainly is missed, but his teaching and training live on. He still lives on in my mind, and always will.

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Like most children growing up, I did not have a strong sense of my father's day-to-day life. I knew that he worked long hours. I knew that he often went in on weekends to see patients. I knew that he often brought home charts for dictations, slides to review, and surgical videos. He would have the videos playing while we worked out in the evening (my siblings and I all knew the steps of cataract surgery before we had finished high school). As I got older, I came to appreciate that he did this because he loved what he was doing.

Dad always wanted everyone around him to be happy. For myself and my siblings, he wanted us to find something we enjoyed doing, something that we would want to do every day, and then strive to be the best at it that we could. He never made any effort to push me into ophthalmology, or even medicine, except by the example he provided. The joy he had in his work helped me decide my path. I'm so thankful this gave me the opportunity to work with him at meetings and on outreach surgical trips.

He always encouraged me to push myself surgically, always saying, "oh yeah, you have the skills to do that," when I would

discuss tough cases or new techniques with him. In him, I had the ultimate phone support for these hard cases and hard decisions. I knew he would answer any time I called with questions. Many know that this was not a special benefit I had by being family. He would do that for anyone who called him at any time.

He cast an enormous shadow in ophthalmology, one that I long ago accepted I would never get out of, but I can continue to do what he wanted, which is to try to make the world around me better and to be the best I can be. The world (and my personal world) is poorer for his loss, but rich in the legacy he has left for us.

Optometry

OUTLINE

Optical Coherence Technology in Glaucoma Diagnosis

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Keywords

Optical coherence tomography; Optical coherence tomography angiography; Glaucoma; Optic disc; Ganglion cell layer; Retinal nerve fiber layer; Parapapillary vasculature

Key points

- Optical coherence tomography is a common technology in ophthalmologic and optometric practice.
- Optical coherence tomography can objectively image the peripapillary retinal nerve fiber layer, ganglion cell and inner plexiform layers, and the peripapillary retinal vasculature.
- Abnormalities in the peripapillary retinal nerve fiber layer, macular region, and peripapillary vasculature have been shown to occur in glaucoma.
- Optical coherence tomography provides an objective, quantifiable assessment of ocular structure that can be used to assist and enhance glaucoma diagnosis.

Introduction

Glaucoma is a multifactorial disease consisting of characteristic damage to the optic disc, retinal nerve fiber layer (RNFL), and visual field, additionally involving numerous risk factors including race, age, family history, and intraocular pressure at levels incompatible with ocular health of the individual [1,2]. Glaucoma diagnosis has traditionally been accomplished through patient risk factors assessment, optic disc clinical and photographic analysis, as well as automated threshold perimetric testing. There exist limitations with this traditional approach, though. Many risk factors are currently unknown, and those that are known may be improperly assessed and their impact is not universally agreed upon. Clinical optic disc assessment is a challenging learned technique not possessed equally among all clinicians, and there exists no normative database for comparison. Threshold perimetry has an inherent limitation in that it is a subjective psychophysical test that depends on patient interaction and responses and the learned skills of the perimetrist. As an adjunct to clinical examination, spectral domain optical coherence tomography (SD-OCT) technology is increasingly being integrated into glaucoma evaluation to provide a more objective method of assessment that may lead to more accurate and earlier diagnosis [3].

Optical coherence tomography retinal nerve fiber layer analysis in glaucoma diagnosis

Optical coherence tomography is an imaging technique based on interferometry, comparing the coherence between near-infrared light reflected off the retina and light reflected off a reference mirror. The returning light is compared with the reference light and allows computer reconstruction of the underlying tissue with quantitative measurements that can be subsequently compared with a validated, normative database [3].

Peripapillary RNFL analysis is the SD-OCT parameter most commonly used for glaucoma diagnosis, drawing from measurements of retinal ganglion cells (RGC) throughout the retina [4]. An inherent limitation of this parameter is the high degree of physiologic variability between individuals and the subsequent difficulty in universally applying a normative database [4]. Macular thickness and ganglion cell complex assessment is also used to overcome this limitation because there is less anatomic variability of RGCs in this area and pathologic defects are more easily differentiated from anatomic variants. In addition, OCT angiography also has been investigated as another objective measure because peripapillary loss of retinal capillaries is being recognized as an early change in glaucoma [5].

There are several clinically available SD-OCT devices that can measure RGC tissue and assess this information in a variety of parameters that are subsequently measured against individual proprietary normative databases. Most devices will assess anatomic quadrants of superior retina, inferior retina, nasal retina, and temporal retina (in some form) as well as look at overall average RNFL thickness. There may also be subgroup assessment of individual clock hours or more defined anatomic areas such as inferior temporal or superior temporal. The parameters assessed are reflections of the branded technology and vary by device (any informational inclusion or exclusion of branded technology throughout this article neither implies superiority nor inferiority of any device.)

In a pooled meta-analysis, Kansal and associates [2] noted that information for average, superior, and inferior RNFL parameters were

better at differentiating glaucoma from normal populations than for nasal and temporal areas: this was consistent across glaucoma subgroups.

Dong and colleagues [6] found that current SD-OCT RNFL thickness parameters have good diagnostic accuracy and help clinicians in determining severity stages and differentiating normal from glaucomatous eyes in the early stages. Their assessment was that average circumpapillary RNFL thickness and inferior sector RNFL thicknesses were the SD-OCT parameters with the best diagnostic accuracy, followed by superior quadrant thickness values in terms of sensitivity [6]. Macular parameters were also seen to have increasing importance in the management of glaucoma. The investigators also found that evaluating optic nerve head (ONH) parameters with SD-OCT was useful in glaucoma diagnosis. Segmentation of the ONH and identification of Bruch membrane opening allowed for better measurement of the ONH rim and RNFL thickness. It was concluded that combined assessment of circumpapillary RNFL and macular and ONH parameters is useful for glaucoma diagnosis at different levels of severity [6].

Mittal and colleagues [7], in evaluating 2 commonly used SD-OCT devices (Cirrus, Carl Zeiss, Dublin, CA, USA, and Optovue, Freemont, CA, USA) found that the average RNFL thickness and superior RNFL thickness of both the devices and inferior ganglion cell complex (GCC) of RTVue device best differentiated normal subjects from all-stage glaucomatous eyes. For the Cirrus device, average RNFL thickness and superior RNFL thickness performed better than other parameters in differentiating early glaucoma from moderate and advanced disease. For the RTVue device, average, superior, and inferior RNFL thickness and inferior GCC parameters had the highest discriminating ability in differentiating advanced from early and moderate glaucoma. The investigators concluded that average RNFL thickness had the highest ability to distinguish different stages of the disease. No significant difference was found between either device in different severity levels [7].

While assessing the diagnostic accuracy of SD-OCT in eyes with preperimetric glaucoma, ocular hypertension, and early glaucoma, Aydoğan and associates [8] found that average RNFL thickness had the greatest accuracy for preperimetric glaucoma and eyes with early glaucoma. Average RNFL thickness was a risk factor for both conditions. The diagnostic ability of average RNFL and average GCC thickness increased along with disease severity [8].

In comparing parameters generated by the Cirrus SD-OCT to red-free photograph-documented RNFL defects (Fig. 1), it was seen that the thickness map had the best diagnostic value and was superior to quadrant and clock hour maps in identifying true RNFL defects [9].

A purported benefit of using OCT technology for glaucoma assessment is the ability to diagnose the disease earlier when compared with automated perimetry. In a study group that included 75 eyes of 75 patients suspected of glaucoma followed as part of the Diagnostic Innovations in Glaucoma study, researchers found that significant differences were seen in the RNFL as examined by SD-OCT up to 8 years before development of visual field defects. In addition, up to 35% of eyes had abnormal average RNFL thickness 4 years before development of visual field loss and 19% of eyes had abnormal SD-OCT results 8 years before field loss. The conclusions were that RNFL thickness assessment with SD-OCT was able to detect glaucomatous damage before the appearance of visual field defects on standard automated perimetry and that there were significantly large lead times in many subjects [10].

Optical coherence tomography macular analysis in glaucoma diagnosis

SD-OCT evaluation of macular parameters is complementary to RNFL analysis in the diagnosis of glaucoma. The macula contains approximately 50% of the eye's RGCs arranged in a multilayered pattern, making this area a theoretically more sensitive location to determine glaucomatous damage when compared with evaluation of the smaller diameter RGC axons, which make up the peripapillary RNFL [11]. SD-OCT evaluation of the macular region does not directly image RGCs, but instead allows segmentation and thickness measurement of retinal layers where RGC cell bodies (ganglion cell layer [GCL]), dendrites (inner plexiform layer), and axons (nerve fiber layer) are located [12,13].

Instrument proprietary software protocols differ in their segmentation of retinal layers used for the evaluation of macular parameters in glaucoma and are therefore not interchangeable between devices. The most common protocols consist of evaluation of the ganglion cell layer and inner plexiform layer (GCIPL) or the GCC, which is composed of the RNFL, GCL, and inner plexiform layer [12].

The Cirrus ganglion cell analysis (Fig. 2) report includes thickness maps (see Fig. 2A) and deviation maps (see Fig. 2B) of the GCIPL in each eye and horizontal B-scan with superimposed delineation of the outer boundary of the GCL and IPL (see Fig. 2C). Color-coded sectoral GCIPL thickness (see Fig. 2D) and summary table (see Fig. 2E), which includes the average and minimal GCL and IPL thickness, are provided, which includes comparison with an age-matched normative database.

Macular parameters are reproducible and have a similar diagnostic ability to RNFL parameters in the detection of glaucoma [14,15]. Information determined by each imaging strategy is complementary, as RNFL parameters more easily detect damage outside of the macular region, where GCIPL or GCC measurements may be better at detecting glaucomatous damage within the macular region [16].

Macular damage in glaucoma is typically arcuate in pattern, similar to RNFL thinning, and is commonly associated with RNFL abnormalities in the same hemifield [15]. Owing to the anatomic asymmetry of the projection of RGC axons in the retina toward the optic disc introduced by the horizontal angular difference between the center of the fovea and the optic disc center, inferior glaucomatous RNFL thinning has a higher propensity to cause detectible macular ganglion cell damage when compared with superior RNFL thinning [12,16].

Macular parameters are less impacted by structural variation between individuals and may provide an advantage in detection of glaucoma over RNFL evaluation in highly myopic eyes with increased axial length, myopic disc tilt, vessel deflection, and large peripapillary crescent [17].

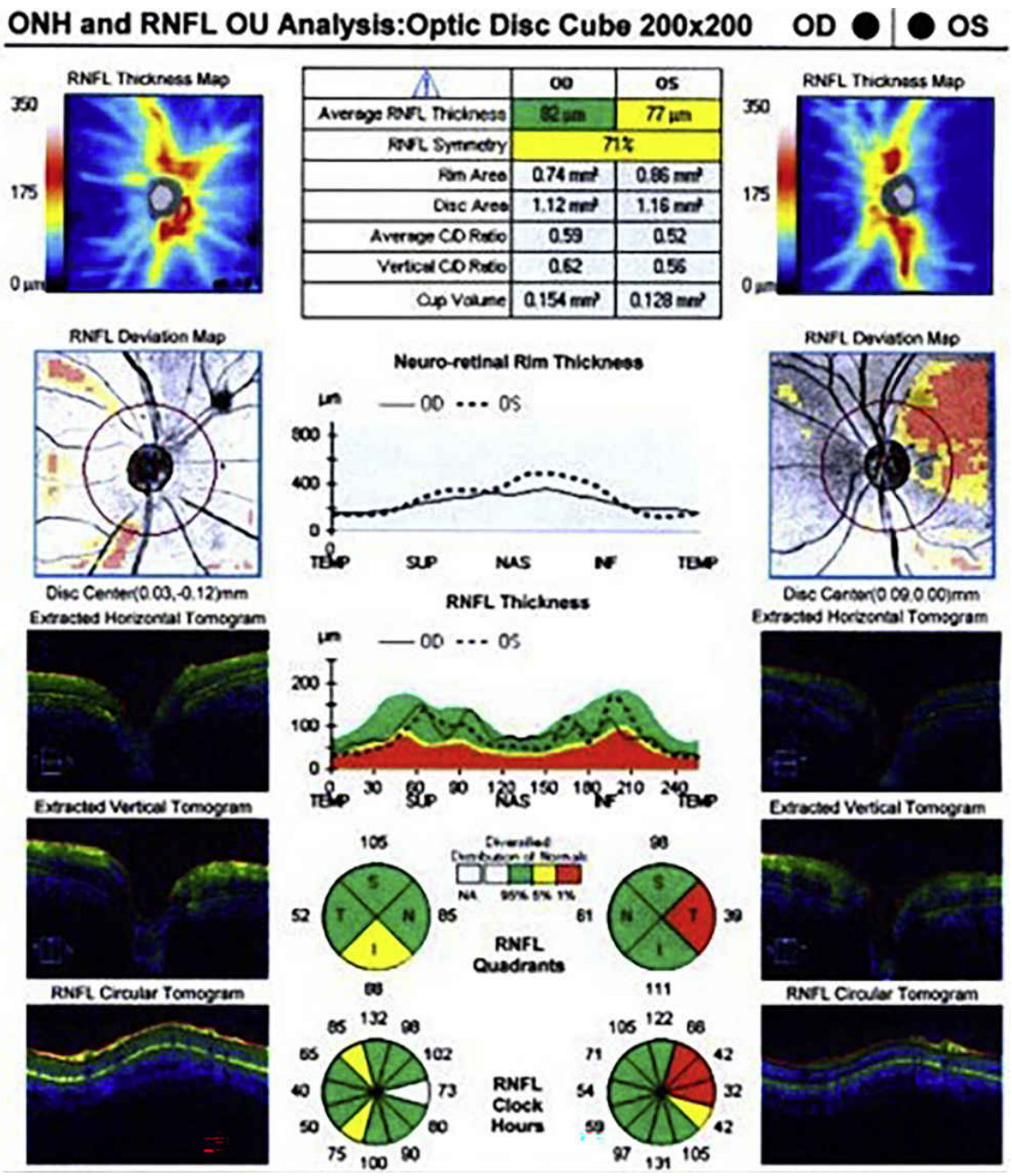

FIG. 1 Cirrus SD-OCT Optic Disc Cube analysis of the optic nerve head and peripapillary RNFL. Statistically significant departures from the normative database on the RNFL deviation map, RNFL quadrants, and RNFL clock hours parameters are notated in red and green pixels and color codes.

In eyes with macular pathology such as epiretinal membrane, diabetic maculopathy, macular hole, or macular drusen careful evaluation of the GCIPL or GCC and direct evaluation of the OCT B-scan should be performed for differentiation of glaucomatous from nonglaucomatous

damage and potential errors in automated segmentation [18]. In addition, GCIPL or GCC damage, which respects the vertical midline, should be suspicious for a postchiasmal event rather than glaucoma [18]. The utility of evaluation of macular parameters by OCT in glaucoma may be impacted by retinal and postchiasmal pathology.

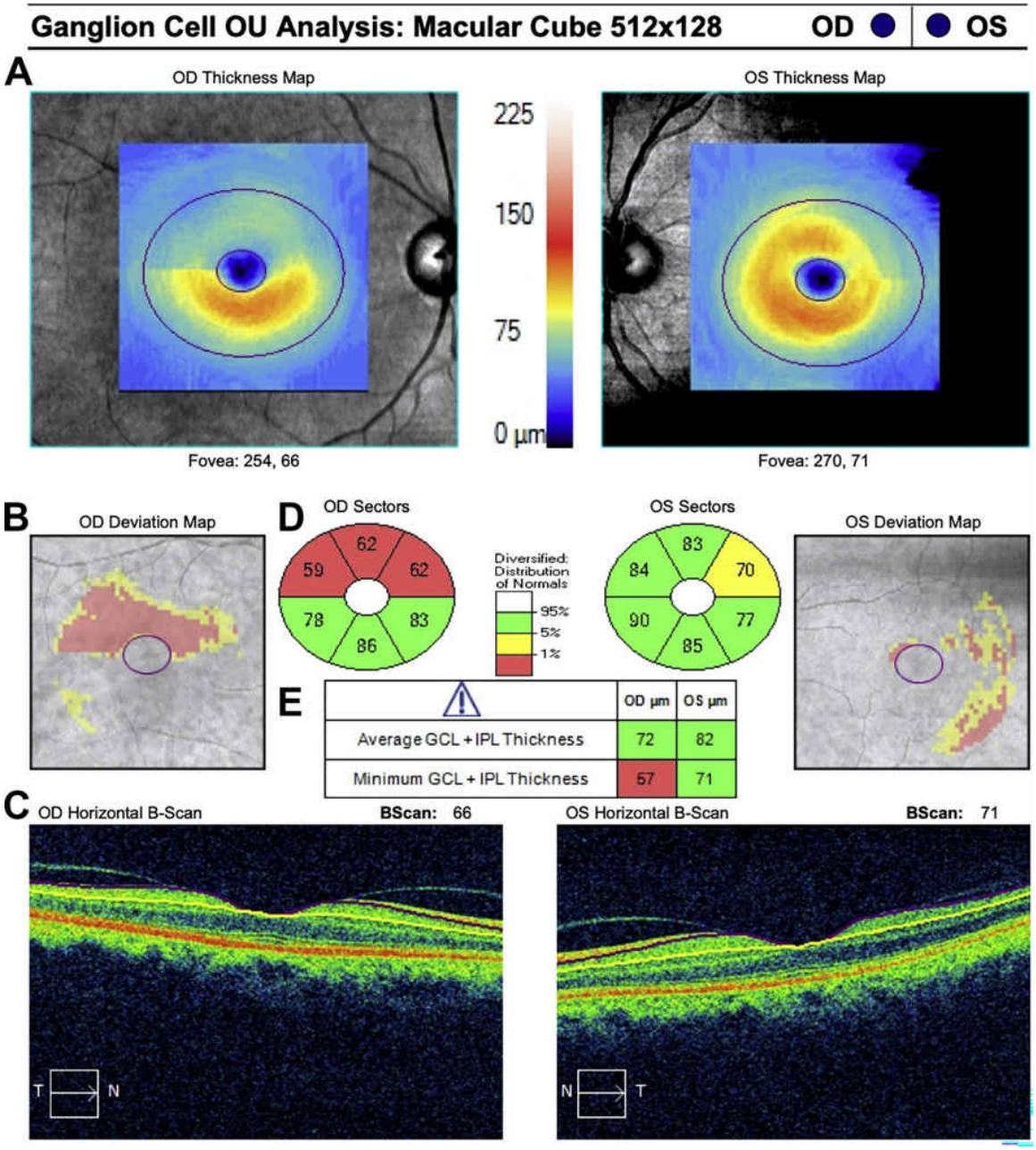

FIG. 2 Cirrus report of the ganglion cell analysis in primary open-angle glaucoma. (*A*) Thickness map. (*B*) Deviation Map. (*C*) Horizontal B scan. Note abrupt delineation along the horizontal raphe on the thickness map and the statistically significant departure from the normative database on the OD deviation map and OD sectors parameters.

When using SD-OCT for either RNFL or macular assessment, one must be aware of the possibility of obtaining false-positive and false-negative results. In one study involving Cirrus SD-OCT, 149 eyes from 77 healthy participants were imaged and it was seen that the false-positive rate was as high as 26.2%. Factors determined to be involved in false-positive

assessments included longer axial length and smaller disc area [19]. Issues such as poor image quality and lower signal strength can contribute to a false-positive assessment in normal eyes. The factors that significantly affected the false-positive RNFL color code results using SD-OCT were axial length and disc area, which may significantly affect the specificity of SD-OCT. Therefore, axial length and disc area should be considered during RNFL thickness profile analysis.

Although false-positive SD-OCT results may lead to overdiagnosis and unnecessary treatment, more concerning would be false-negative results wherein analysis may indicate an abnormal eye falling into the normative data range and incorrectly being assessed as normal. Features that may contribute to a false-negative assessment include acquisition errors and erroneous segmentation of tissues by the device, allowing the results to fall within the normative database [20]. When interpreting any global sector analysis, it is imperative to remember that substantial amounts of anatomic areas are being assessed to give an overall value. When this happens, a small RNFL defect may be present but the area may result in an overall value that falls within a device's normative database [21]. In addition, true RNFL defects located at the edge of inferior and superior temporal zones may occur in areas that are naturally anatomically thin and fall within a normative database, subsequently being inappropriately classified as normal [21].

Optical coherence tomography angiography in glaucoma diagnosis

The contributory role of vascular abnormality to disease development and progression in glaucoma has received renewed interest with the commercial availability of optical coherence tomographic angiography (OCTA). OCTA is a repeatable and reproducible noninvasive imaging technology that can be applied to evaluate the microvasculature of the peripapillary and macular region as a complementary tool for the diagnosis and detection of progression in glaucoma.

OCTA technology uses motion contrast to detect movement of erythrocytes through the microvasculature of the eye including retinal and small choroidal vessels to construct multilayered constructs of the vasculature [22,23]. Fluctuations in phase or intensity of sequential OCT B-scans performed in the same retinal location over very rapid time periods are detected and images are decorrelated to detect movement of red blood cells through retinal and choroidal vessels [22,23].

Three-dimensional OCTA images are reduced to two-dimensional reports, which include en face maps of retinal and choroidal microvasculature indicated by a bright signal. Dark areas on the report represent areas of no detectable blood flow. Parameters that are included on the report vary, but most commonly include vessel density (percentage of pixels with perfused vasculature in a measured area) and may include perfusion density (total area of perfused vasculature in a measured area), flow index (average flow signal in a measured area), and area measurement of the foveal avascular zone.

Superficial retinal capillaries are branches of the central retinal artery, whereas the short posterior ciliary arteries supply deeper retinal capillaries, choroidal vessels, and the prelaminar and laminar regions of the optic nerve [24]. The anatomic understanding of vascular supply to the RNFL of the peripapillary region, GCL of the macular region, and the laminar and prelaminar regions of the optic nerve make evaluation of both superficial and deep vascular parameters potentially beneficial in the diagnosis of glaucoma.

The superficial capillary plexus perfuses the RNFL in the peripapillary region and the GCL in the macula and seems to be preferentially damaged in glaucomatous eyes as detected by OCTA [24–26]. Localized loss of the choriocapillaris in the focal regions of peripapillary atrophy may also be

detected in glaucomatous eyes [24,27]. Clinical application of imaging of deep vasculature remains limited with commercially available systems owing to susceptibility to projection artifacts [23,26].

Reduced vessel density detectable by OCTA correlates with level of glaucomatous damage (Fig. 3) [23,28–30]. Vessel density decreases with advancing disease [24,25,27,29] and is highly correlated with visual field parameter [23,28] and OCT RNFL and GCC parameters [27]. Reduced vessel density parameters detected by OCTA have been determined to be an indicator of disease progression [24,27,29]. However, in the detection of early glaucoma, RNFL, GCC and GCIPL parameters seem to have improved diagnostic ability when compared with OCTA parameters alone (Fig. 4) [28,30].

Evaluation of vessel density parameters for detection of structural progression may be especially useful for eyes with advanced disease or eyes with high myopia [31,32]. In advanced disease, a measurement floor is reached when RNFL, GCC, and GCIPL parameters do not change with further disease progression; however, no detectable floor has been determined for macular vessel density parameters on OCTA [31].

The complexity of neurovascular coupling where neuronal activity and underlying systemic factors may regulate local blood flow makes it challenging to evaluate whether microvascular changes cause RGC damage or if reduction in vessel density is a result of RGC damage owing to lower metabolic demand of dysfunctional RGCs [25–27,29].

Challenges in the application of OCTA parameters to clinical care include difficulty interpreting images because of the presence of artifacts [23]. OCTA is based on the detection of motion, which makes eye tracking software and image processing algorithms necessary to remove movement artifacts created by saccades and ocular drift during image acquisition [23]. Projection artifacts, where the image of vessels in the superficial retina casts a shadow on deeper retinal layers resulting in duplication of the superficial capillary plexus with the appearance of detectable flow in outer retinal layers, can limit the utility of information in the deeper retinal and choroidal microvasculaure [23,26].

Systemic conditions that reduce ocular blood flow including hypertension and diabetes mellitus also reduce vessel density parameters on OCTA in nonglaucomatous eyes, and this must be considered during interpretation [33].

The lower and upper thresholds for detection of movement of red blood cells are parameters that are not adjustable on commercially available

systems but are relevant to understand the limitations in determination of flow on OCTA. Thresholds for detection of movement are determined with the intention to maximize the utility of the information provided, to limit signal noise artifacts, and keep image acquisition time similar to that of a typical SD-OCT scan [22]. As erythrocyte flow may be expected to slow before complete loss of the capillary beds, capillary dropout or reduced vessel density may be falsely determined by OCTA when in fact erythrocyte movement is present in vessels, although at a speed that it is less than the minimum threshold for detection [22].

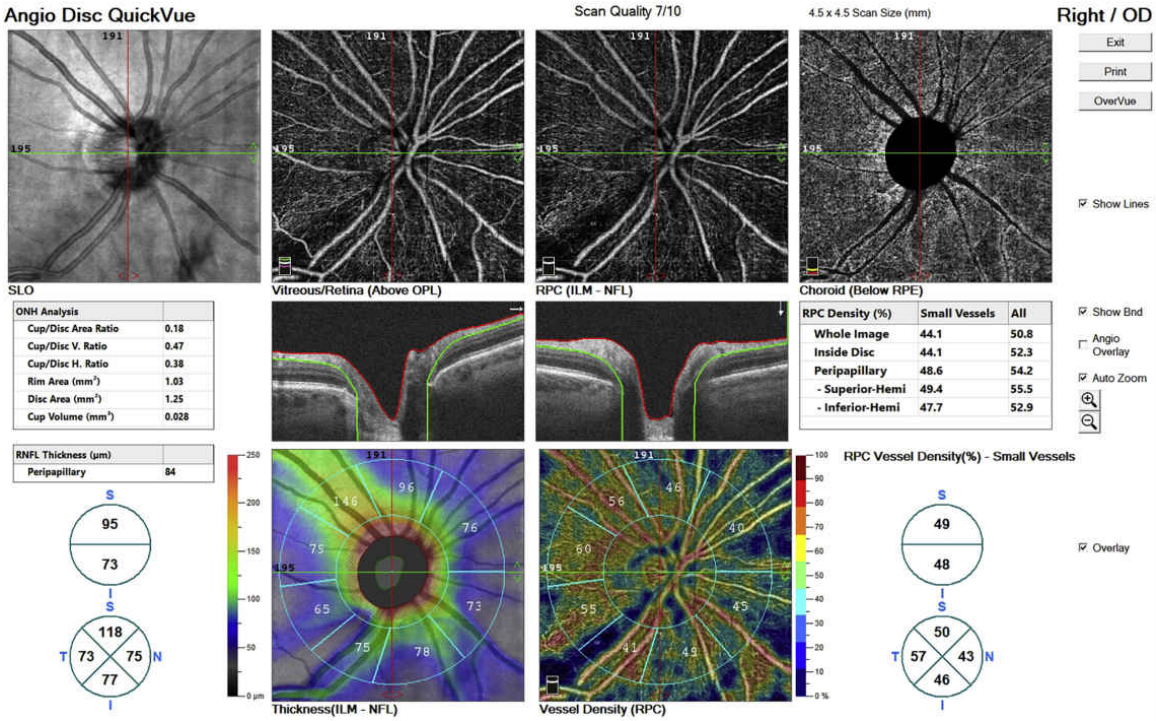

FIG. 3 Compromised RNFL and radial peripapillary capillaries (RPC) from early glaucoma in the right eye. The hemifield and quadrant analysis are showing compromised RNFL inferiorly with thinner micron measurements (95 vs 73; 118 vs 77). The RNFL thickness maps are showing RNFL dropout inferiorly (bottom middle). The adjacent vessel density map (measured in percentage) reveals a wedge defect in the inferior temporal region corresponding to that seen in the RPC image. The hemifield is intact, and quadrant analysis is showing mild decrease in RPC percent (right side). (*From* Caldwell, G. OCT Angiography for Glaucoma. Modern Optometry. October 2019. Available at: https://modernod.com/articles/2019-oct/oct-angiography-for-glaucoma?c4src=article:infinite-scroll. Accessed January 2, 2021).

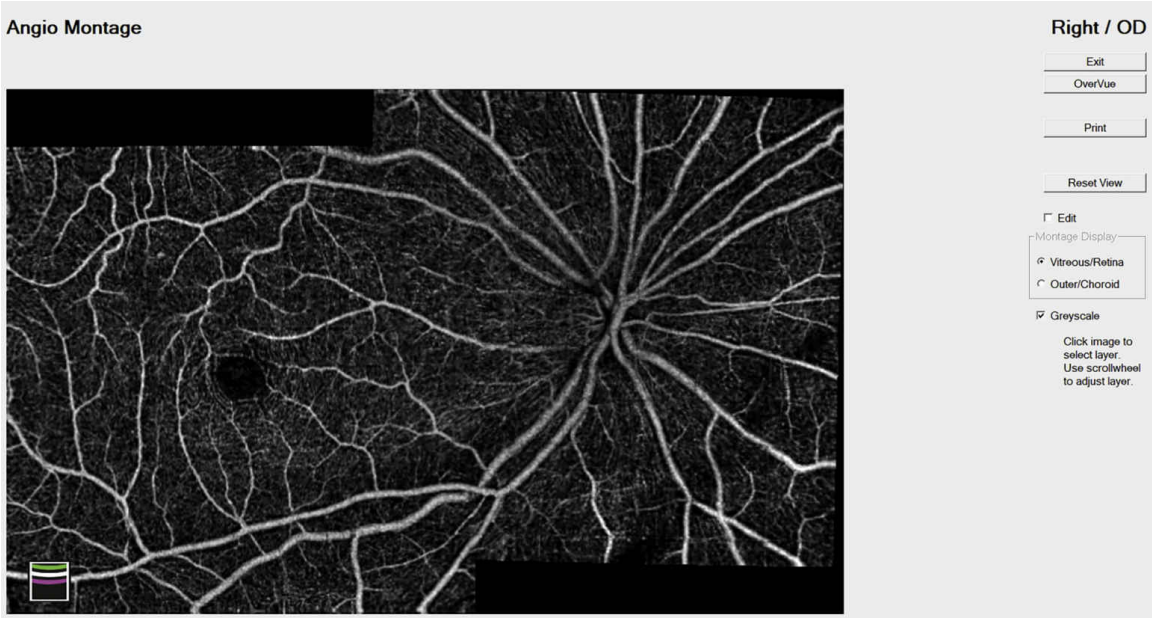

FIG. 4 This is a montage image of the right eye with primary open-angle glaucoma showing the capillary dropout in the inferior temporal region; it is a classical wedge defect. Notice how it spares the macula. (*From* Caldwell, G. OCT angiography for glaucoma. Modern Optometry. October 2019. Available at: https://modernod.com/articles/2019-oct/oct-angiography-for-glaucoma?c4src=article:infinite-scroll. Accessed January 2, 2021).

Early detection and diagnosis of glaucoma requires an assessment of risk factors, clinical examination including optic disc and RNFL analysis, and functional evaluation with threshold perimetry. SD-OCT analysis of the peripapillary RNFL, macular GCC and GCIPL, and angiographic assessment of the optic disc and RNFL blood supply lend an objective and quantifiable evaluation of anatomic structure that has been shown to be affected by glaucoma, thus enhancing our clinical ability to detect disease. Potential artifacts that influence image capture and data interpretation must always be borne in mind.

Clinics care points

- Peripapillary RNFL evaluation is a commonly accepted method of assessing patients for glaucoma.
- Ganglion cell complex and ganglion cell/inner plexiform layer analysis has been shown to be sensitive to changes occurring from glaucoma due to a more regular anatomy than that seen in the peripapillary RNFL.
- Concurrent maculopathies have the potential to render optical coherence tomographic measurements of the ganglion cell complex and ganglion cell/inner plexiform layer inaccurate and must be identified and considered when applying this information in glaucoma evaluation.
- There is increasing evidence to support optical coherence tomographic angiography changes in the peripapillary vasculature as valuable diagnostic information in glaucoma evaluation.
- There exists the potential for false-positive and false-negative assessments from optical coherence tomography and must be considered when interpreting these evaluations in glaucoma diagnosis.
- Optical coherence tomography is a valuable, objective assessment of structure that can be used adjunctively with clinical evaluation, functional visual field testing, and assessment of additional risk factors in glaucoma diagnosis.

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An Update on Neurodegenerative Disease for Eye Care Providers

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Keywords

Neurodegenerative disease (NDD); Alzheimer disease (AD); Parkinson disease (PD); Progressive supranuclear palsy (PSP); Multiple system atrophy (MSA); Dementia with Lewy bodies (DLB); Corticobasal degeneration (CBD); Posterior cortical atrophy (PCA)

Key points

- Despite varied underlying pathologic conditions, visual and ocular signs/symptoms are prevalent in all neurodegenerative diseases (NDD). These ocular findings may help differentiate among neurodegenerative processes.
- All NDDs cause retinal thinning, but patterns and severity differ. Alzheimer disease (AD) and multiple system atrophy affect the more peripheral superior retina, whereas Parkinson disease (PD) affects the papillomacular bundle. Corresponding visual field defects can occur.
- Patients with NDD present with reading difficulty. A common contributing factor in PD is convergence insufficiency and impaired contrast sensitivity.
- Eye movement disorders are prevalent in NDD. Markedly reduced vertical eye movements or supranuclear gaze palsy suggests progressive supranuclear palsy.
- Visual hallucinations are most common in dementia with Lewy bodies (DLB). Early and frequent occurrence of hallucinations helps distinguish DLB from AD, both of which have early cognitive deficits.

Introduction: neurodegenerative disease and the eye

Neurodegenerative disease definition

Neurodegenerative diseases (NDD) are conditions in which the cells of the central nervous system atrophy or do not function properly. These conditions tend to progressively worsen, and effective disease-modifying agents are still elusive [1]. Many diseases that may fall under the umbrella of NDD are associated with dementia or advanced age. Other NDDs, such as multiple sclerosis and glaucoma, do not necessarily have these associations. The focus of this article is on those NDDs with advanced age and dementia associations, specifically, Alzheimer disease (AD) and the parkinsonian syndromes. Posterior cortical atrophy (PCA) is also included, which can be a variant of AD [2]. The specific parkinsonian syndromes include the typical Parkinson disease (PD), and the atypical: progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and corticobasal degeneration (CBD) [3]. Clinical characteristics of AD and typical PD are listed in Table 1. Additional distinguishing features of the atypical parkinsonian syndromes are listed in Table 2.

Varied pathophysiology of neurodegenerative diseases

The various NDDs associated with dementia have several different potential underlying pathologic conditions, but all include abnormal protein deposits in pathologic brain tissue, which are associated with the disease mechanism. Interestingly, not all the parkinsonian syndromes share a common underlying pathologic condition, and some of them actually share an underlying pathologic accumulation of tau with AD (Table 3) [3].

Prevalent visual and ocular associations of neurodegenerative disease

Despite varied underlying pathologic conditions and clinical presentations among the NDD, a commonality is that ophthalmologic signs and symptoms are prevalent yet often underreported by patients and overlooked by eye care providers (ECPs) [5]. Although the visual and ocular findings associated with NDD are not always specific for a particular disease, unique clinical findings may help differentiate one neurodegenerative process from another.

Table 1 Clinical characteristics of Alzheimer disease versus Parkinson disease

Alzheimer disease	Parkinson disease
Progressive memory impairment	Bradykinesia (slowness of movement)
Impaired executive function (decision making and multitasking)	Rigidity and/or resting tremor
Behavioral changes (irritability and disengagement)	Postural instability (later in disease)
Circadian rhythm sleep disturbances	Responds to dopaminergic therapy
Olfactory dysfunction	Olfactory dysfunction

Data from Refs. [1–3]

Table 2 Distinguishing systemic features of atypical parkinsonian syndromes

Lewy body dementia	Multiple system atrophy		Progressive supranuclear palsy	Corticobasal degeneration
Dementia with visual hallucinations early in disease **Fluctuating cognition** **REM sleep behavior disorder**	Autonomic dysfunction early • Orthostatic hypotension (falls) • Loss of bladder control Cognitive function well preserved Rapid progression (shorter life span)		Impaired vertical gazes Postural instability: prone to backwards falls Mild executive dysfunction Facial dystonia Micrographia	Asymmetric limb involvement early in disease Impaired cognition early Profound rigidity Dysarthria Impaired pursuits and saccades Ideomotor apraxia (inability to imitate gestures)
	MSA-P subtype (predominant parkinsonism)	*MSA-C subtype (predominant cerebellar ataxia)*		
	Motor dysfunction similar to PD	Gait and limb ataxia Dysarthria Gaze-evoked nystagmus Ocular dysmetria		

Data from Refs. [1–4]

Role of eye care providers in neurodegenerative disease

If properly educated on the potential clinical manifestations of NDD, ECPs can play a vital role in identification and management. Collaboration of ECPs with neurologists in the diagnosis and management of NDD can vastly improve the quality of life of patients. The following paragraphs focus on the current literature regarding the visual and ocular manifestations of AD and parkinsonism to help ECPs become more familiar with how and why these conditions may manifest on an eye examination.

Visual and ocular associations of neurodegenerative disease

Eyelid function in neurodegenerative disease

Eyelid abnormalities are frequently one of the early signs of an NDD (Table 4). Possible abnormalities include change in palpebral aperture, blink reflex, and blink rate.

Eyelid retraction

It is important to examine palpebral apertures in NDD, specifically looking for eyelid retraction. Visible sclera above the superior limbus, consistent with eyelid retraction, is prominent in PSP but rare in PD. In PSP, it is this eyelid abnormality, in addition to ocular motor abnormalities, that are described in later discussion, which will help to differentiate it from other conditions, such as PD and MSA [6,7].

Apraxia of eyelid opening

The inability to initiate voluntary opening of the eyelid following a period of eyelid closure is known as eyelid apraxia and can be seen in some parkinsonian syndromes, particularly PSP [6]. The apraxia may occur upon awakening from sleep or a nap and thus may not be evident on clinical examination. Therefore, it is important for ECPs to inquire about the need for patients to have to manually lift their eyelids in order to open their eyes. Clinicians should take care to not mistake ptosis for apraxia of eyelid opening. Although ptosis may be present in early-onset PD, it is not a typical presentation of PD or other acquired NDDs [7].

Blepharospasm and reflex blepharospasm associated with bright stimulus

Blepharospasm, involuntary forceful eyelid closure owing to contraction of the orbicularis oculi, is often associated with apraxia of eyelid opening in NDD. Blepharospasm is also more common in atypical PD, particularly PSP and MSA [7,8]. Reflex blepharospasm, which occurs in response to a strong auditory or visual stimulus, has been suggested as a unique feature of atypical Parkinson syndromes, particularly PSP [8]. On clinical examination, a distinguishing feature of PSP patients may be their response to light stimulus with forceful eyelid closure consistent with reflex blepharospasm, making pupil testing challenging [7].

Table 3 Characteristic micropathology

Alzheimer	Parkinsonian syndromes				
AD	**PD**	**DLB**	**MSA**	**PSP**	**CB**
Extracellular amyloid-β (Aβ) plaques **Intracellular neurofibrillary tangles (composed of tau)** **Neuritic plaques from neuronal injury** **Can have Lewy bodies**	Lewy bodies (intracytoplasmic neuronal inclusions made up in large part of α-synuclein) Higher percentage of Lewy bodies in substantia nigra (SN) and locus coeruleus Significant neuronal loss in the SN pars compacta and pontine locus coeruleus	Lewy bodies (intracytoplasmic neuronal inclusion made up of α-synuclein) Found throughout neocortex, brainstem nuclei, and limbic structures Also pathologic condition similar to AD	Glial (oligodendroglia) cytoplasmic inclusions may contain α-synuclein and tau Myelin degeneration Neuronal loss in putamen, caudate nucleus, SN, locus coeruleus, pontine nuclei, inferior olivary nucleus, Purkinje cells of cerebellum, intermediolateral cell columns	Tau inclusions in neurons (neurofibrillary tangles) Tau-positive astrocytes (tufted astrocytes) Neuronal loss of the anteroposterior midbrain	

Data from Refs. [1–4]

Table 4 Visual and ocular associations of neurodegenerative diseases

	Alzheimer	Parkinsonian syndromes				
	AD	PD	DLB	MSA	PSP	CBD
Eyelid		Ptosis rare Apraxia of eyelid opening (later in disease course)		Blepharospasm Apraxia of eyelid opening	Eyelid retraction Blepharospasm Apraxia of eyelid opening (early in disease course)	Apraxi eyelid openin
Cornea/dry eye	Increased blink rate early in disease course Decrease in corneal sensitivity Reduced tear break-up time and decreased Schirmer test values	Decreased spontaneous blink Increased reflex blink Reduced tear volume	Delayed and sustained blink reflex	Very decreased spontaneous blink	Extremely decreased spontaneous blink	
Cataracts	Equatorial supranuclear cataract	Increased nuclear sclerotic cataract frequency More prominent posterior subcapsular cataract				
Retina	Aβ plaque deposition concentrated in superior quadrant RNFL thinning in superior retina Reduced blood supply of deep vascular plexus	p-syn deposition in retinal ganglion cells RNFL thinning at papillomacular bundle Reduced blood supply of superficial vascular plexus	p-syn deposition in retinal ganglion cells	RNFL thinning of superior quadrant	RNFL thinning at peripapillary region Thinning of ONL; thickening of OPL	RNFL thinnin superio and tempor thicken of ONL

Table Continu

	Alzheimer	Parkinsonian syndromes				
	AD	PD	DLB	MSA	PSP	CBD

	Alzheimer	Parkinsonian syndromes				
	AD	PD	DLB	MSA	PSP	CBD
Ocular motility	Saccadic intrusions Decreased saccadic velocity Hypometric saccades Increased latency to initiate saccades High errors on antisaccades Impaired smooth pursuit	Saccadic intrusions Hypometric saccades especially vertically No blink suppression during saccades Impaired pursuits with cog-wheel (jerky) movements Convergence insufficiency	Increased saccadic latency	Hypometric saccades Abnormal pursuits Ocular misalignment Nystagmus in MSA-C Decreased vestibular-ocular reflex suppression	Vertical gaze paresis Saccadic intrusions Large square wave jerks Hypometric saccades (early stage) Slow saccades, more so vertically (later stage)	Increased saccadic latency Blinks may be used to initiate saccades Impaired smooth pursuits

Data from Refs. [6–34]

Abnormal glabellar blink reflex

From a clinical standpoint, the glabellar reflex, testing reflex blink, is often used to identify NDD. Light tapping above the bridge of the nose elicits a blink reflex. With repetitive tapping, normal individuals will habituate, and no longer blink [9]. Patients with PD and PSP, however, may continue to blink with repetitive tapping. If the patient exhibits a delayed and sustained blink reflex, this is more characteristic of DLB [10].

Spontaneous blink rate

A typical blink rate is 15 to 20 blinks per minute (bpm). Blink rates outside of this range, both hyperkinetic and hypokinetic, may indicate an NDD. Dopamine in the nigrostriatal pathway from the midbrain promotes spontaneous blinking [11]. In PD, there is a decrease in dopamine, which leads to a decrease in spontaneous blink rate [11,12]. In PSP, the spontaneous blink rate is even more notably decreased as low as 5 bpm [13]. This decrease in blink contributes to the high occurrence of dry eyes. Conversely, in early mild cognitive impairment, cortical hyperexcitability is thought to increase dopaminergic activity, resulting in an increased blink rate. Thus, increased eye blink rate has been proposed as an early biomarker for identification of dementia and potentially early AD [14].

Anterior segment findings in neurodegenerative disease

Anterior segment manifestations of NDD can overlap with both eyelid function and posterior segment findings in NDD. Possible abnormalities, including dry eye syndrome, glaucoma, and cataracts, are not specific to NDD; however, these conditions must be assessed and managed in patients with NDD in order to improve quality of life. In addition, many of these clinical findings are being studied as potential biomarkers for NDD.

Dry eye syndrome

Dry eye syndrome is present in both AD and PD. In addition to the described changes in blink rate, there are also changes in tear quality and tear production. In AD, there is a quick tear break-up time and low Schirmer values, indicating inadequate tear film. In PD, as the disease progresses, there is further decrease in the amount of tear production and tear volume [12].

Corneal changes

Corneal changes may also have some association with dry eye syndrome in NDD. In AD, there is a decrease in cholinergic fibers, which leads to decreased corneal sensitivity [12]. In PD, studies have demonstrated a decrease in corneal nerve fiber length and density, greater deep nerve tortuosity, and an increased number of nerve beadings indicating damage [15].

Cataracts

The crystalline lens does show changes with some of the NDDs. In AD, equatorial supranuclear cataracts can develop secondary to aggregation of the Aβ protein and be seen on fully dilated AD patients [16]. In PD, there is not a specific type of cataract that is seen, but there is an increase in frequency of nuclear sclerotic cataracts as well as tendency for more prominent posterior subcapsular cataracts [5].

Anterior chamber

In some patients who have open-angle glaucoma (OAG) but have not been diagnosed with AD, the aqueous humor has demonstrated apolipoproteins and transthyretin, which are considered AD biomarkers. These biomarkers, when present, have been linked with more severe OAG [17].

Posterior segment findings in neurodegenerative disease

With the advent of optical coherence tomography (OCT) and OCT angiography (OCT-A) and their increased accessibility, there has been a focus in the literature on using these techniques to evaluate the retina and its biomarkers in the setting of NDD. Various retinal layers and their vascular supply have been shown to be affected in certain NDDs, although there is still debate regarding these associations and their pathophysiology.

Retinal nerve fiber layer and ganglion cell layer thinning: association of neurodegenerative disease with glaucoma

Retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thinning are general nonspecific biomarkers for NDDs, including glaucoma. Patients with AD and PD have been shown to have a higher prevalence of glaucoma in the setting of normal-tension intraocular pressures (IOP), which suggests that patients with NDD are more at risk for developing glaucoma [5,18].

Retinal deposits in neurodegenerative disease

In the case of AD, Aβ plaques concentrate in the superior retinal quadrants [19]. The accumulation of Aβ plaques in and around degenerating melanopsin retinal ganglion cells (RGCs) may help explain why AD can cause disruption in circadian rhythm [20]. The Aβ deposits can be detected in living patients using curcumin fluorescent imaging, which may be helpful in monitoring disease progression [21]. Although this is not currently a widely available test, it may be something that could be more accessible in the future.

In contrast to AD, in PD, there is accumulation of phosphorylated a-synuclein (p-syn). There may be a positive correlation between p-syn deposits in the retina with disease stage in PD and DLB [22].

Patterns of axonal loss in neurodegenerative disease

In AD, because of accumulation of Aβ plaques predominantly in the superior retina, there is thinning of the RNFL and RGCs in this area [19,23]. The reported pattern of axonal loss in PD is similar to that of mitochondrial optic neuropathies, in which the temporal sector of the optic nerve and the papillomacular bundle is affected [20]. This pattern of loss affects the parvocellular RGCs, which may help distinguish PD from AD and MSA, both of which affect the magnocellular RGCs instead (Fig. 1) [20,24].

Degree of retinal nerve fiber layer loss can help differentiate among neurodegenerative diseases

Patients with PSP have been reported to have even lower peripapillary RNFL values and thinner inner retinal segment layers compared with PD [25]. Studies of PSP patients demonstrated a decreased thickness of the outer nuclear layer (ONL) and increased thickness of the outer plexiform layer (OPL), whereas PD patients demonstrated the opposite; the resulting ONL/OPL ratio was able to differentiate between PSP and PD [26].

Optical coherence tomography angiography in neurodegenerative disease

Studies with OCT-A have reported a diminished blood supply in both AD and PD. In AD, there is a reduced blood supply of the deep vascular plexus potentially owing to the Aβ plaque accumulation. In PD, there is a reduced vascular density of the superficial vascular plexus [27].

Afferent visual function in neurodegenerative disease

NDD patients do not typically show a loss of visual acuity until later in the disease progression, but they may exhibit decreases in other afferent visual functions earlier in the disease process, such as contrast and color impairment, visual field defects, and reduced pupillary light responses [35,36]. As demonstrated above, the neurons of the retina are affected in NDD in a similar fashion as neurons of the brain. The association between changes in the retina and brain is so strong that the use of afferent visual function findings has been proposed as additional biomarkers for disease presence and progression [37,38].

Visual field defects follow retinal and optic nerve changes

Visual field defects in NDD can be secondary to effects at various locations along the visual pathway. An increased risk of glaucoma, in and of itself, can cause associated visual field defects [39]. The patterns of visual field loss can be consistent with the retinal findings in different diseases as described in the discussion of retinal axonal loss above. The preferential loss of the smaller parvocellular axons in PD and the larger magnocellular axons in AD and MSA can account for differences in visual field loss in these conditions (see Fig. 1). The effect on the papillomacular bundle or temporal sector of the optic disc can be more associated with central visual field changes. Conversely, in AD and MSA, there is preferential thinning of the superior quadrant of the optic nerve that could be associated with inferior visual field defects [19,23]. In AD, loss of cell bodies has been found to occur simultaneously with loss of axons and associated myelin sheaths within the white matter of both the optic nerve and the optic tract [40].

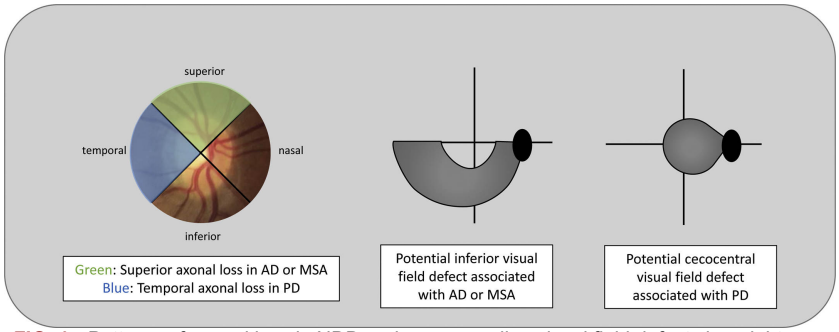

FIG. 1 Patterns of axonal loss in NDD and corresponding visual field defects in a right eye.

Occipital visual field maps and higher cortical functioning

Functional MRI occipital visual field maps (VFMs) have demonstrated irregularities in the organization of posterior VFMs in AD. These changes may be responsible for the visual symptoms seen in AD, including not only visual field and contrast sensitivity changes but also problems with higher cortical

functioning, including visual attention, visual processing speed, color discrimination, visuospatial processing, and facial recognition [41].

PCA is an extreme example of impairment of these higher cortical functions, in which there is not only functional but also structural evidence of degeneration of the occipital, parietal, and posterior temporal lobes bilaterally on imaging [42]. PCA is thought to be an atypical variant of AD in 80% of cases [2]. PCA patients often present to the ECP with unexplained disabling visual deficits and complaints of inability to read. In these patients, the retina and visual pathway are intact, but cortical atrophy is affecting the visual processing centers.

Homonymous hemianopia can be an early sign of posterior cortical atrophy

Homonymous hemianopia, frequently denser inferiorly, is an early sign of PCA and may occur before other abnormalities of higher-order visual processing. It is the presence of field defects and the eventual atrophy of the visual processing areas that lead to unexplained difficulty with reading, impaired color vision testing, and omission of letters during visual acuity testing [2,42]. With time, these patients will develop episodic memory impairment characteristic of AD.

Contrast sensitivity abnormalities

Impaired contrast sensitivity has been documented in AD and PD [37,38]. Studies have demonstrated that visual contrast sensitivity as measured with frequency doubling technology (FDT-2 24-2 visual field; Welch Allyn, Skaneateles Falls, NY, USA) is a predictor of cerebral amyloid, tau deposition, and temporal lobe atrophy. It is uncertain if the reduced contrast sensitivity in AD is related to the accumulation of amyloid and tau in the retina, the brain, or both [37]. ECPs may consider using FDT as a screening tool in patients suspected of NDD. If a patient fails FDT screening, and no other ocular pathologic condition is found on examination, this could be a means of identifying NDD [43].

Color vision deficiencies

Impaired color discrimination is a manifestation of both AD and PD [38,44,45]. Color vision deficiency in NDD is a complicated process, particularly in those with cognitive impairment. Color perception relies on both an intact sensory system in the retina to stimulate the visual cortex and recognition of the colors from stored memories [44]. Thus, studies have focused on determining color perception abilities through the Farnsworth-Munsell 100 hue test, which relies minimally on memory [45].

Abnormal contrast sensitivity and loss of color discrimination mainly affecting short (blue) wavelength stimuli have been documented in AD and may also apply to PCA. The effect on the magnocellular pathway in AD may be related to the impairment with motor perception and loss of achromatic contrast in PCA. A formal neuropsychological assessment can determine which cognitive domains are affected, and whether the disorder seems to be localized to the occipital and parietal regions, and therefore, consistent with PCA [42].

Pupil responses

AD patients were found to have decreased pupillary light reactivity based on pupillometry measures [46]. The efferent pupillary control is also affected in AD. Pupil dilation increases with cognitive activity. Therefore, AD patients who have reduced cognitive ability would exhibit larger pupil sizes because of compensatory cognitive effort [47].

Efferent visual function in neurodegenerative disease

Just as NDD can affect the afferent visual system, it can also affect the efferent visual system, as the authors have already demonstrated with pupils. However, more commonly, changes in ocular motility can be seen, including ductional abilities, convergence, pursuits, and saccades. In some cases, even nystagmus can be seen. Identifying and managing these clinical findings not only could help the ECP consider the possibility of a neurodegenerative process but also aid in differentiating among the various NDDs, and in turn, improve patient quality of life.

Ocular motility abnormalities are prevalent in neurodegenerative disease

Because accurate, smooth eye movements involve a complex cortical process combining many sensory inputs and motor outputs throughout the cortex, it is not surprising that ocular motility abnormalities are present in many NDD patients. The primary mechanisms for oculomotor dysfunction are not fully understood in PD nor AD, but given that each disease progresses differently, there is likely a difference. Abnormalities associated with AD may be more related to inattention and inability to fixate, whereas PD motility deficits are more related to abnormal neuronal motor input [28]. Regardless of the mechanism, eye movement disorders are prevalent in patients with NDD, and particularly the parkinsonian syndromes. The oculomotor abnormalities commonly manifest as symptoms of blurred vision, diplopia, and difficulties with visual tasks [5].

Pursuits and saccades

As Table 4 shows, most NDDs show some abnormality of saccadic and/or pursuit movement [36]. Patients with PD have hypometric voluntary saccades and reduced accuracy [29]. Patients with AD have longer latencies in saccadic tasks and have higher error rates on antisaccade tasks [30,31]. Clinical evaluation of eye movements should be performed in both horizontal and vertical directions. Patients with PD, particularly those with PSP, will show greater abnormalities with vertical movements [6].

Ductional limitations

To differentiate PSP from other parkinsonian syndromes, markedly reduced vertical ductions or a supranuclear gaze palsy early in the disease process would be expected (Fig. 2) [32]. A supranuclear gaze palsy would manifest as difficulty with ductions and versions of vertical gaze, in the setting of improved ability in that same gaze with use of the oculocephalic reflex, or Doll's head maneuver (Fig. 3) [6,33].

Convergence insufficiency

Convergence insufficiency (CI) is a typical oculomotor issue consistent with PD and parkinsonian syndromes. These patients are commonly symptomatic, and this likely contributes further to reading difficulties [34]. CI is not commonly documented in AD.

Nystagmus

There are a few oculomotor movements that do help differentiate conditions, particularly among the parkinsonian syndromes. For example, nystagmus is not typical of PD, but if present, it may indicate cerebellar involvement, and this would be more typical of an Multiple System Atrophy – predominant cerebellar ataxia [32].

Hallucinations in neurodegenerative disease

Hallucinations, or the perception of external stimuli where none exists, are a major association of NDDs. These hallucinations are commonly visual, but can also be auditory, olfactory, or tactile [48,49].

Hallucinations could elicit a range of emotions in the patient from enjoyment to indifference to fear. They could also lead to false beliefs or delusions. Patients may be hesitant to discuss their hallucinations because they fear they will sound crazy or may be put into a nursing home. Care is often sought from ECPs when visual hallucinations are experienced, because these can be distressing for patients and/or caregivers and can contribute to reduced quality of life [50]. Eye doctors need to be aware of these visual hallucinations and be able to identify, manage, and educate about them. New or worsening hallucinations in a patient with an established diagnosis of an NDD may be another reason to recommend neurologic care evaluation and possible change in treatment regimen [48,51].

Mechanisms and risk of hallucinations

The exact mechanisms of hallucinations are being studied and are not yet fully established. However, the type of abnormal protein deposition seems to be associated because tauopathies and

synucleinopathies have different hallucination risks. Hallucinations are more common in the synucleinopathies of PD and DLB and are less common in the tauopathies of AD, PSP, MSA, and CBD [49].

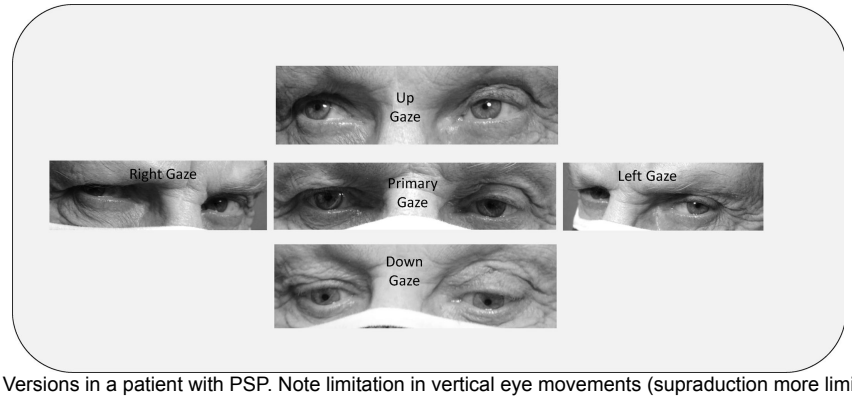

FIG. 2 Versions in a patient with PSP. Note limitation in vertical eye movements (supraduction more limited than infraduction).

FIG. 3 Supranuclear gaze palsy with versions versus doll's head. Upgaze ability with versions (*top*). Upgaze ability with doll's head testing (*bottom*). Improved upgaze ability with doll's head testing indicates a supranuclear gaze palsy in this patient with PSP.

Hallucinations can help to differentiate among neurodegenerative diseases

There are differences in likelihood and frequency of hallucinations, with the Lewy body diseases (PD and DLB) having the greatest prevalence (Table 5). As many as 70% of patients with DLB experience hallucinations, whereas these occur in only up to 20% of AD patients [50,52]. In addition, visual hallucinations occur later in the disease process in AD, but occur early on in DLB [48]. Because both these conditions have cognitive deficits as an early part of the disease process, the presence or absence of hallucinations can help differentiate among them.

Hallucinations in dementia with Lewy bodies

In DLB, the hallucinations tend to be progressive, starting as illusions and ultimately manifesting as complex detailed formed visual images [52]. These visual hallucinations are such a critical feature of DLB that they are one of the core clinical features listed in the revised criteria for the clinical diagnosis of probable and possible DLB [53]. In DLB, where visual hallucinations occur early, eye doctors may be the first health care provider to suspect a neurodegenerative process and be able to recommend neurologic consultation for diagnosis and treatment.

Hallucinations in Alzheimer disease

Visual hallucinations are associated with reduced visual acuity in AD. For this reason, patients with AD need to get updated refractions and should wear their glasses regularly if possible. In addition, any other causes of reduced visual acuity, such as cataracts, should be resolved surgically if possible, to help reduce visual hallucinations [51]. Similarly, an audiology referral may be indicated to help them attain their best possible auditory acuity with hearing aids in order to decrease auditory hallucinations [48].

Visual and ocular side effects of neurodegenerative disease treatments

ECPs must be aware of potential ocular associations of NDD treatment. Medications used in PD often aim to increase dopamine levels either directly, by supplying precursors (ie, Levodopa), or indirectly, via inhibiting enzymatic breakdown (ie, catechol-*o*-methyltransferase [COMT] inhibitors and monoamine oxidase [MAO] inhibitors). Anticholinergic medications may be used in PD [54]. Some Food and Drug Administration (FDA) -approved medications for PD are listed in Table 6. Rivastigmine is the only FDA-approved medication for PD-associated dementia, but some providers opt to use AD medications instead.

Table 5 Visual hallucinations in neurodegenerative diseases

AD	PD	DLB	MSA	PSP	CBS
	Parkinsonian Syndromes				
Possible in late stage	Possible	Common in **early** stage (part of diagnostic criteria)	Uncommon	Uncommon	Uncommon

Data from Refs. [48,50,52]

Medications used in the treatment of AD fall into the 2 following categories based on their mechanism of action:

- Cholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine)
- *N*-methyl-D-aspartate (NMDA) receptor antagonist (Memantine) [78]

The medications used in patients with PD and AD can have ocular effects, both positive and negative, which are briefly discussed later and are also summarized in Table 6.

Adverse sequela

Dopamine agonists, often first-line treatments in PD, have been associated with ocular dyskinesias and potential exacerbation of visual hallucinations [36]. Anticholinergic medications are associated with dry eye symptoms. Amantadine, which is used in both patients with PD and AD, has been shown to cause corneal edema as well as development of intraepithelial corneal deposits. These corneal conditions can cause a reduction in vision, but fortunately, are reversible with drug discontinuation [70–72].

Adverse effects can be caused not only by use of medications but also by their discontinuation. For example, stopping Donepezil may precipitate acute angle closure glaucoma [74].

Associated improvement in neurodegenerative disease manifestations

Fortunately, some medications may lessen ocular manifestations of NDD. For example, Donepezil may increase contrast sensitivity, which, as discussed above, may be reduced in AD patients [77]. Donepezil has also been shown to reduce IOP, which may be of particular benefit given the association of glaucoma and NDD [76]. Although some medications may exacerbate PD-associated hallucinations, Pimavanserin is the first FDA-approved drug for treatment of hallucinations in PD [69].

The examples above are a few of the many drug-induced ocular effects that must be considered in patients with NDDs. ECPs must carefully review a patient's current medications, look for visual and ocular effects, and keep neurology informed of their findings.

Future avenues: neurodegenerative disease, the eye, and the visual system

Expected increase in prevalence of neurodegenerative disease

The elderly population, aged 65 and older, is expected to increase significantly over the next 30 years [79]. This increased population, in turn, is bound to increase the prevalence of age-related NDD. ECPs need to be ready for this change in the population that they serve and prepare for the fact that they will have a greater role to play in both the diagnosis and the management of NDD.

Table 6 Food and Drug Administration–approved medications used to treat neurodegenerative disease (as of December 2020)

	Mechanism of action	Generic drug name	Trade name Oral administration unless stated otherwise	Adverse and beneficial ocular effects that have been reported from some medications in each class
PD	Dopamine precursor	Levodopa	Inbrija (inhalation powder)	Increased dopaminergic activity • Ocular dyskinesia [5,55–57] • Possible exacerbation of visual hallucinations [58–60] • Mydriasis [61] • Blurred vision • Double vision • Blepharospasm after excessive dose • Improvement of blepharospasm [62] • Improvement of apraxia of eyelid opening [63,64] • Increased blink rate [13]
		Carbidopa-levodopa	Sinemet Parcopa (orally disintegrating tablet) Rytary (extended release [ER])	
	COMT inhibitor, inhibits breakdown of levodopa	Entacapone	Comtan	
		Tolcapone	Tasmar	
		Opicapone	Ongentys	
	Dopamine precursor + COMT inhibitor	Carbidopa/levodopa + entacapone	Duopa Stalevo	
	Dopamine agonist	Rotigotine	Neupro (transdermal patch)	
		Pramipexole	Mirapex	
		Ropinirole	Requip	
		Apomorphine	Apokyn (injection) Kynmobi (sublingual)	
	MAO-B inhibitor, inhibits breakdown of levodopa	Selegiline	Eldepryl Zelapar (oral disintegrating tablet)	
		Rasagiline	Azilect	
		Safinamide	Xadago	
	Anticholinergic	Benztropine	Cogentin	Decreased cholinergic activity • Dry eye [65,66] • Mydriasis ○ IOP elevation in narrow angles [67] • Esotropia [68]
		Trihexyphenidyl	Artane	
	Serotonin receptor (5HT2A) antagonist	Pimavanserin	Nuplazid	• Treatment of hallucinations [69]

Table Continued

	Mechanism of action	Generic drug name	Trade name Oral administration unless stated otherwise	Adverse and beneficial ocular effects that have been reported from some medications in each class
PD and AD	NMDA receptor antagonists	Amantadine	Symmetrel Gocovri (ER) Osmolex (ER)	• Intraepithelial corneal deposits [70–72] • Exacerbation of visual hallucinations [36,73]
	Cholinesterase inhibitor	Rivastigmine	Exelon	• Angle closure glaucoma risk upon withdrawal [74]
AD	Cholinesterase inhibitor	Donepezil	Aricept	• IOP reduction [75,76] • Increased contrast sensitivity [77]
		Galantamine	Razadyne	
	NMDA receptor antagonist	Memantine	Namenda	• Exacerbation of visual hallucinations

Data from Refs. [5,13,36,55–77]

During the next 30 years, it is hoped that advances will also be made in terms of understanding these individual disease processes and translating that into increased availability of novel biomarkers and treatment in the form of disease modifying drugs.

Optimal biomarkers involve eyes and vision

Because it is thought that early intervention would likely provide the best chance of future treatment success, attention will be focused on identifying preliminary biomarkers of the various NDD while still in the initial, subclinical stages. The optimal biomarkers will be inexpensive, noninvasive, and able to be assessed easily throughout the entire population. These preferred qualities make sensory and perceptual biomarkers very advantageous [37]. Among the special senses, vision stands out at the forefront of desirable biomarkers for several reasons. First, vision is the only special sense that gets regularly evaluated in most of the population. Second, a comprehensive eye examination includes not only a refraction and ocular health assessment but also evaluation of the afferent as well as the efferent visual system.

Summary: neurodegenerative disease, the eye, and the visual system

Eye care providers as screeners of neurodegenerative disease

The complex nature of the visual system and the fact that it incorporates both afferent and efferent processes put primary ECPs in the perfect position to be screeners for NDD. As such, ECPs need to be aware of how these conditions can manifest as a group as well as individually, even before patients start to experience the telltale features of dementia and/or parkinsonism.

As shown above, there is already a substantial amount of data regarding how the NDDs can manifest on an eye examination, in terms of anatomic location as well as clinical presentation. Ocular assessment could conceivably be part of the diagnostic criteria for NDD in the future. One must remain on the lookout for novel functional analyses of the visual system as well as future tools to measure vascular and inflammatory changes in the eye that can act as specific biomarkers of NDD [80]. However, until that time, ECPs need to be aware of the many potential presentations, consciously assess these features in their older adult patients, inquire about nonvisual/ocular symptoms, and perform cursory assessments of cognitive function when indicated (Tables 7 and 8).

Early identification and neurology referral is key

The goal is to identify patients early and refer them for formal neurologic evaluation as soon as there is any suspicion of a potential neurodegenerative process. Although some NDD processes currently have more treatment options than others, early identification and education are still necessary for the best possible future quality of life of these patients. They deserve the choice to start physical therapy to counteract potential future rigidity and hypophonia of parkinsonism, understand the potential for hallucinations so they are not frightened or embarrassed when these occur, make plans with family about future care should they develop significant dementia, and have more time to make educated choices about potential future use of medications for NDD.

Table 7 Helpful examination elements to consider in known or suspected neurodegenerative disease

Afferent tests	Efferent tests	Ocular health assessment	Cognitive assessment
• **Contrast acuity** • **Farnsworth-Munsell hue test** • **Visual field testing** ○ **Kinetic perimetry** ▪ **Goldmann** ▪ **Automated**	• Eyelid function ○ Palpebral aperture ○ Blink rate • Near point testing • Cover testing in multiple gazes • Doll's head maneuver • Ductions/versions • Saccades	• Dry eye ○ Tear break up time ○ Schirmer test • OCT ○ RNFL ○ GCL ○ OCT-A	• Mini-mental state examination • Montreal Cognitive Assessment • Cookie theft picture (Boston Diagnostic Examination)

Data from Refs. [6–25], [26–47], [81–92]

Eye care providers help improve quality of life of patients with neurodegenerative disease

In addition to being on the front lines of screening for NDD, primary ECPs will also play a critical role in helping to improve patient quality of life once these conditions manifest clinically. For example, ECPs may help patients maximize their visual function by enhancing contrast with use of filters, address and

overcome reading issues with use of prisms and reading stands as indicated, reduce Alzheimer-related hallucinations by referring for cataract surgery, and control other visual/ocular symptoms, such as dry eye associated with parkinsonism (Table 9). In addition, by identifying eye findings typical of a certain NDD, ECPs can help neurologists arrive at the correct diagnosis and treatment protocol.

Table 8 Pertinent history questions to consider in known or suspected neurodegenerative disease

Visual function	Cognitive function	Motor function
• **Diplopia** • **Reading difficulty** • **Dry eyes** • **Change in eyelid appearance** • **Inability to open eyelids** • **Blepharospasm** • **Increased or decreased blink rate** • **Visual field loss** • **Poor contrast** • **Impaired color perception** • **Difficulty moving eyes** • **Seeing things that are not really there**	• Attention • Memory • Cognitive speed • Self-control • Ability to focus • Ability to follow directions • Handling of emotions • Change in language fluency • Confusion • Changes in sleep behavior ○ Dream reenactment	• Resting tremor • Rigidity/stiffness • Slow movements • Flattened facial expression • Change in handwriting (micrographia) • Change in voice (hypophonia) • Shuffling gait • Postural instability/falls • Autonomic dysfunction ○ Incontinence ○ Constipation ○ Bradycardia ○ Orthostatic hypotension

Data from Refs. [1–25], [26–53]

Table 9 Helpful hints for ophthalmic management of neurodegenerative disease patients

Alzheimer disease	
• **Ensure patient achieves best-corrected visual acuity to prevent or decrease visual hallucinations** • **Put patient's name on their glasses if they live in a care facility to ensure best-corrected vision** • **Use filters to enhance contrast and reduce photosensitivity**	• Recommend lubricating drops with dry eye syndrome • Consider referral for cataract surgery, especially if patients are experiencing hallucinations • Discuss the possibility of visual hallucinations with family • Consider audiology evaluation to reduce auditory hallucinations
Posterior cortical atrophy	
• **Suggest separate distance and reading glasses if patient has inferior visual field loss**	• If there is suspicion of PCA in an undiagnosed patient, consider neurocognitive assessment
Parkinson disease	
• **Suggest reading stand if patient has hand tremors** • **Recommend lubricating drops with decreased blink rate, use of filters to enhance contrast and reduce photosensitivity**	• Consider BI prism at near for convergence insufficiency • Refer back to neurology for consideration of medication change if experiencing visual hallucinations
Progressive supranuclear palsy	
• **Suggest reading stand to hold material higher if patient has difficulty looking down** • **Suggest separate distance and reading glasses if patient has difficulty with vertical eye movements**	• Consider vertical yoked prism if patient has difficulty looking up (BU OU) or down (BD OU) • Recommend lubricating drops with decreased blink rate or dry eye syndrome

Abbreviations: BI, base-in; BU OU, base-up prism both eyes; BD OU, base-down prism OU.

Data from Refs. [84–92]

Table 10 Neurodegenerative disease patients benefit from a team-based approach

Specialty	Examples of care provided
Neurologists	Diagnose and treat NDD, assess effectiveness/side effects of NDD medications
Neuropsychologists	Assess cognitive function to help diagnose NDD and determine needed resources
Eye care providers	Manage visual and ocular manifestations of NDD, improve visual function
Physical therapists	Improve gait, movement, speed, and balance
Occupational therapists	Help with activities of daily living, make recommendations for patient safety
Speech therapists	Manage speech, language, and swallowing disorders
Audiologists	Assess and manage auditory effects of NDD, including hallucinations
Sleep specialists	Address REM behavior disorder and other sleep issues
Mental health providers	Assess and manage emotional and psychological needs

Expected surge of research into neurodegenerative disease

ECPs must recognize their unique position as having the combination of accessibility, understanding of a complex system of the body that distinctively incorporates both afferent and efferent function, as well as the appropriate tools and training to be on the forefront of assessing for visual and ocular biomarkers of NDD. As such, ECPs must keep up with the expected surge of publications in this area in order to stay aware of the most updated information and continue to work closely with their colleagues in various specialties to maximize the quality of life of patients with NDD (Table 10).

Clinics care points

- Specific pertinent history questions related to visual function, cognitive function, and motor function are critical in evaluating neurodegenerative disease.
- Neurodegenerative diseases can demonstrate specific afferent, efferent, and ocular health findings that can aid in diagnosis and specific management plans.
- Eye care providers can help improve patient quality of life by ensuring best possible visual function, enhancing contrast, reducing photosensitivity, prescribing prisms, recommending reading stands, and treating dry eye.
- Visual hallucinations can occur in neurodegenerative disease and in some cases are even part of the diagnostic criteria. Medications can both cause and treat these hallucinations.
- Patients with neurodegenerative disease benefit from a team approach. Eye care providers are an integral part of the neurodegenerative disease care team.

Disclosure
None of the authors has any conflict of interest to disclose related to this article.

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Neuroanatomical Structures in Extraocular Muscles and Their Potential Implication in the Management of Strabismus

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Keywords

Extraocular muscles; Sensory receptors; Oculomotor anomalies; Strabismus

Key points

- Human extraocular muscles contain neural structures important for the development and maintenance of binocular vision.
- Strabismus and other oculomotor anomalies may be attributable to developmental delay or acquired dysfunctions associated with these structures.
- Treatment options and their potential implications are discussed.

Introduction

Recent studies have promoted the concept that structures associated with extraocular muscles and the surrounding canopy of connective tissue play important roles in the control of eye movements, yet the neural substrate underlying their function is not fully resolved.

Structural and functional changes occur in the human oculomotor system over the entire course of life. While structural rigor and muscular force gradually increase during postnatal development, the reverse effect occurs during the process of senescence. The oculomotor system must make long-term adjustments of the motor signal, in addition to all the short-term adjustments needed to compensate for functional fluctuations. The ability to perform constant fine-tuned corrections requires knowledge about the exact positions of the eyes. Extraocular muscles contain structures with unique sensory features, suggesting a potential capacity to monitor the position of the eyes in relation to the orbit, as well as the movement of associated fibrous structures. This type of extraretinal information enables the brain to compute the efferent signals required to retain ocular alignment during conjugate and disconjugate eye movements, as well as for holding the eyes stable in the new position of gaze. Broader neural functions are required if the gaze shift is facilitated by a contraction of muscles in the neck and torso. In such cases, somatic proprioception and vestibular information assimilates with visual and extraretinal information to create an optimal behavioral response. Dysfunctions in sensory integration may cause dyspraxia, loss of balance, and disruption of binocular alignment and strabismus. The latter anomaly is one of the most common eye conditions in children and represents a significant public health issue. The etiology and pathophysiology of this condition is not fully resolved, yet seemingly attributable to disturbance of ocular proprioception or proprioceptors. These factors should be taken into consideration in the management of strabismus and other binocular vision anomalies.

Furthermore, several of the supranuclear structures receiving proprioception interact with pools of neurons involved in decision making, memory, and other cognitive functions. This indicates that ocular proprioception serves more neural functions than previously assumed. The notion that these functions can be augmented through noninvasive therapeutic regimens should not be dismissed.

The current article seeks to review some of the unique neuroanatomical structures in human extraocular muscles and their neural circuits. Knowledge about the potential role of ocular proprioceptors might expand our understanding of the etiology of strabismus and other oculomotor anomalies. (The views promoted in this paper are founded on the author's previous research and pertinent literature within the field of neuroscience.)

Structure and function of human extraocular muscles

Early differentiation and postnatal refinement of muscle fibers in the extraocular muscles is essential for normal development of binocular vision [1]. Muscle-fiber composition seems to be genetically predetermined, and the morphogenesis is almost complete at birth. The fibers are broadly classified based on the morphologic features that are critical to their function. Singly innervated fibers (SIFs) are most common and constitute more than 80% of the fiber population. Their efferent innervation consists of large diameter axons ensheathed by myelin, terminating on single neuromuscular junctions. Collectively, these coarse muscle fibers produce a forceful contraction, sufficient to counteract the opposing viscoelastic forces, and execute a saccadic eye movement.

The multiply innervated fibers (MIFs) are less common and constitute the remaining 20% of the fiber population. Most efferent axons are small and lightly myelinated, forming numerous minute nerve terminals along the entire length of the muscle fiber (Fig. 1). MIFs do not propagate an action potential but produce instead slow-graded contractions. They are fatigue resistant and ideal for facilitating smooth-pursuit eye movements, gaze holding, and prolonged convergence [2]. The notion that these fine-tuned muscle fibers play a vital role in the development, and maintenance of binocular vision is strengthened by the presence of receptors, located at their distal tendon [3].

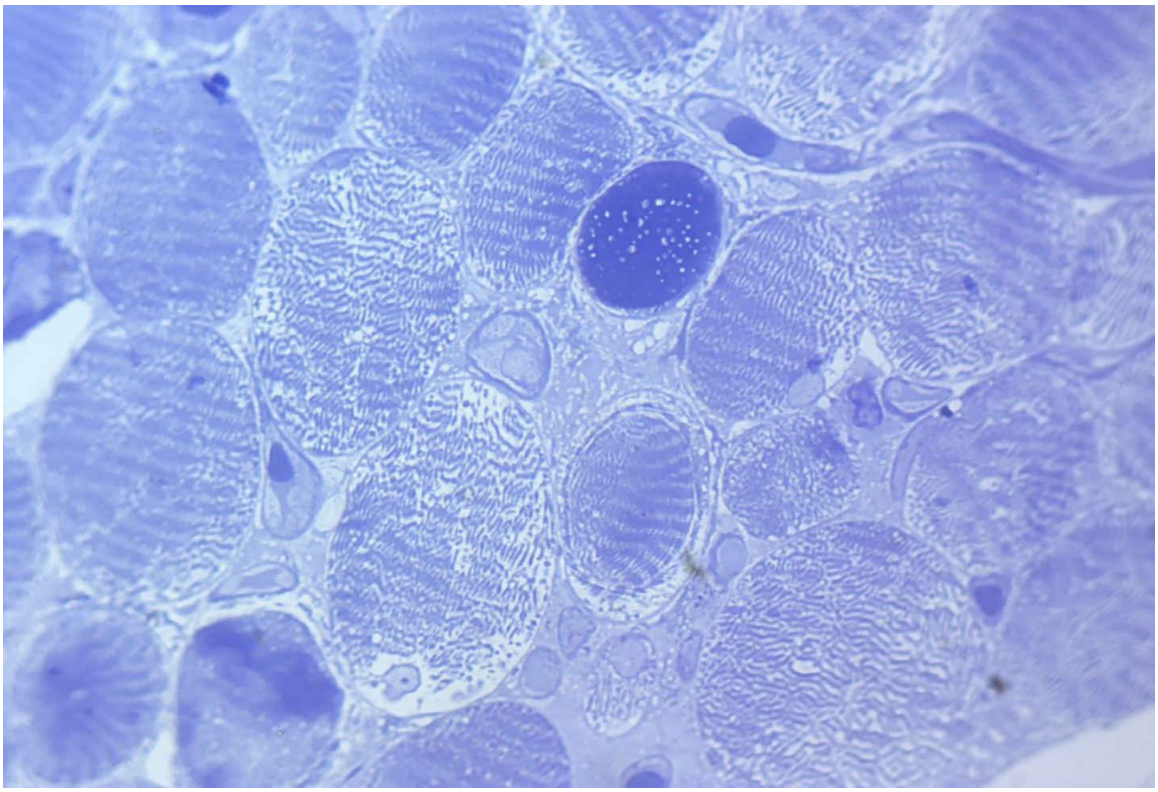

FIG. 1 Transverse section of the medial rectus muscle showing the morphologic characteristics of SIF and MIF fibers. The singly innervated fibers have large diameters and abundance of sarcoplasmic reticulum. The multiply innervated fibers are smaller and more densely stained (represented by the small dark fiber in the center of the micrograph).

Sensory receptors in human extraocular muscles

Muscle spindles

Spindles in human extraocular muscles have peculiar morphologic features and do not fully conform to the structural organization of their somatic counterparts. Peculiarities are present in both adult and infant muscle samples and hence not attributable to aging. The capacity of muscle spindles to provide effective proprioception, therefore, have been questioned [4]. In recent years, the attention has shifted to the tendon receptors, assumed to have a better proprioceptive capacity.

Tendon receptors

Human extraocular muscles lack the classic Golgi tendon organs found in somatic muscles and extraocular muscles of other species. Instead, they have myotendinous cylinders, also referred to as palisade endings. These structures are located in the distal end of MIFs. Nerve terminals arising from small myelinated axons are distributed between strands of contractile material in the junction between muscle and tendon. Cylindrical sheets of collagen encapsulate the neural elements to protect them from the mechanical force created by the adjacent muscle fibers (Fig. 2). This neuromuscular arrangement is consistent with that of other mechanoreceptors, indicative of a capacity to monitor active contraction as well as passive stretch [3,5]. Myotendinous cylinders reside in all cross-sectional regions of both the global and orbital layer of extraocular muscles. They, therefore, are in a position to provide the brain with information about the force generated by fibers pulling on the scleral collagen, as well as from fibers pulling on the surrounding canopy of connective tissue.

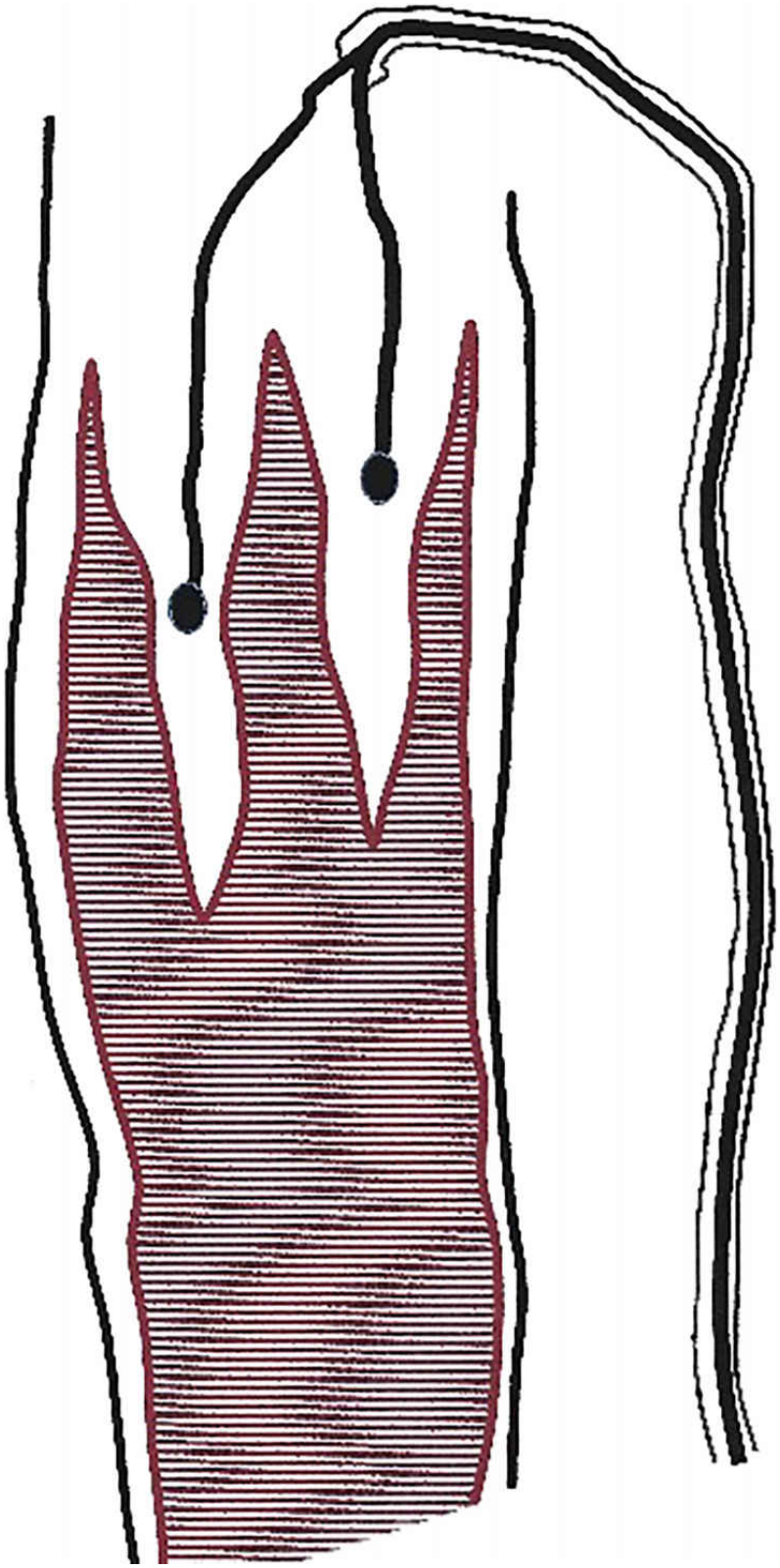

FIG. 2 Drawing to show the structural organization of the myotendinous cylinder. A recurrent small myelinated nerve fiber (*thick black line*) bifurcate

and terminates in between strands of muscular material (illustrated in *red*). Sheets of cylindrical shaped collagen (*black lines*) encapsulate the structure.

The orbital fiber layer (muscle fibers facing the orbit) envelopes the global layer in a "C"-shaped fashion. As the muscle fibers project toward the equator of the globe, they form sleeves of dense collagen [6]. The sleeves encircle the bulk of each muscle and function as pulleys. Demer [7], who promoted the concept, elegantly demonstrated that these structures act as mechanical origins of extraocular muscles and influence each muscles direction of pull. He also demonstrated that the subunits of each muscle can be activated independently.

This augments the complexity of oculomotor control and suggests that even horizontal rectus muscles may contribute in vertical excursion of the eye [7]. The neural substrate underlying pulley activity and compartmental innervation awaits further research, yet it is reasonable to assume that disruption of ocular proprioception has an adverse effect on their function [8].

The role of proprioception in oculomotor control

The eye is light in weight and the gravitational force remains relatively constant during eye movements. Furthermore, in contrast to many other somatic muscles, there is no external variable load acting on the extraocular muscles. These fundamental differences led to a long-standing controversy between 2 classic concepts. Helmholtz based his idea on the notion that the brain only needs a copy of the efferent signal in order to predict the position of the eye and to subsequently adjust the visual representation. In contrast, Sherrington advocated that the information about eye position is provided by muscle proprioceptors. Recent comparative and clinical studies have indicated that these concepts may not be mutually exclusive [5]. The latter concept has gained more support in recent years through clinical experiments in which somatic proprioception is found to influence a subject`s registered eye position. The effect (also demonstrated in the Jendrassik Maneuver) is attributable to changes in sensory feedback from MIF non-twitch neurons [9].

The neural pathway for proprioception

The ophthalmic division of the trigeminal nerve is assumed to be the primary neural pathway for ocular proprioception. Observations of a gradual decline in conjugacy, following disruption of this pathway in primates, indicates that proprioception plays a role in the long-term control of ocular alignment [10]. Clinical observations of oculomotor deficits in patients with pathologic conditions involving the ophthalmic nerve add credence to this view [11]. The primary afferent neurons reside in the trigeminal ganglion and electrophysiological evidence exists of proprioceptive projections to the superior colliculus, cerebellum, and cerebral cortex [12].

The cortical areas are interconnected by reciprocal pathways and have additional projections to the superior colliculus. Eye position information thus is available to all cortical areas involved in eye movement regulation, comprising the frontal eye field, the supplementary eye field, dorsolateral prefrontal cortex, parietal eye field, and the medial superior temporal area. Neurons in the latter area participate in motion perception and in the regulation of smooth-pursuit eye movements. The neuronal activity in this region varies depending on whether the movement is caused by an object movement or an eye movement. The ability to distinguish between the two is indicative of extraretinal input from MIFs [13].

It is of interest that many of the cortical and subcortical structures involved in eye movement regulation, such as the dorsolateral prefrontal cortex and hippocampus, also are involved in cognitive functions. Recent studies within the field of neuropsychology suggest that the oculomotor system and hippocampal memory systems interact in a reciprocal manner, and that they not only influence one another, but are interdependent [14].

The neural substrate for the control of eye movements

Extraocular muscles act functionally as 3 antagonistic pairs, receiving reciprocal innervation. They also have motor correspondence with the synergistic muscles of the other eye to ensure synchronized horizontal eye movements (Hering's law). The receptors associated with MIFs are in a unique position to monitor this type of activity, allowing the brain to compare the forces generated by the contraction of the 2 synergistic muscles with the opposing forces generated by the 2 antagonists. Detailed histologic studies, using high-resolution techniques, have revealed that MIFs have a more generous supply of unmyelinated nerve fibers than previously assumed (estimated motor unit of 1:1). This indicates that the oculomotor system can make muscle-force increments by activating one single muscle fiber at the time. This outranks all other somatic muscles in terms of motor control [15].

The motor neurons innervating the MIFs have modest cross-sectional diameters, reflecting the size of their axons (Fig. 3). They are located toward the periphery of the nuclei involved in ocular rotation (III, IV, and VI). The more prominent motor neurons, innervating the SIFs are accumulated in the core of the nuclei [16]. A third group of neurons resides in the oculomotor nuclear complex (Edinger-Westphal nucleus), giving rise to the parasympathetic innervation of the ciliary muscle. Histologic studies have revealed sensory nerve terminals residing in the latter muscle [17]. Their morphologic features indicate that they have a potential capacity to convey information about the accommodation that occurs during disconjugate eye movements.

Electrical recordings from the motor neurons innervating extraocular muscles suggests that their activity is influenced by 2 distinct premotor circuits: 1 that encodes the velocity and duration of the movement; and 1 that provides the tonic discharge needed to hold the eye in the new position of gaze. Once the velocity signal has completed the saccadic movement, the signal is converted into a position signal (neural integration). If the position signal is insufficient or disrupted, eccentric eye position cannot be maintained. Hence, although MIFs are in the minority in human extraocular muscles, they seem to play a vital role in ocular alignment and fixation stability [18].

The anatomic substrate of the neural integrator is not fully resolved, but a variety of supranuclear structures seem to participate in this process, including nucleus prepositus hypoglossi, interstitial nucleus of Cajal, and cerebellum [13]. The latter structure contains multisensory neurons with the ability to cross-reference and process information from the various sensory systems. The cerebro-cerebellum receives input from the cortical regions (including visual cortex), the spino-cerebellum receives input from proprioceptors in somatic and extraocular muscles, whereas the vestibulo-cerebellum receives input from the semicircular canals. This neural arrangement, which forms the basis for making adjustments to eye movements in relation to body movements and posture, have been elegantly demonstrated through various clinical studies [19]. A growing body of evidence suggests that dysfunctions in neural integration are implicated in a broad spectrum of somatic motor anomalies as well as binocular vision anomalies.

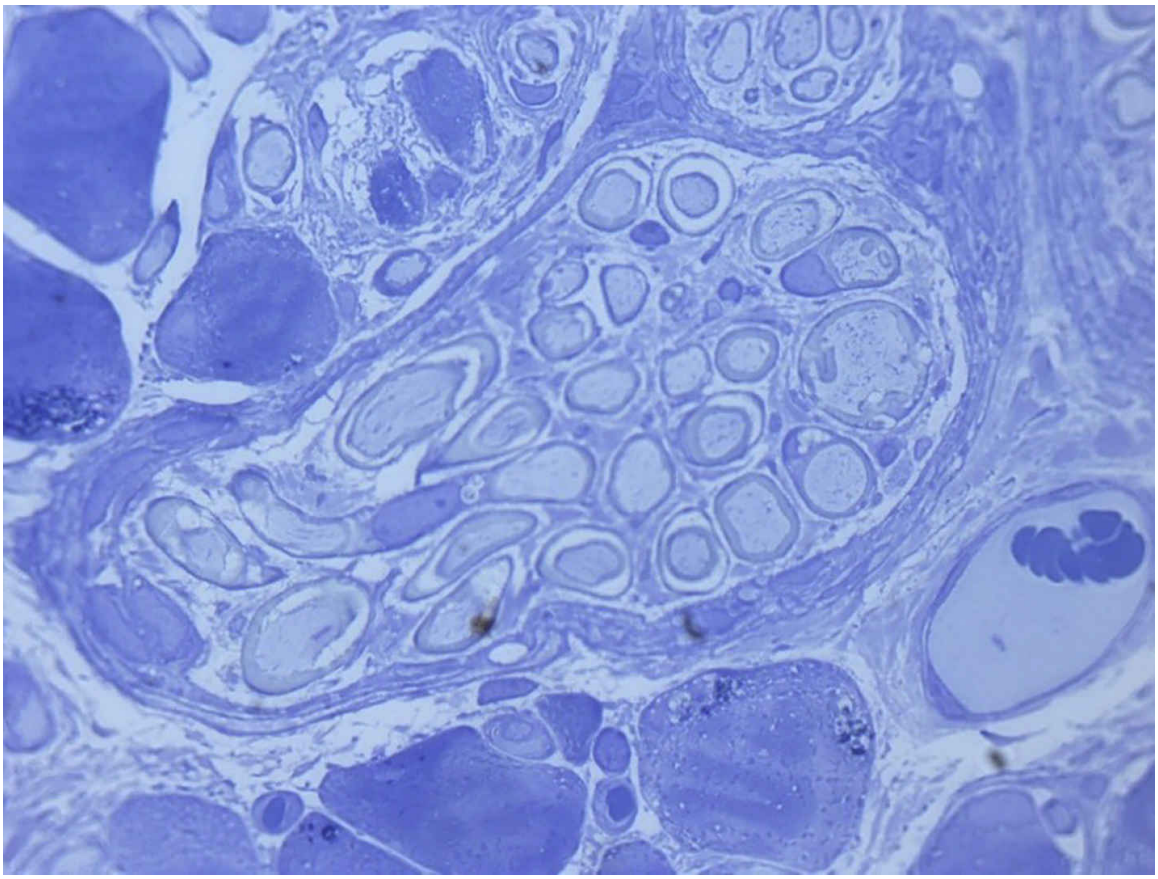

FIG. 3 Transverse section of myelinated nerve fibers showing the spectrum of nerve fiber diameters.

Binocular vision anomalies

Strabismus is a common ocular anomaly with an estimated global prevalence of 3% to 5% [20]. The condition is broadly classified in terms of the direction of the deviation, constancy, and comitance. Epidemiologic studies indicate that esotropia appears more often than exotropia; most cases are manifest and usually of concomitant origin [21].

The clinical characteristic of a concomitant strabismus is that the angle of deviation typically remains the same during all directions of gaze. Hence, the condition is seemingly not attributable to a specific muscle or cranial nerve. The misalignment is commonly diagnosed in patients with congenital or early-onset strabismus. The etiology is unresolved but dysfunctions of eye muscle proprioception during the sensitive period of development has been advocated. This view is supported through histologic studies where immature receptors were found in muscle samples obtained from subjects with congenital strabismus [22]. Structural anomalies of this kind were not observed in muscle samples obtained from normal subjects or from those with acquired incomitant strabismus.

Proprioception also might play a role in the sequela of incomitant strabismus. The clinical characteristic typical of this type of strabismus is that the angle of deviation changes during different directions of gaze, usually caused by neurogenic, myogenic, or mechanical-restriction anomalies. However, long-standing incomitant deviations may become concomitant with the passage of time, arguably caused by a gradual resetting of synergistic muscles [23]. This kind of neural tuning requires information about eye position, which suggests that proprioceptive information may arise even from paralytic muscles.

Current concepts in the diagnosis and management of strabismus

Many treatment options exist in the management of oculomotor anomalies. The choice of therapy by tradition is based on the clinician's personal preferences and a careful examination of the patient. A recent study on the effect of shared decision making in adult strabismus care revealed that patients do not always understand what the different treatment options entail. Satisfaction, hence, was significantly higher among the patients who were actively included in the decision-making process [24]. Traditionally, the options fall into 2 distinct categories, nonsurgical and surgical treatment.

Nonsurgical management of strabismus

Optical corrections

Accommodative esotropia is a common form of strabismus that is classically corrected with spectacles or contact lenses if the condition is fully accommodative. However, many of these patients develop partial accommodative esotropia over time and may need surgery to correct the residual angle of deviation. Clinical studies indicate that a spectacle correction promptly after onset of the condition gives the best prognosis [25]. The therapeutic effect of an early optical intervention is attributable to the binocular alignment that is usually established. A secondary effect is arguably the increased coherence between the proprioceptive signal arising from the smooth muscles of the ciliary body and the signal arising from extraocular muscles. A third therapeutic effect may be associated with the alleviation of the excessive force generated by both the intrinsic and extrinsic ocular muscles. Histologic studies have revealed that free nerve endings reside in the connective tissue strands bridging the oculomotor plant with the periorbita. These nerve endings resemble nociceptors with a potential capacity to create pain when subjected to mechanical stress. Their location and morphologic features have led to the opinion that they contribute to the discomfort and tension frequently reported by patients during prolonged convergence or when the eyes are forced into eccentric positions of gaze [26].

The use of small reading adds and prisms to relieve various forms of ocular discomfort is well documented in the literature [27]. The notion that some of the therapeutic effect is attributable to a reduction in neuromuscular tension and reduced sympathetic activity cannot be dismissed. In cases of infantile esotropia, with no prominent refractive error, other methods of treatment usually are considered.

Neuromuscular stimulation through exercise

The beneficial effects of physical exercise, such as muscular hypertrophy and angiogenesis, is well documented in the literature. Accumulating evidence exists for increased neurogenesis [28]. The effect of training to correct eye movements and visual-motor deficiencies are not explored to the same extent, yet many of the benefits seem to be the same [29]. However, achieving muscular hypertrophy may not be imperative in the

treatment of oculomotor anomalies. Only small amounts of force are required to move the eyes, and many authorities promote the view that ocular misalignments are more attributable to neural abnormalities, rather than myogenic dysfunctions [12]. This suggests that oculomotor therapy should target neural circuits, synaptic connections, and specific premotor regions in the brain. The cerebellum is renowned for its neuroplasticity and ability to learn and express procedural memories. Comparative studies of primates indicate that these abilities rely on long-term stimulation and input from sensory systems [30]. The same seems to be the case in man. Patients with cerebellar dysfunctions respond well to conventional musculoskeletal therapy by improving gait, balance, and hand-eye coordination [31]. Input from ocular proprioceptors seem to contribute to the maintenance of these important functions. Studies in which body sway was found to increase after strabismus surgery in children, seem to support this view [32].

Therapy aiming to enhance oculomotor functions and hand-eye coordination is arguably best achieved through stimulation of MIFs, because they have a direct impact on the cerebellum through their proprioceptive input. Visual tracking of moving targets and other methods of stimulating MIFs also may serve to attenuate neurodegeneration.

Systematic and repetitive neuromuscular activity ensures a rapid release and reuptake of transmitter-substance, which has proved to be imperative for retaining synaptic structural stability. Histologic studies of human extraocular muscles have demonstrated that efferent nerve fibers tend to detach themselves from inactive muscle fibers. A further rearrangement of the efferent innervation will occur if the redundant axons find new targets (polyneural innervation) [15]. Similar hypotrophic tendencies have been observed in pathologic conditions associated with mitochondrial dysfunction [33]. Hence, consistent with neuromuscular systems elsewhere in the body, it seems imperative to keep the activity in the oculomotor system above a critical level, especially during the early stages of life. A postnatal delay occurs in the proliferation of myotendinous receptors. Their complement and morphologic features are seemingly not fully developed until the age of 5 [3]. These findings have recently been confirmed in extraocular muscles of various mammals [34]. Hence, the cerebellum and other supranuclear structures involved in the tuning of oculomotor activity are seemingly deprived of adequate information about eye position in the sensitive period of development. Consequently, the ability to monitor and adjust for neurogenic and myogenic changes is

limited. A potential delay in the development of other sensory systems or ambiguity in the information they provide may augment the chances of developing strabismus.

Surgical management of strabismus

Strabismus surgery attempts to align the eyes by strengthening (resection), weakening (recession), or by changing the direction of pull of one or more of the extraocular muscles (Table 1). These surgical procedures have been applied and refined over many years. During a resection procedure, a bit of the distal part of the muscle is removed. The shortened muscle is then reinserted onto its original location on the sclera. This surgical intervention stands in contrast to the recession procedure in which the distal insertion is detached and reinserted more posteriorly, without altering muscle length. Although both procedures will change the muscle`s rotational effect on the eye, the functional and neurogenic implications are quite different. In terms of functional implications, the shortening of a muscle changes the length-tension relationship and increases the muscle`s pull on the scleral collagen.

The neurogenic implications are associated with the number of receptors manipulated or removed, during the surgical procedure.

However, these potential implications will vary depending on the morphologic features of the muscle that is operated. Preliminary results from histologic studies on muscle samples obtained during strabismus surgery indicate that larger esodeviations can be surgically corrected (resection) without disrupting the myotendinous region, compared with exodeviations. This is due to the nature of the tendon in the temporal rectus, which is significantly longer than its counterpart in the medial rectus [35]. This may be a contributing factor to the difference of surgical outcomes between manifest exotropia and esotropia [36]. Postoperative changes in spatial localization and other perceptual parameters may be primarily associated with those cases where the myotendinous receptors have been compromised [37].

Table 1 General principals behind strabismus surgery

Type of procedure	Effect on muscle
Recession	Weakened
Myotomy	
Myectomy	
Posterior fixation suture	
Resection	Strengthened
Tucking	
Advancement	
Injection of botulinum toxin	Weakened
Injection of growth factors (experimental)	Strengthened

Summary and discussion

The degree to which disruption of ocular proprioception is attributed to strabismus and other oculomotor anomalies remains unclear, yet from this review, it seems legitimate to argue that ocular proprioceptors facilitate the following biological functions:

- Development of visual functions

  The myotendinous cylinders, located at the distal end of MIFs, seem to contribute to the development of stable bifoveal alignment. Receptors with similar morphologic features reside in the ciliary body, suggesting that proprioception also is involved in the modulation of the coarsely preprogrammed relationship between convergence and accommodation.

  The developmental timeline for myotendinous cylinders seems to be significantly longer than for other receptors. Hence, information about the position of the eyes in relation to the orbit may be the weakest sensory signal in the early stages of the developmental period.
- Tuning and adaptation

  Morphologic alterations occur in the visual system with the passage of time, and the oculomotor system must make adaptations in response to all structural changes caused by growth and aging. This capability seems to rely on receptors in the extraocular muscles, as suggested in several histologic and clinical studies.
- Visual processing and adjustments of the visual representation

  Neurons in the extra striate visual areas are able to distinguish between displacements of a retinal image caused by an object movement versus an eye movement. This requires knowledge about the ocular rotation that has taken place. Accumulating evidence suggest that this information is provided by the receptors associated with the slow-contracting MIFs.
- Balance and equilibrium

  The cerebellum provides balance and equilibrium through input from vision, somatic proprioception, and the vestibular system. The neural contribution from the respective systems

is elegantly demonstrated through the Romberg test or similar methods based on the same theoretic principal. The notion that ocular proprioceptors also contribute is indicated through various histologic and clinical studies.

- Plasticity

  Evidence, accumulated over the past decades indicates that the brain has a significant capacity to reorganize pathways, create new synaptic connections, and synthesize new neurons. This capacity seems to rely on sensory input. Information arising from ocular proprioceptors are conveyed to a broad spectrum of supranuclear structures and may contribute to the plasticity and the adaptation processes that occur in these regions of the brain. Some of these regions also are involved in executive functions. Cognitive skills are known to develop gradually over time, and the notion that ocular proprioception facilitates this development cannot be dismissed.

- Double insertion of the distal tendon

  Extraocular muscles pass through collagen structures near the equator of the globe, acting as muscle origins (pulleys). This concept challenges our conventional understanding of the muscle's oculorotary actions, and the role they play in the pathophysiology of strabismus. The position of pulleys is critical to the rotational properties of the various muscles, yet the neural substrate for pulley activity is not fully resolved. Observations of receptors in the orbital fiber layer of extraocular muscles adds credence to the notion that proprioception may be involved in the dynamics of these collagen structures.

- Innervation of muscle compartments

  It has been demonstrated that the functional differentiation of extraocular muscles allows the oculomotor system to control individual compartments and subunits of each muscle with a high degree of independence. It is reasonable to argue that adjustments of their activity are monitored in the same manner as seen in somatic muscles.

- Neural integration and gaze holding

  The MIFs are fatigue resistant with the ability to make minute adjustments to eye position in response to changes detected

through their sensory receptors. This type of neuromuscular arrangement represents a minute sensory-motor control loop, which facilitates gaze holding at the starting point and endpoint of eye movements. Muscle-fiber composition seems to vary considerably between individuals, and a low concentration of MIFs may thus have functional implications for both gaze holding and fixation stability.

The current review supports the notion that our understanding of the external world relies on the brain's ability to obtain and process information from different sensory systems. The summation of this information provides the basis for our perception, decision making, and subsequent behavior. From this standpoint, clinical evaluation of one single sense has a limited diagnostic value, unless it is put into context with the input from the other senses.

Many treatment options exist in strabismus management, comprising optical corrections, occlusion, surgical procedures, Botox injections, or ocular exercises. Their therapeutic approach is very different in respect to their effect on proprioceptors and proprioception.

Cumulative evidence supports the notion that stimulation of the various sensory systems can enhance a variety of biological functions, not limited to binocular vision and perception. This is the conceptual framework of many treatment regimens, comprising various avenues of orthoptic treatment, vision therapy, and multisensory therapy. However, not all patients may be suitable candidates for ocular eye exercises or visual stimulation.

Strabismus surgery holds long traditions in the treatment of oculomotor anomalies. Previous studies on the outcome of strabismus surgery have indicated that various perceptual parameters may be affected, which may be attributable to disruption of proprioceptors or their neural pathways. However, more recent studies indicate that disruption of proprioception may occur to a lesser extent that previously assumed.

Summary

The main conclusion that can be drawn from this review is that proprioception plays an important role in development and maintaining binocular vision. It also is legitimate to argue that proprioception supports perceptual and cognitive functions. These views are founded on results from histologic research and comparative and experimental studies. Therefore, future research should be conducted in more realistic clinical settings so that the therapeutic effects and potential side effect of the various surgical as well as nonsurgical treatment regimens can be identified and documented. Such undertaking could prove beneficial to the clinical and scientific literature.

Disclosure

The author declares that there is no conflict of interest.

Clinics care points

- Disruption of proprioception from extraocular muscles may jeopardize the oculomotor system's ability to adapt to structural changes caused by growth and senescence. Hence, clinical evaluation of ocular proprioception is warranted in the diagnosis and management of both developmental and acquired oculomotor anomalies.
- Multiply innervated muscle fibers are fatigue resistant. Individuals with a genetically predetermined low composition of these fibers hence are predisposed to oculomotor anomalies associated with smooth-pursuit eye movements, gaze holding, and fixation stability.
- Sensory input is known to increase neural plasticity and adaptation. Tracking slow-moving objects will stimulate multiply innervated muscle fibers and activate their associated receptors. This will initiate neural activity in a variety of supranuclear structures and may enhance their function.
- The neuromuscular junctions in human extraocular muscles are labile and the metabolic activity must be kept above a critical level to avoid detachment of the efferent nerve terminal. Ocular exercise can serve to attenuate neuromuscular degeneration.
- The cerebellum plays a vital role in retaining balance and hand-eye coordination. Rivalry between the sensory information it receives may cause neural integration disorders. The Romberg test, and other clinical tests based on the same theoretic principal, represent valuable diagnostic tools in the evaluation of somatic and oculomotor anomalies.
- The distal tendon in the temporal rectus muscle is long, compared with its counterpart in the medial rectus muscle. Therefore, larger resections can be performed on the temporal rectus muscle, without disrupting sensory receptors, compared with resections on the medial rectus.

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Pediatric

OUTLINE

Prenatal Diagnosis of Retinoblastoma

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Keywords

Retinoblastoma; Prenatal diagnosis; Fetus; Obstetric ultrasound; Fetal MRI; Cell-free DNA; Amniocentesis

Key points

- Prenatal diagnosis of retinoblastoma is possible in families at risk using a combination of genetic testing, high-resolution targeted ultrasound of the fetal globes, and fetal MRI.
- Early diagnosis of retinoblastoma is important, as the doubling time is extremely fast (approximately 15 days).
- Early term or late preterm delivery allows initiation of therapy with the goal of maximizing the chance of preserving vision and avoids devastating complications such as metastatic disease and death.

Introduction

Retinoblastoma makes up 3% of all childhood cancers and is the most common intraocular tumor [1]. The tumor is aggressive, with an estimated doubling time of approximately 15 days [2,3]. Early diagnosis is important, as survival rates for children with small tumors approach 100% [4]. Given that 40% of retinoblastomas are heritable [5], this can be accomplished in families at risk with the overarching goal of achieving a complete cure. Clinical consequences of late diagnosis include vision loss, metastatic disease, and death [6].

Incidence

The worldwide incidence of retinoblastoma is estimated as 1:15,000 to 1:20,000 livebirths [7]. The mean age-adjusted incidence rate in the United States is 11.8 cases per million children aged 0 to 4 years [8]. Bilateral tumors (see later discussion) typically present around 12 months, in comparison to their unilateral counterparts that present around 24 months [2].

Risk factors

Genetic predisposition is the main risk factor for retinoblastoma. Race, environmental factors, and gender are not risk factors.

Genetics

There are 2 main types of retinoblastoma: heritable and sporadic. Sporadic retinoblastoma corresponds to approximately 60% of the cases, is always unilateral [9], and carries a 6% risk of recurrence for the offspring [10,11]. Heritable retinoblastomas correspond to 40% of the remaining cases. They are bilateral in 80%, unilateral in 15%, and trilateral (bilateral retinoblastomas plus a midline suprasellar or pineal primitive neuroectodermal tumor) in 5% of the cases [4,12,13]. Regardless of whether tumors are heritable or sporadic, they are usually diagnosed during the first 5 years of life, with a median age at diagnosis of 18 to 20 months [14,15]. Thus, any observation of leukocoria constitutes an indication for referral to a pediatric ophthalmologist to rule out retinoblastoma [14].

This article focuses on heritable retinoblastomas because these are the ones amenable to prenatal screening and diagnosis. Heritable retinoblastomas can be caused by a sporadic somatic mutation or as an inherited mutation in the germline cells and are at increased risk for osteosarcomas, melanomas, and brain cancer [16,17], requiring lifelong monitoring. They constitute a textbook example of a Knudson's 2 hit hypothesis [18]. This hypothesis explains why the

retinoblastoma gene (RB1) found on chromosome 13, which is genetically recessive, displays a dominant inheritance pattern with one mutated copy of the tumor suppressor gene being passed down to the offspring [4,12]. Normally, tumor suppressor genes require both copies to be defective in order for the disease to express and be detrimental to the individual [4]. Dr Knudson hypothesized that, in the case of retinoblastoma, inheritance of the mutated copy of RB1 is the "first hit" or predisposing event [18]. The "second hit" occurs when there is a random genetic mutation of one of the rapidly dividing cells of the retina [18]. With 2 mutated tumor suppressor genes, tumor growth progresses uninhibited without one of the regulation steps in the cell growth process. As mentioned earlier, retinoblastomas tend to present as bilateral multifocal tumors because the germline contains the mutated RB1 gene [4].

Tumor staging

Tumors are graded from A to E from least to most severe using the International Classification for Intraocular Retinoblastoma [19–21]. Group A tumors are less than or equal to 3 mm, confined to the retina, 3 or more mm away from the fovea, 1.5 mm or more away from the macula, and with no vitreous seeding [19–21]. Staging progresses to grades B, C, and D, as tumors become larger and involve more of the eye [19–21]. Group E tumors involve more than 50% of the globe and effectively destroy the eye either anatomically or functionally [19–21]. Group E retinoblastomas may present with neovascular glaucoma, massive intraocular hemorrhage, and/or aseptic orbital cellulitis. Tumors may extend beyond the anterior vitreous face and touch the lens. Diffusely infiltrating tumors, phthisis, or pre-phthisis are also considered Group E [19].

Treatment

Treatment guidelines customized to the stage of the tumor are associated with improved therapeutic success [19,21].

Group A retinoblastoma can be treated with conservative measures such as transpupillary thermotherapy, laser coagulation, or cryotherapy [1]. These methods aim to shrink the tumor by selectively sclerosing the arteries with increased heat, coagulating the arteries feeding the tumor, or by causing endovascular damage at freezing temperatures, respectively [1]. Transpupillary thermotherapy has also been shown to have a synergistic effect when combined with Carboplatin in vivo resulting in increased tumor cell death [22]. Combining transpupillary thermotherapy and chemotherapy is associated with lower rates of tumor recurrence 4 years after treatment, from approximately 35% with chemotherapy alone to 17% with the combined therapy [23,24]. For Group B retinoblastomas, focal laser ablation and cryotherapy have been the mainstays of

treatment. Currently, more emphasis is being placed on primary treatment with intraarterial chemotherapy, especially when the tumor is unilateral and the macula is involved. Laser ablation close to the macula could potentially lead to vision loss, making intraarterial chemotherapy more often the chosen method of treatment [21,25]. Group C and D tumors are preferentially treated with systemic or intraarterial chemotherapy due to the greater tumor burden [26–28]. Treatment with intraarterial chemotherapy is used predominantly in unilateral treatment, whereas systemic chemotherapy is the preferred initial treatment of bilateral disease [26–28]. Group E tumors can eventually require enucleation after failed attempts to salvage the globe [29]. Intraarterial chemotherapy is being implemented to attempt to treat these tumors before they metastasize, so far with mixed results [25]. Systemic chemotherapy is typically still required if there are high-risk features seen on pathology after enucleation [30].

Prenatal diagnosis

Rationale

As stated earlier, the goals of prenatal diagnosis in families at risk for retinoblastoma are to preserve vision, avoid enucleation, metastatic disease, and death. Because most tumors occur in the proximity of the fovea and macula, early diagnosis may be the only real chance to preserve vision. The only drawback of prenatal diagnosis is the potential for early delivery of the fetus in the late preterm or early term periods, which is associated with small but real risk factors such as respiratory distress and hyperbilirubinemia [31]. Thus, these complications must be considered and weighed against the risk of loss of vision or life due to delayed treatment. When the hyperbilirubinemia is severe, for example, hepatotoxic chemotherapy agents such as etoposide and vincristine need to be adjusted to prevent liver damage or increased hyperbilirubinemia. Nonetheless, preliminary studies show that when retinoblastoma is diagnosed using prenatal ultrasound and an early term delivery is planned, that the outcomes for the patient are beneficial [32,33]. These outcomes include improved vision and less invasive therapy, making the slight risk of early term labor worth the reward of improved quality of life [32,33]. If prenatal diagnosis is unavailable in a patient with a familial history of heritable retinoblastoma, an ophthalmologic examination under anesthesia should be performed within the first day of life [32,34].

Prenatal genetic testing

Prenatal genetic testing can be accomplished by preimplantation genetic diagnosis or prenatal genetic testing using chorionic villus sampling, amniocentesis, or fetal blood sampling [10,35]. A recent exciting development for prenatal genetic diagnosis of retinoblastomas has been reported by Gerrish and colleagues [36] who performed noninvasive prenatal diagnosis by analyzing cell-free fetal DNA for the germline RB1 mutation in the maternal blood of 12 pregnancies. It is hoped that such testing strategy will become commercially available in the near future to facilitate the screening of families at risk as early as 8 weeks of gestation.

Once identified, it is well known that fetuses with the RB1 germline mutation have a close to 100% risk of bilateral retinoblastomas. These fetuses can thus be delivered early at approximately 36 to 38 weeks with immediate postnatal ophthalmologic examination and treatment. Soliman and colleagues [33] provided evidence regarding the effectiveness of this approach. The investigators compared 2 cohorts of fetuses at risk for heritable retinoblastoma, the first consisting of spontaneously delivered neonates who were examined

within 1 week of birth and who were confirmed postnatally to carry the family's RB1 mutant allele (Cohort 1), against a second cohort of fetuses identified prenatally by amniocentesis and delivered between 36 and 38 weeks (Cohort 2). All infants eventually demonstrated tumors in both eyes. However, tumors of fetuses in Cohort 2 were significantly smaller and less threatening to vision loss at presentation compared with Cohort 1 (8/12 fetuses in Cohort 2 had stage CT1a/cT1a or cT1a/cT10 tumors compared with 1/8 in Cohort 1, [P = .02]). Furthermore, a higher proportion of children in Cohort 2 achieved treatment success (11/12) compared with 3 of 8 children in Cohort 1 (P = .002). Importantly, there were no complications related to early delivery for fetuses in Cohort 2.

Prenatal imaging in fetuses at risk for retinoblastoma

A few published studies highlight the possibility of diagnosing retinoblastomas in utero by ultrasound and/or MRI [6,34,37–42]. Maat-Kievit and colleagues [38] reported in 1993 on the incidental prenatal ultrasonographic diagnosis of a large retinoblastoma at 21 weeks in a family with no prior history. At the time of presentation, the tumor extended outside the right orbit to cover most of the face and also extended to the ipsilateral middle cranial fossa. A second case was reported by Salim and colleagues [39] at 38 weeks. The tumor presented as a solid mass within the left orbit and extended to the left face, left frontal, temporal, and parietal regions; this was also an incidental diagnosis in a patient at no risk who was examined by ultrasound due to trouble breathing. Toi and colleagues [37] reported retrospective data obtained from prenatal screening of 21 mothers and 23 fetuses at risk for retinoblastoma by ultrasound. Among 2 fetuses with retinoblastomas confirmed after birth, one had a 3.7 mm lesion detected at 33 weeks. Paquette and colleagues [34] performed a prospective screening imaging study using ultrasound and MRI on 6 fetuses at risk for retinoblastoma. Ultrasonographic studies were performed every 4 weeks beginning at 16 to 20 weeks and every 2 weeks in the third trimester. Fetal MRIs were performed using 1.5 T magnets at the same time as the first ultrasound and thereafter every 8 weeks. One fetus had an elevated 2 to 3 mm tumor detected by ultrasound at 37 weeks; however, 2 additional minimally elevated tumors in the contralateral eye were not detected. None of the tumors were detected by MRI. Investigators from the Royal Children's Hospital of Melbourne in Australia published in 2014 on a retrospective study of prenatal and immediate postnatal findings of fetuses at risk for retinoblastoma who had prenatal imaging by ultrasound and/or MRI from March 2008 to March 2013 [6]. None of the 5 patients diagnosed with retinoblastoma after birth were identified prenatally by ultrasound, although only 2 had ultrasonographic images of the globes that were considered adequate after rereview of the images. One patient had bilateral posterior pole lesions detected by fetal MRI at 35 weeks [6].

Stathopoulos and colleagues [40] diagnosed a 15 × 10 mm tumor by ultrasound at 35 weeks in a patient at risk. The fetus was delivered at 36 weeks due to severe preeclampsia. Chemotherapy was initiated after birth, and follow-up at 6 months showed tumor resolution and normal vision for both eyes. The last reported case to date is that of a child incidentally diagnosed with a large 15 × 15 × 12 mm tumor in the left eye at 39 weeks [41]. Although the tumor was confirmed after delivery, treatment by intraarterial chemotherapy was initiated only 4 weeks after birth. At the time of treatment, multiple smaller equatorial lesions and exudative retinal detachment were also identified. The patient had a contralateral smaller tumor that was treated by laser, with a recurrence requiring additional laser treatment 2 months thereafter.

The authors recently reported a case of a 19-year-old female pregnant patient diagnosed with bilateral retinoblastomas when she was 2 years old and, therefore, at risk for the development of bilateral retinoblastoma in her offspring [42]. The patient declined invasive prenatal genetic diagnosis, and the fetus was imaged by high-resolution ultrasound beginning at 32 weeks. The examination showed elevated 1.6 × 0.6 mm hyperechogenic mass in the retinal surface of the right eye consistent with retinoblastoma (Fig. 1), which increased to 2.1 × 0.9 mm at 33 weeks. An additional plaque-like retinoblastoma was diagnosed in the left eye at 34 weeks (Fig. 2). A fetal MRI confirmed the tumors and showed no evidence of a trilateral retinoblastoma (Fig. 3). Both tumors increased in size by 36 weeks, prompting early delivery. Tumors were confirmed, and a second smaller tumor in the right eye was also identified (Figs. 4 and 5). Because the baby had physiologic hyperbilirubinemia, he was treated with carboplatin instead of protocol RET0231 (carboplatin, vincristine, and etoposide). Follow-up examination at 23 days of age showed 76% and 81% decrease in tumor bulk for the right eye tumors and no significant change for the plaque-like left eye tumor.

Protocol for Prenatal Diagnosis of Retinoblastoma

The authors' current protocol for prenatal screening and diagnosis of retinoblastoma is outlined:

- Prospective mothers at increased risk of transmitting an RB1 mutation to their offspring are counseled by a geneticist and ocular oncologist.

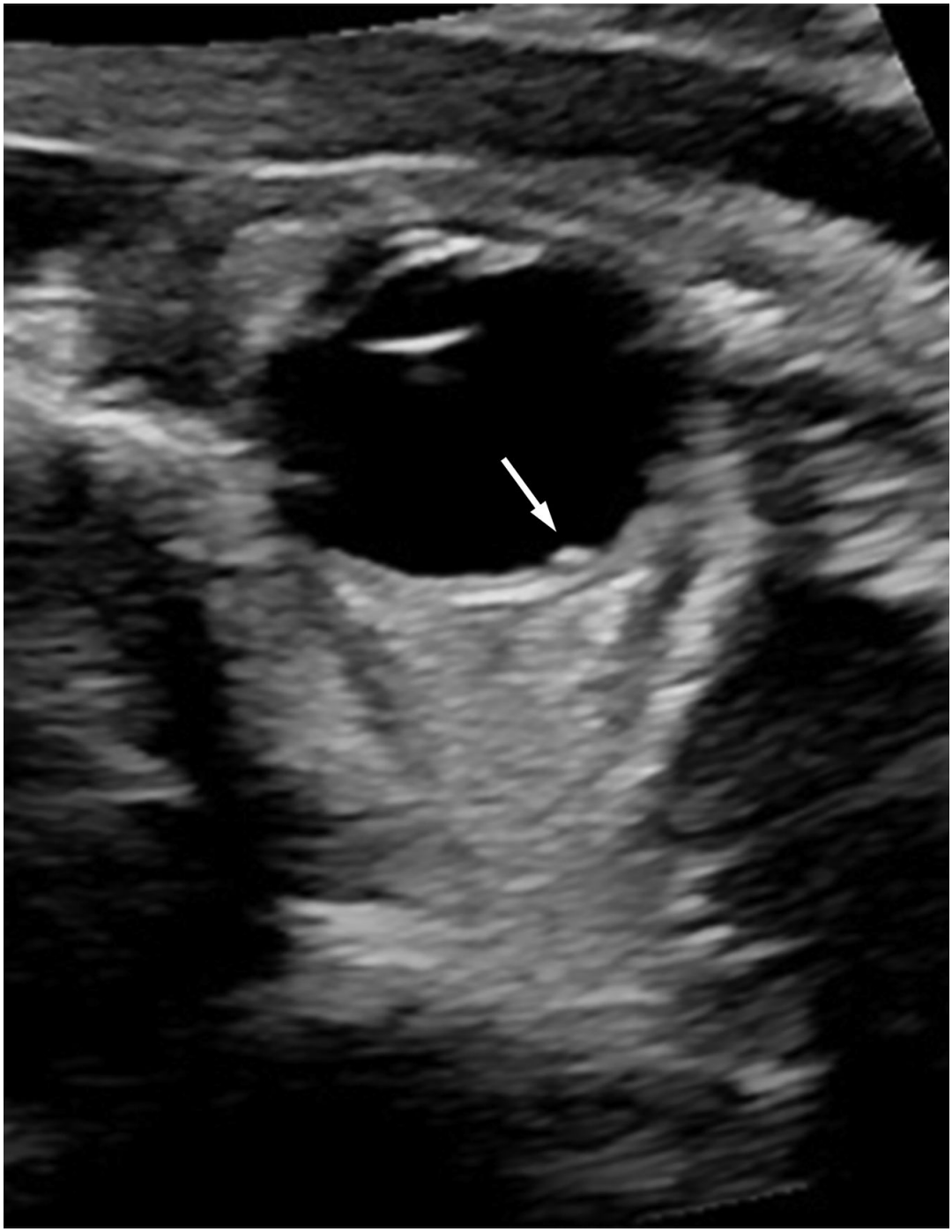

FIG. 1 Prenatal ultrasound of the right orbit shows a 1.6 × 0.6 mm oval hyperechogenic focus overlying the retina (*arrow*) located temporally to the optic nerve consistent with retinoblastoma.

(*From* Goncalves LF, Ramasubramanian A, Grebe T, Riemann M, Moncrief D, Cornejo P. Prenatal diagnosis of bilateral retinoblastomas by multimodality fetal imaging: case report and review of the literature. Clinical Imaging 2021;78:121-126; with permission.*)*

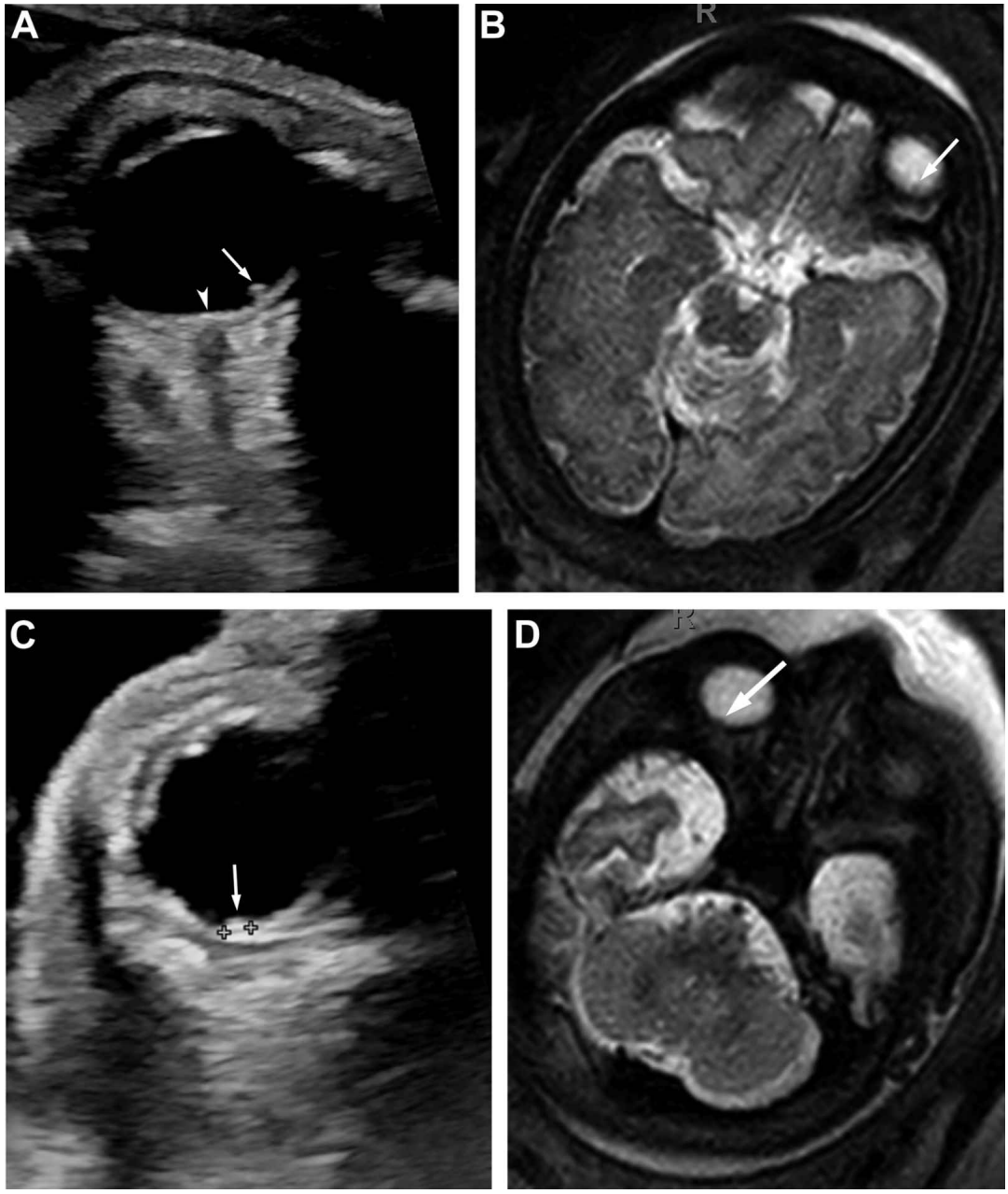

FIG. 2 (*A*) Ultrasound of the right orbit at 34 weeks shows a stable small retinoblastoma (*arrow*). The spatial relationship between the tumor and the optic nerve (*arrowhead*) can be clearly seen in this image. (*B*) A 3-mm thick T2-weighted fetal MRI image of the right orbit obtained the same day to rule out a pineal mass (trilateral retinoblastoma) shows a tiny hypointense focus in the retina (dashed *arrow*) consistent with the retinoblastoma seen by ultrasound on (*A*). The retinoblastoma is easier to identify by ultrasonography. Ultrasound of the left orbit at 34 weeks uncovered a new plaque-like retinoblastoma in the left globe (*arrow* in *C*). This plaque-like retinoblastoma can also be seen on the fetal MRI image of the left orbit obtained the same day (*dashed arrow* on *D*) but only after correlating closely with the ultrasound image (*C*).
(*From* Goncalves LF, Ramasubramanian A, Grebe T, Riemann M, Moncrief D, Cornejo P. Prenatal diagnosis of bilateral retinoblastomas by multimodality

fetal imaging: case report and review of the literature. Clinical Imaging 2021;78:121-126; with permission.)

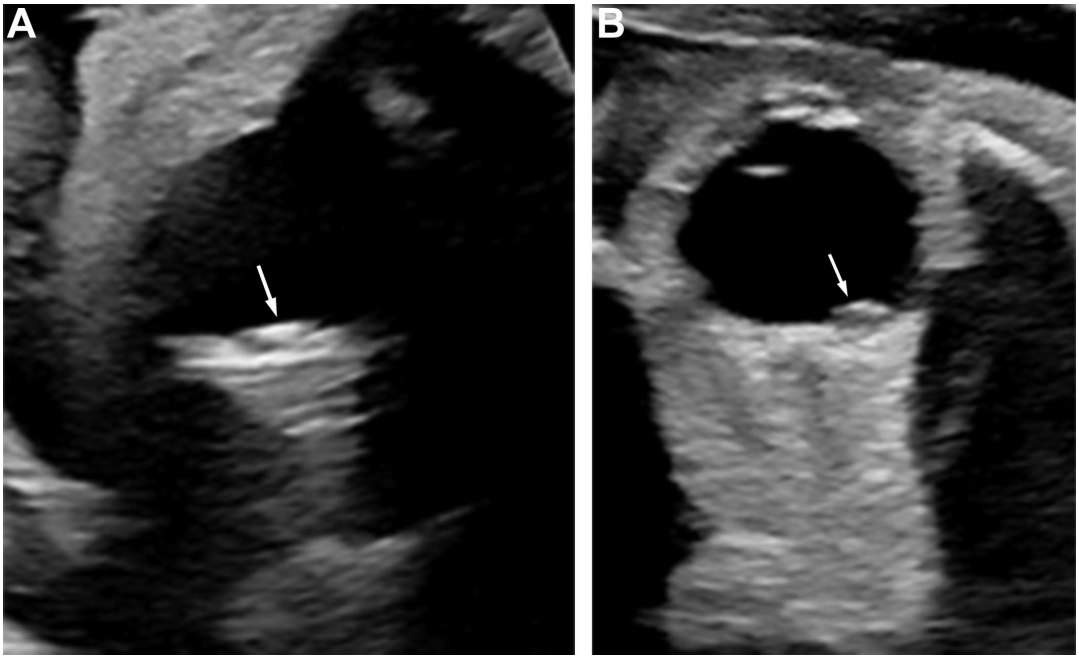

FIG. 3 Follow-up ultrasound at 36 weeks shows interval growth of both retinoblastomas (*arrows* in *A* and *B*). (*A*) Left orbit. (*B*) Right orbit. (*From* Goncalves LF, Ramasubramanian A, Grebe T, Riemann M, Moncrief D, Cornejo P. Prenatal diagnosis of bilateral retinoblastomas by multimodality fetal imaging: case report and review of the literature. Clinical Imaging 2021;78:121-126; with permission.*)*

- The authors recommend prenatal genetic diagnosis for those with a known RB1 mutation.
- In case of a negative RB1 test, no further screening is required.
- In case of positive RB1 testing or if the family declines genetic testing, weekly multimodality fetal imaging using high-resolution ultrasound and MRI is started at 32 weeks.
- A fetal MRI is performed at 34 weeks to rule out trilateral retinoblastomas.

Summary

One of the biggest indicators of successful retinoblastoma treatment is the time of diagnosis. Any advancements in screening or treatment that can be done earlier would show a better outcome for the patient. A retinoblastoma diagnosis has become less devastating in recent years due to advancements in early detection and customized treatment regimens [17,21,24,29,43]. Because doubling time is a huge contributor to worse prognosis, the earlier the retinoblastoma is detected and visualized, the better the outcome will be for the patient [2,15,33,36,44]. Retinoblastoma has become a curable cancer with an easier detection rate in recent years through the advancements in technology in early screening mechanisms [33,36]. Advancements such as prenatal diagnosis are very important in catching early stage bilateral retinoblastoma in patients with a strong familial history of retinoblastoma [33,36]. Early detection can lead to early term labor and potentially save the child's vision in one or both eyes. Genetic screening tests as well have been a great advancement in recent years because they are able to take a sample of the fetal DNA from mom's blood and confirm if the baby has the mutated copy of the RB-1 gene [36]. More efforts should be made to improve access to lifesaving techniques such as ultrasound and genetic testing worldwide. There is still limited access to prenatal ultrasound currently due to the requirement of a trained multispecialty retinoblastoma team [34]. More work should be done to increase access to lifesaving screening tools and diagnostic tools such as genetic testing for retinoblastoma and prenatal ultrasound. These tools have been proved to improve prognosis for patients and preserve vision [33,34,45]. Future research should be put into how accurate these tests are at diagnosing retinoblastoma as well as the benefits versus risks associated with early delivery in a child with bilateral retinoblastoma. There have been a lot of advancements in genetic detection of retinoblastoma, and further work needs to be done in order to accurately describe the pathway associated with an RB1 gene mutation [12,33,46]; this could help further understand when and where secondary tumors might recur as well [47–49]. Efforts should be made to investigate the risks and benefits to prenatal ultrasound testing in cohorts of heritable retinoblastoma cases. The mother and baby’s risk involved with inducing early term labor should be weighed against the benefits of early treatment.

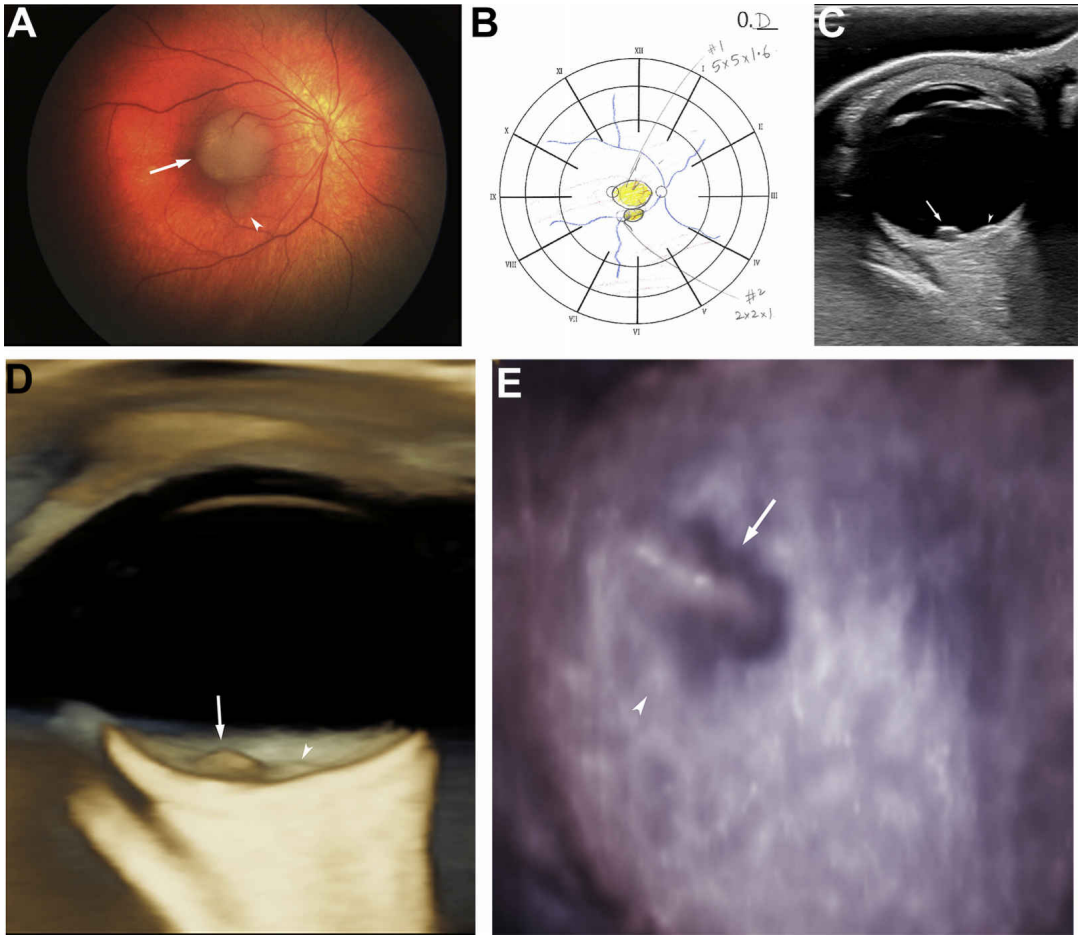

FIG. 4 RetCam photography (*A*) and corresponding retinal drawing (*B*) of the right eye at age 4 days. The larger tumor (*arrow*) was diagnosed prenatally and involved the fovea. A tiny smaller tumor seen inferiorly and adjacent to the larger tumor (*white arrowhead*) was not seen prenatally. Postnatal ultrasonographic images of the right globe. Axial 2-dimensional (2D) (*C*), axial 3D (*D*), and en face 3D rendered image of the retina (*E*) show the main (*arrowhead*) and satellite (small *arrowhead*) tumors. (*From* Goncalves LF, Ramasubramanian A, Grebe T, Riemann M, Moncrief D, Cornejo P. Prenatal diagnosis of bilateral retinoblastomas by multimodality fetal imaging: case report and review of the literature. Clinical Imaging 2021;78:121-126; with permission.*)*

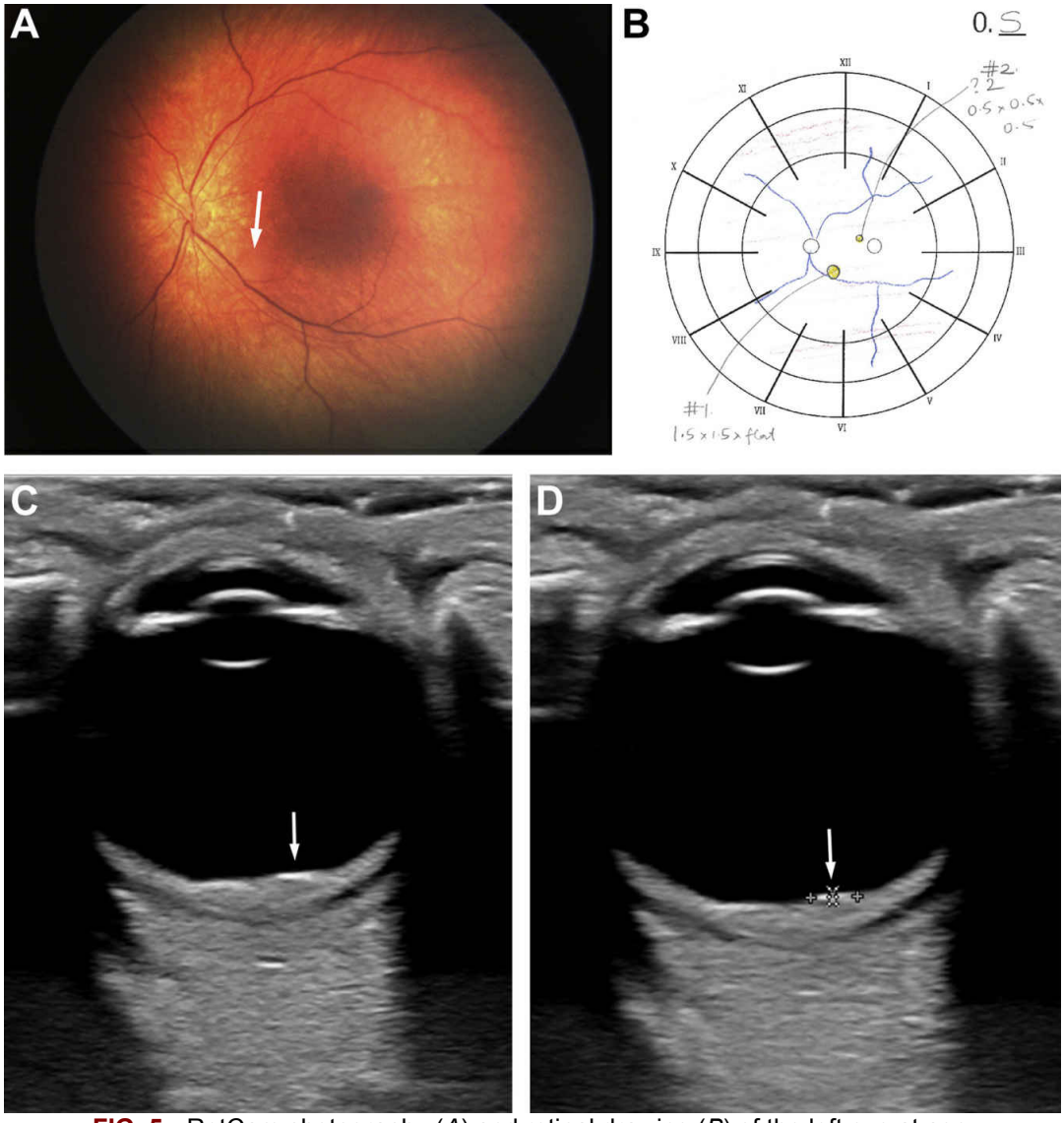

FIG. 5 RetCam photography (*A*) and retinal drawing (*B*) of the left eye at age 4 days. The larger plaque-like tumor was diagnosed prenatally and is located inferotemporally to the optic nerve (*arrow*). A questionable submillimeter tumor was suspected adjacent to the macula. Plaque-like retinoblastoma seen by orbit ultrasound (*arrow*) (*C*) with measurement calipers seen in (*D*). The submillimeter tumor suspected during examination under anesthesia (*A* and *B*) could not be identified by ultrasound.
(*From* Goncalves LF, Ramasubramanian A, Grebe T, Riemann M, Moncrief D, Cornejo P. Prenatal diagnosis of bilateral retinoblastomas by multimodality fetal imaging: case report and review of the literature. Clinical Imaging 2021;78:121-126; with permission.*)*

Retinoblastoma is still the most common ocular tumor in the world but luckily mortality and significant morbidity can be lessened with improved targeted chemotherapy treatment combined with radiation [23,50,51]. Intraarterial chemotherapy has been one of the greatest advancements in recent years, but it needs further time and evaluation to fully optimize this treatment

[25–27,29]. Although there has been a lot of advancements in treatment of retinoblastoma with chemotherapy, particularly with intraarterial chemotherapy, there is still a place for systemic treatment such as intravenous chemotherapy due to its effect on limiting metastatic disease [25,28,29]. Further work should be done to look into periocular treatment such as subconjunctival and intravitreal injections [29,44,51]. These techniques show promise in their isolated treatment area, but more research needs to be done to whether or not their side effects are worth their treatment effectiveness. Future research should look into tumoricidal drugs or other modalities that can treat the cancer with limited toxicity.

In conclusion there has been a lot of advancements in the treatment and discovery of retinoblastoma that have led to higher success rates and a decrease in necessary enucleations [29,43,51]. Retinoblastoma is still a very prevalent childhood cancer, so further research is necessary to really dial in and optimize treatment regiments. This research should be used to further advance treatment guidelines for different stages of retinoblastoma as well as the age of diagnosis. Currently treating groups, A, B, and C retinoblastoma, have a relatively good prognosis with more work needed to be done in order to increase the success rate associated with treatment of group D and E retinoblastoma [23,44,51]. Whether the tumor is unilateral, bilateral, or trilateral should also be taken into consideration because this will affect whether or not to use a more systemic or localized approach [28,51,52]. Guidelines need to be established for how and when to monitor for secondary cancer appearance in patients with retinoblastoma, especially those who have undergone radiation therapy [47–49]. As of right now there is no uniform guideline and the decision of when and how to screen for secondary cancer is very much up to the patient and their primary health care provider's opinion. Further efforts should be made to limit the disparities that exist in health care with more focus being put on cases of retinoblastoma that are present in Asian countries [53]. Improved access to medical advances such as prenatal ultrasound and genetic testing could greatly decrease the number of progress cases in these countries and prevent vision loss [33,36]. The future of retinoblastoma research is increasingly promising with groundbreaking discoveries happening frequently. Multidisciplinary collaborative research between ophthalmology, oncology, diagnostic and interventional radiology, genetics, and pharmacy should be done in order to create the best treatment option for patients with retinoblastoma.

Clinics care points

- Refer mothers with a personal or family history of retinoblastoma to an ocular oncologist and geneticist.
- Prenatal genetic testing is currently available through chorionic villus sampling or amniocentesis.
- Noninvasive prenatal genetic testing using cell-free DNA has been reported, and implementation into clinical practice is awaited with interest at the time of this writing.
- Prenatal targeted imaging of the fetal globes can detect even small tumors. Examinations should be preferably performed at centers with multidisciplinary teams that have experience in ocular ultrasound and MRI.

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Current Management of Pediatric Glaucoma

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Keywords

Childhood glaucoma; Congenital glaucoma; Examination under anesthesia; Goniotomy; Trabeculotomy

Key points

- The management of childhood glaucoma has greatly improved in terms of a better classification system, development of newer diagnostic modalities, better anesthesia techniques, and medical and surgical treatment.
- The interest in ocular biometry (axial length, pachymetry, etc.) and imaging techniques (ultrasound biomicroscopy, handheld optical coherence tomography, etc.) has increased over time, resulting in better diagnosis and treatment.
- The importance of examination under sedation for the frequent evaluation of children with glaucoma is now recognized, as this helps avoid the adverse effects of repeated general anesthesia.
- The role of oral propranolol has been described in children with Sturge-Weber syndrome with choroidal hemangioma to prevent intractable choroidal effusions and exudative retinal detachments.
- Glaucoma drainage devices and cyclophotocoagulation (endoscopic, transillumination) procedures are increasingly used for children with multiple failed surgeries.

Introduction

Childhood glaucoma is a treatable cause of blindness provided it is recognized, diagnosed, and treated in time [1]. WHO has estimated that it is responsible for blind years (second only to cataract) [2]. Although congenital glaucoma is a rare disease in terms of prevalence among ophthalmic diseases (0.01% to 0.04%) [3], it accounts for 4.2% to 5.0% of blindness in the pediatric population [4,5] and 2% to 15% of individuals in blind institutions. Prompt diagnosis and surgical treatment can prevent blindness in most of these infants. Preservation of any vision during a child's formative years is important, to avoid a lifetime of blindness.

The fundamental pathophysiology of all childhood glaucoma, regardless of the cause, is impaired outflow through the trabecular meshwork, causing an increased intraocular pressure, which leads to optic neuropathy, ocular enlargement, and corneal changes including corneal edema, haab's striae, or opacity; this could be due to a developmental abnormality (nonacquired) or due to acquired causes such as trauma, surgery, inflammation, etc. It is clear that childhood glaucoma per se is an umbrella term that comprises a vast variety of diseases including those that occur at birth, those that are developmental in nature but manifest later, and those that are due to acquired causes [6]. It is imperative to know exactly what condition one is dealing with, because the treatment and prognosis depends largely on what the underlying disease is.

There has been a growing interest in childhood glaucoma in recent years, probably partly due to greater survival of small infants with the developments in neonatal care and the greater dissemination of modern ophthalmic care to hitherto underdeveloped regions. Unlike adult glaucoma, the management of childhood glaucoma is difficult owing to the varied nature and prognosis of the disease and the need of ensuring normal visual development of the immature growing eye. Pediatric glaucoma is difficult to classify because children often present with a variety of ocular or systemic findings frequently attributable to underlying genetic defects.

The management of childhood glaucoma has improved in many ways, which include better classification methods and understanding of the disease, newer diagnostic modalities, improvements in anesthesia procedures, and surgical treatment options that have improved significantly since goniotomy was first described by Barkan [7] and trabeculotomy was first described by Burian and Smith [8,9]. Because of rapid developments in molecular biology techniques, it is now much easier to understand the pathophysiology of the disease by unraveling the underlying genetic abnormality.

In this chapter the authors look at recent advancements seen in the world of childhood glaucoma. This would include the development of a novel unified classification system, newer surgical procedures, and the exciting potential of genetic research in this condition.

Standardized nomenclature

For all phenotypically and genotypically heterogeneous diseases, a universally accepted nomenclature and easy-to-use classification helps to develop standards of care and promotes widespread collaboration and development of new advancements. The Childhood Glaucoma Research Network (CGRN) has developed a standardized nomenclature and classification system that was ratified by a consensus statement at the IXth World Glaucoma Association at Vancouver, 2013 [10] and was later adopted by the American Academy of Ophthalmology [11]. This classification will be used during the course of this review of pediatric glaucoma.

Diagnosis

The age of diagnosis depends on the national criteria for pediatric patients.

- United States: younger than 18 years
- United Kingdom, Europe, Asia: younger than 16 years

Table 1 depicts the diagnostic criteria adopted by the Childhood Glaucoma Research Network (CGRN) [10].

Classification

Childhood glaucoma had no uniform classification system. The terms congenital glaucoma and developmental glaucoma were used interchangeably. Some of the earlier classifications proposed by various investigators include the following:

Table 1 Definitions of glaucoma and glaucoma suspect as per Childhood Glaucoma Research Network classification

Glaucoma	Glaucoma suspect
Intraocular pressure (IOP)-related damage to the eye **At least 2 of the following criteria are present:** **1. IOP > 21 mm Hg; investigator discretion is required for children who are examined under anesthesia due to variable effects of anesthesia on IOP measurement** **2. Optic disc changes:** **• Optic disc cupping or progressive increase in cup-disc ratio** **• Cup-disc asymmetry of ≥ 0.2 or focal rim thinning** **3. Corneal findings: Haab's striae or diameter ≥ 11 mm in newborn, > 12 mm in child < 1 y, or > 13 mm any age** **4. Progressive myopia, myopic shift, or an increase in axial length out of keeping with normal growth** **5. Reproducible visual field defect consistent with glaucomatous optic neuropathy**	No IOP-related damage to the eye At least 1 of the following criteria are present: 1. IOP > 21 mm Hg on 2 separate occasions 2. Suspicious optic disc appearance for glaucoma, that is, increased cup-disc ratio for size of optic disc 3. Suspicious visual field for glaucoma 4. Increased corneal diameter or axial length in setting of normal IOP

Adapted from Beck A, Chang TC, Freedman S. Section 1: Definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, editors. World Glaucoma Association Consensus Series-9: Childhood Glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2013. pp. 3–10.

- Hoskins and colleagues [12] (classified the disease as per anatomic defects such as isolated trabeculodysgenesis or associated dysgenesis of the iris and/or cornea)
- Schaffer and colleagues [13] (isolated congenital glaucoma, associated with congenital anomalies or acquired glaucoma)

- Walton and colleagues [14] (addition of other disorders in the classification by Schaffer and colleagues)

The CGRN classification [10] is the currently used standard classification system, and it has classified childhood glaucoma into 4 broad segments, as depicted in Table 2.

Fig. 1 depicts the CGRN Flowchart that is, a guide to reaching a diagnosis for any child presenting with glaucoma.

Representative pictures of the most commonly seen entities of childhood glaucoma are shown in the following pictures (Figs. 2–5).

Diagnostic techniques

Intraocular pressure measurement and current understanding of its role in pediatric glaucoma

Applanation tonometry is the gold standard for IOP measurement. The Goldmann or Perkins applanation tonometer (GAT/PAT) (in the outpatient department/examination under anesthesia, respectively) is commonly used. However, there are many children who are cooperative for slit-lamp examination but do not cooperate for GAT. For these cases, many newer tonometers have been developed such as tonopen, noncontact tonometry or iCare tonometer (Tiolat Oy, Helsinki, Finland) [15–17]. The Tonopen (Reichert Inc, New York, USA) requires the use of topical anesthetic, and the readings are reliable only with lower IOP levels less than 20 mm Hg [15]. With higher IOP, the instrument usually tends to overestimate the IOP with discrepancy as high as 12 mm Hg [16].

The rebound tonometer by iCare is very light in touch, does not require topical anesthesia, and can be performed more easily in younger children as well (Fig. 6). It has been found to have readings within 3 mm Hg as measured with applanation tonometer, and the readings are usually higher than applanation readings [17].

Despite the different modalities available, the measurement of IOP in children is nevertheless challenging. Examination under anesthesia is often necessary for pediatric patients. Different agents used for sedation or general anesthesia have reported having varied effects on IOP [18]. Also, the modalities used for airway management, hemodynamic factors, tonometry technique, and body positioning can all affect IOP measurements. IOP measurement in children is also potentially influenced by other factors such as the type of tonometer used to record IOP, the cooperation of children, eye movement, and the status of the cornea such as edema or opacities [19]. In fact, it is now recognized that the IOP is among the least accurate parameters measured when assessing a child for glaucoma. It is increasingly accepted that the diagnosis of childhood glaucoma should never be made based on IOP alone.

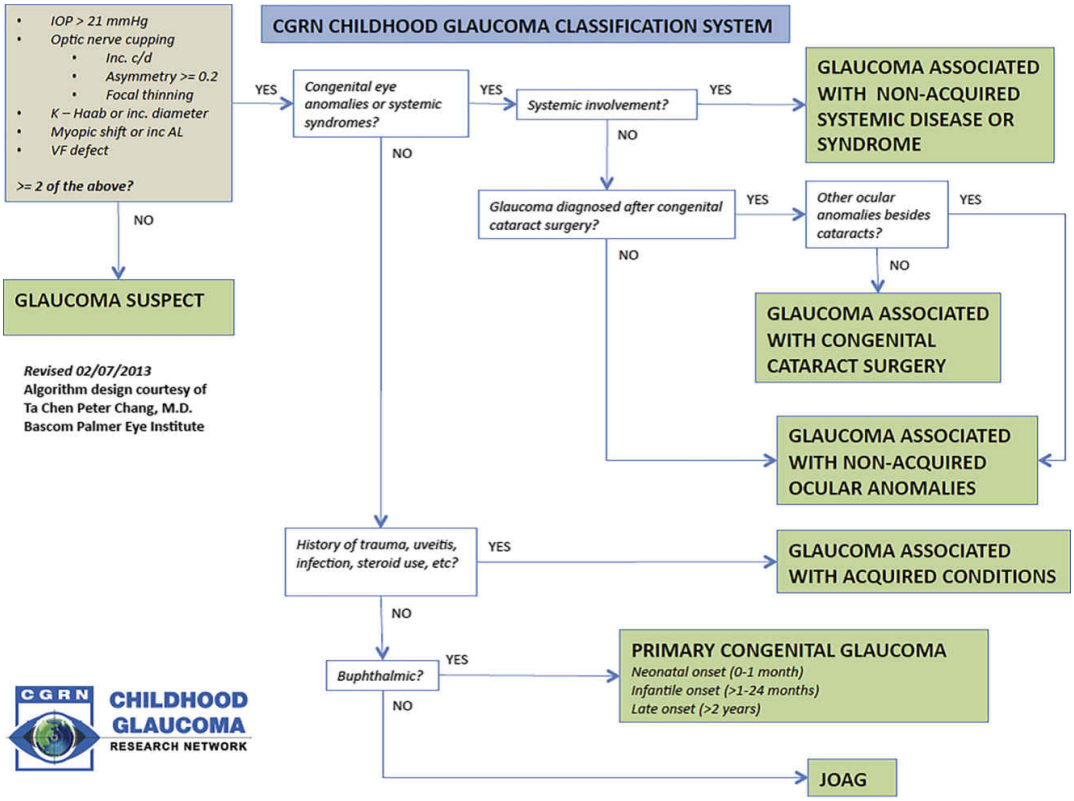

FIG. 1 CGRN childhood glaucoma classification system.
(*From* Robert N Weinreb. Childhood glaucoma: the 9th consensus report of the World Glaucoma Association [2013]; Used with permission of Kugler Publications.)

Table 2 Childhood Glaucoma Research Network classification

Primary childhood glaucoma (isolated angle anomalies) No other ocular or systemic associations	Secondary childhood glaucoma			
	Associated with congenital nonacquired ocular anomalies	**Associated with congenital nonacquired systemic anomalies**	**Acquired glaucoma**	**Secondary acquired glaucoma post-cataract surgery**
1. Primary congenital glaucoma • **Neonatal-onset glaucoma (0–1 mo of age)** • **Infantile glaucoma (1–24 mo of age)** • **Late-onset or late recognized (after 2 y)** **2. Juvenile glaucoma**	Glaucoma associated with ocular anomalies in addition to angle dysgenesis 1. Axenfeld-Rieger anomaly (syndrome if systemic associations) 2. Peters anomaly 3. Ectropion uveae 4. Congenital iris Hypoplasia 5. Aniridia 6. Persistent fetal vasculature 7. Microphthalmos 8. Microcornea 9. Ectopia lentis	Glaucoma and associated nonacquired systemic features 1. Sturge-Weber syndrome 2. Homocystinuria 3. Mucopolysaccharidoses 4. Weill Marchesani syndrome 5. Axenfeld-Rieger syndrome 6. Phacomatoses 7. Neurofibromatosi 8. Congenital rubella syndrome	This group includes secondary glaucoma due to various acquired reasons other than cataract surgery: 1. Uveitis 2. Trauma 3. Steroid-induced 4. Tumors 5. Retinopathy of prematurity 6. Prior ocular surgery other than cataract surgery	Glaucoma after cataract surgery has been given a separate place considering the high frequency of glaucoma following cataract surgery in children

Adapted from Beck A, Chang TC, Freedman S. Section 1: Definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, editors. World Glaucoma Association

Consensus Series-9: Childhood Glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2013. pp. 3–10.

Ocular biometry

The interest in ocular biometry, including axial length and pachymetry, measurements has gradually increased over the years due to the greater understanding regarding the value of these parameters in the clinical evaluation as well as decision-making of children with glaucoma. In a normal eye, corneal power, axial length, anterior chamber depth, and lens power are the major refractive components of the eye, with axial length typically being the single most crucial factor. Other than corneal stretching and axial elongation of the eyeball, the effect of congenital glaucoma on these variables has not been widely studied [20,21]. Eyes with glaucoma usually have larger axial lengths at presentation, which decrease after IOP control and then follow a normal curve as expected for age [22,23]. Biometry could be of immense importance both for the diagnosis of congenital glaucoma in children with borderline IOPs and to detect glaucoma in the fellow eye of patients with presumed unilateral disease. It also may have an essential role in the follow-up of patients with congenital glaucoma who had undergone surgery.

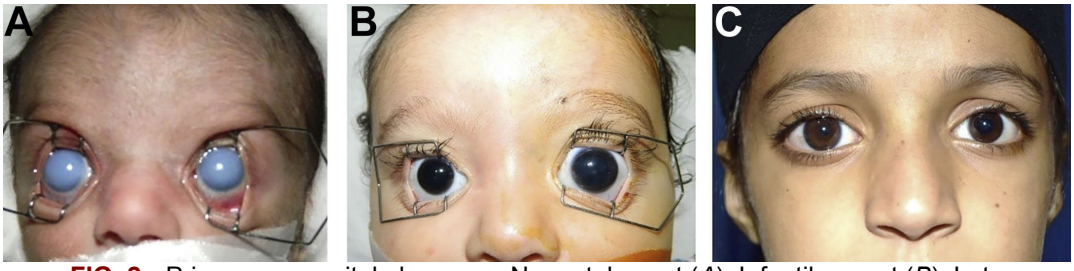

FIG. 2 Primary congenital glaucoma. Neonatal onset (*A*). Infantile onset (*B*). Late onset (*C*).

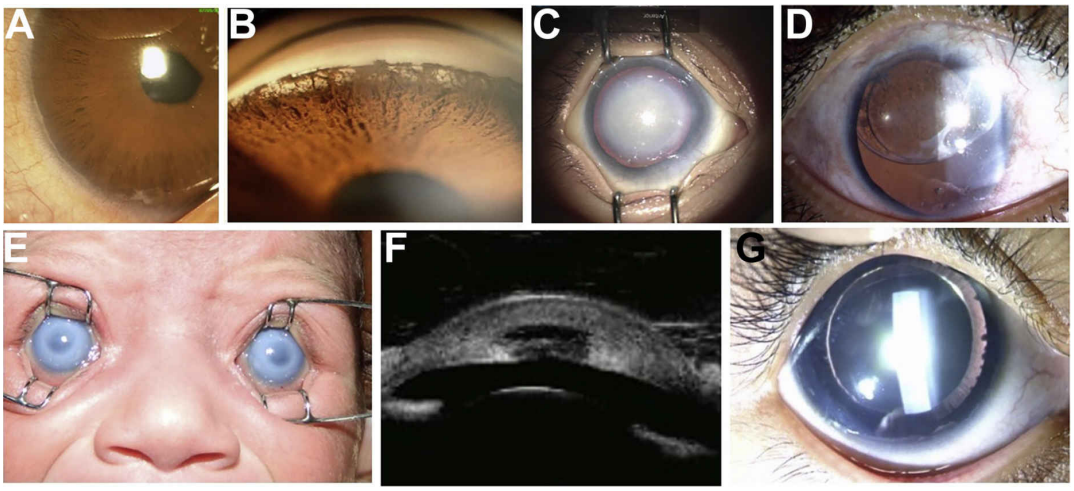

FIG. 3 Glaucoma secondary to nonacquired ocular conditions. (*A*, *B*) Posterior embryotoxon and typical iris processed seen on gonioscopy in Axenfeld-Reiger syndrome. (*C*) Neonatal onset congenital ectropion uveae. (*D*) Aniridia with aniridia keratopathy and IOL seen in the subluxated capsular bag. (*E*) Bilateral Peters anomaly. Not the clear area in the region of the Descemet membrane and posterior stromal defect. (*F*) UBM of the same baby seen in (*E*) showing the posterior stromal defect clearly. (*G*) Microspherophakia.

Patients with congenital glaucoma are known to have thick corneas in the presence of corneal edema, which becomes thinner after IOP control and resolution of corneal edema [24,25]. IOP measurement could also be affected by corneal biomechanical factors in additional to the anatomic thickness. The corneal hysteresis and resistance factor are reportedly decreased in congenital glaucoma, which may affect IOP readings [24]. On the contrary, many eyes with microcornea have thicker corneas [25], which may result in fallaciously higher IOP readings.

It is clear that it is important to rely on numerous other factors such as optic disc evaluation, corneal diameter, and axial length measurements for optimum assessment of the glaucoma status in children.

Refractive error

Refractive changes in children depend on many factors such as genetics, reading habits, and the environment [26,27]. In children with glaucoma, IOP is another factor contributing to the refractive change due to the eye's enlargement. Every millimeter increase in axial length contributes to −2.5 D of myopia, and every dioptre increase in corneal curvature contributes to 1.0 D of myopia [28]. The anterior chamber depth and lens thickness also contributes to the refractive changes [29].

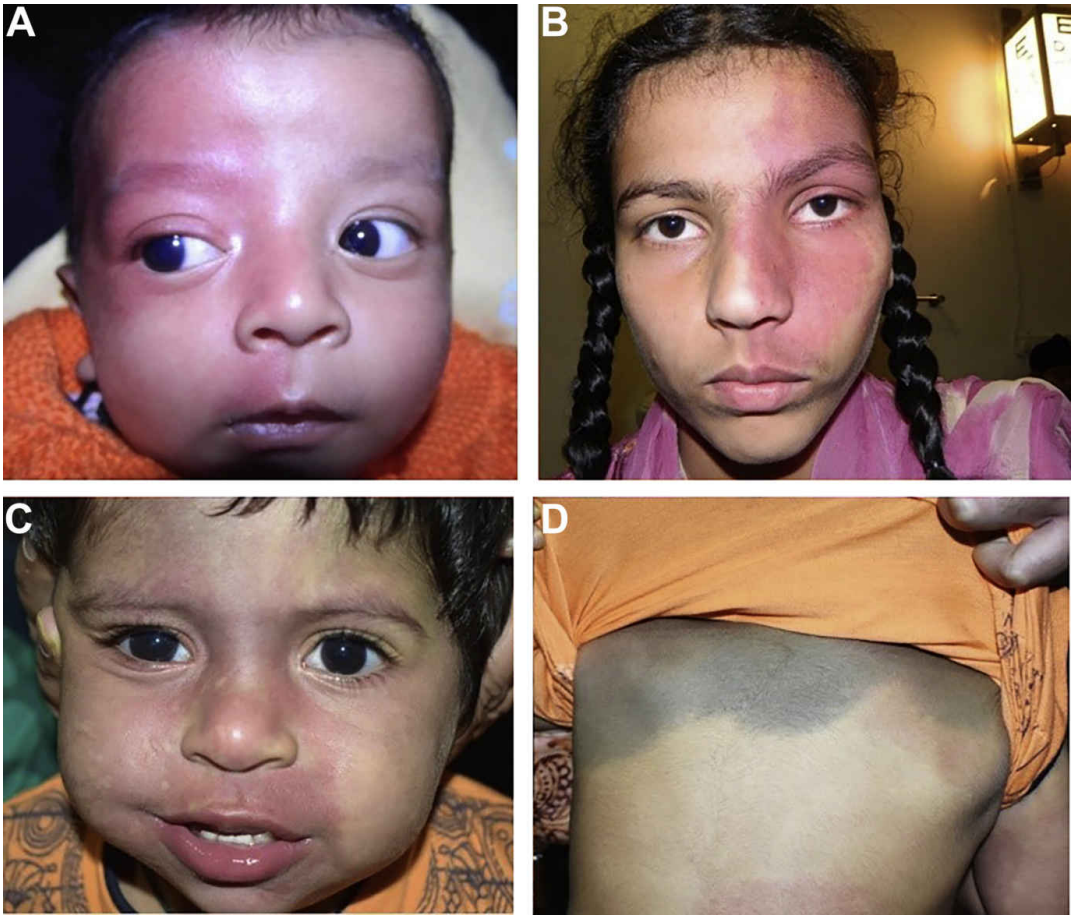

FIG. 4 Glaucoma secondary to nonacquired systemic diseases. Sturge-Weber syndrome. Glaucoma may occur in infancy (*A*), causing buphthalmos, or in late childhood (*B*), causing raised IOP and disc cupping. (*C*, *D*) Klippel Trenaunay syndrome showing the port-wine stain crossing the midline (*C*) and large pigmented area on the back (*D*) and limbs.

Ultimately, the refractive error in an individual is determined by an interplay of corneal/lens power and axial length. In cases of pediatric glaucoma, it has been found that myopia/hypermetropia are not always proportionate to the axial length [30]. There are many factors responsible for emmetropization in childhood glaucoma as well. Corneal enlargement and corneal flattening, a decrease in the axial diameter of the lens due to ocular enlargement and backward movement of the lens, are some of the factors that may be responsible to counteract myopia due to an increase in the axial length.

Ultrasound biomicroscopy

Ultrasound biomicroscopy (UBM) has a great role to play in cases of significant corneal opacification where anterior chamber details are not clear. It can be performed in the outpatient department in cooperative children but needs to be performed under anesthesia/sedation in uncooperative children. For neonates

and cases with smaller eyes and orbits, a clear scan soft sleeve technique is useful (Fig. 7).

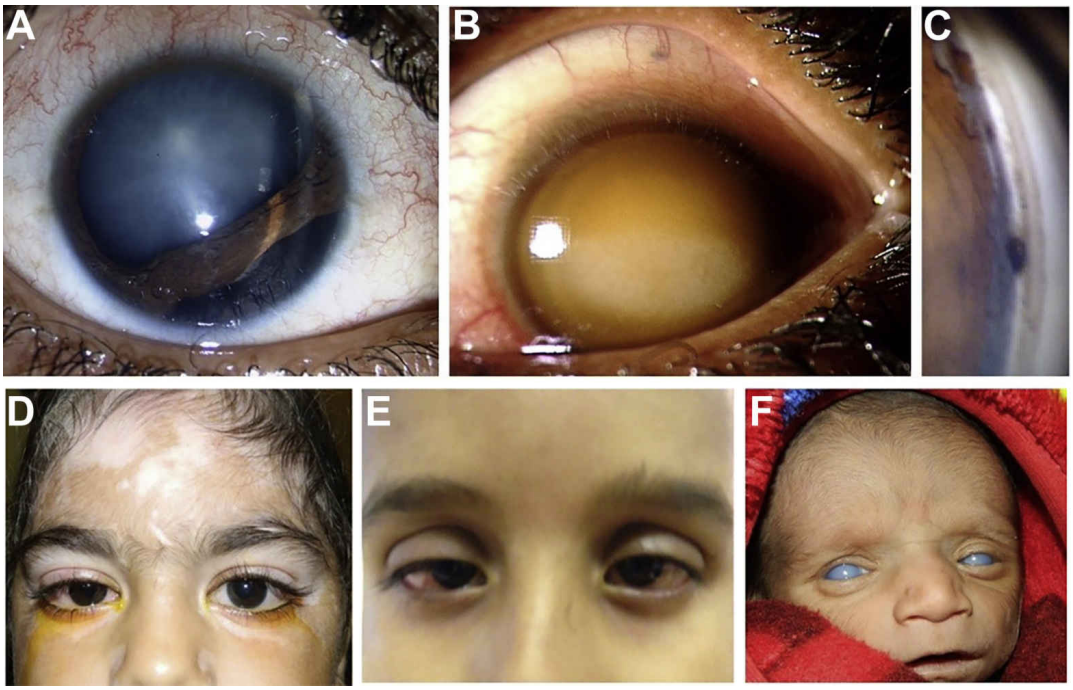

FIG. 5 Acquired childhood glaucomas. Posttraumatic glaucoma showing iridodialysis and traumatic cataract (*A*), corneal blood staining (*B*), and angle recession on gonioscopy (*C*). (*D*) Glaucoma secondary to uveitis in a child with Vogt-Koyanagi-Harada disease. (*E*) Steroid-induced glaucoma in a child with vernal keratoconjunctivitis. (*F*) Neonatal glaucoma in congenital rubella syndrome. Note the typical "monkey facies."

Another potential utility of the UBM is to look for the Schlemm canal and the outflow channels to predict the success rate with angle surgery [31].

Handheld optical coherence tomography

The handheld spectral-domain optical coherence tomography (Envisu 2300, Bioptigen Inc., Research Triangle Park, NC, USA) has been found feasible to look for the anterior segment and posterior segment structures in younger children without sedation or anesthesia [32,33]. It has great potential for accurate assessment of anterior segment structures, and the developing angle, and promises to be of great help in creating a normative database of retinal nerve fiber layer and macular thickness in children. For example, it could be of immense value in prognosticating a baby with aniridia by diagnosing the foveal hypoplasia [34].

Genetic testing

Genetic testing is very important in childhood glaucoma, although it is very complex, as there are many genes that may be responsible for a set of findings and genetic diseases with varied findings. Moreover, primary congenital glaucoma cases are sporadic in greater than 90% cases and familial in less than 10% cases. For genetic testing, there are single gene tests (eg, CYP1B1 for primary congenital glaucoma [PCG], FOXC1 and PITX2 for Axenfeld-Rieger and Peters anomaly; PAX6 for aniridia), multiple gene panels (eg, a set of genes for early onset glaucoma), or whole exome or genome sequencing (for cases where the disease is considered to have a genetic defect, but the disease is complex and genes responsible are not known) [35,36].

FIG. 6 Measurement of IOP using a handheld rebound tonometer while the baby is comfortable in his mother's lap.

Genetic testing, although logistically difficult to offer all patients, has a great role in certain situations, as illustrated in the following section:

1. Positive family history so as to predict which family member has a risk of disease depending on the presence or absence of a mutation in a particular gene, and thus plan for the follow-ups of asymptomatic members can be made accordingly
2. Genetic counseling by predicting the risk of transfer of gene and the disease development

FIG. 7 UBM using a clear scan probe in a neonate with corneal opacity.

3. To predict the prognosis, as PCG cases with CYP1B1 mutations have been found to have a severe disease compared with those without [35].
4. To diagnose a complex case where the diagnosis is not certain so as to prognosticate the disease and for genetic counseling

Anesthesia

Childhood glaucoma cases require repeated anesthesia to monitor IOP, corneal diameter, anterior segment, and posterior segment examination until the children start cooperating for slit-lamp examination and IOP measurement. Repeated anesthesia exposures have been shown to affect brain development and can affect their cognition, behavior, and memory [37]. Many sedative agents including chloral hydrate, pedicloryl, midazolam, and ketamine are used for short-term procedures, with variable success rates [37,38]. A newer sedative agent dexmedetomidine, α-2 agonist, has been found to have better success rates compared with chloral hydrate for the ophthalmic examination of children. It does not cause gastrointestinal side effects as with chloral hydrate and respiratory depression as with midazolam. It can be administered intranasally or intravenously. The intranasal route has been found to have better acceptability, as it does not cause any irritation and avoids the cannulation. A recent study [39] on the evaluation of intranasal 3.5 μg/Kg dexmedetomidine reported success rates of 77.4% with dexmedetomidine alone and 100% when rescue drug midazolam 0.25 mg/kg intranasal was administered. Fig. 8 depicts the examination procedure.

Treatment

Medical treatment

The mainstay of treatment in nonacquired childhood glaucoma is surgical. Medical treatment remains useful as a temporizing measure for IOP control until the surgery is performed or to supplement inadequate IOP control after surgery. There has been an improvement in the available formulations of timolol maleate for use in infants. Topical timolol 0.5% can cause apnea in smaller children due to increased systemic absorption. Timolol 0.25% gel formulation once a day, betaxolol 0.25%, and now timolol maleate 0.1% gel form has been found to have a better safety profile. Timolol 0.1% formulation is gel-based with carbomers (carbopol) and polyvinyl alcohol and has good retention with similar IOP lowering as of timolol 0.5% without systemic side effects [40,41].

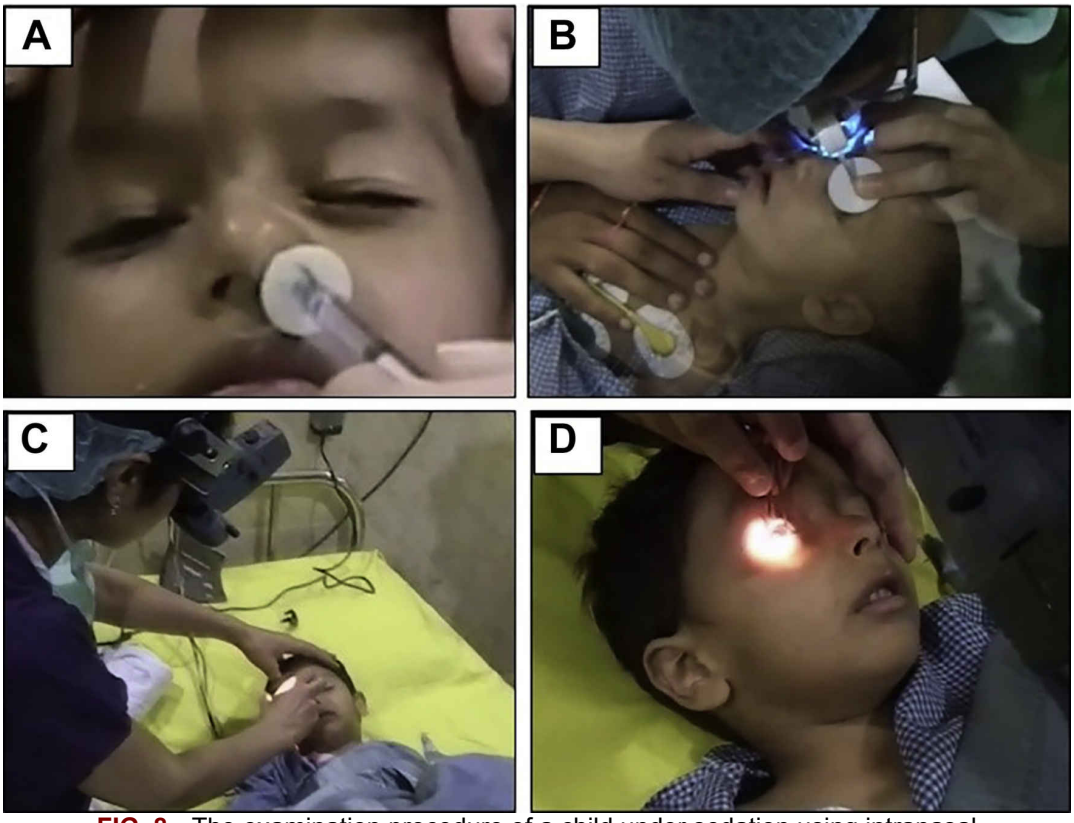

FIG. 8 The examination procedure of a child under sedation using intranasal dexmedetomidine. (*A*) Administration of the drug using mucosal atomization device with half dose in each nostril. (*B*) Intraocular pressure measurement using Perkin applanation tonometer with the child in mother's lap. (*C*) Indirect ophthalmoscopy for the examination of anterior and posterior segments. (*D*) Corneal diameter measurement.

Although the exact mechanism of action and duration of therapy is not known, oral propranolol has been shown to be effective in Sturge-Weber syndrome to prevent/treat choroidal effusions/exudative retinal detachments due to diffuse choroidal hemangioma. A dose of 2 mg/kg/d has been effective, by the presumed mechanisms of inhibiting angiogenesis, apoptosis of proliferating endothelial cells, or vasoconstriction etc. [42,43].

Surgery

Advances in childhood glaucoma surgeries are mainly guided by trials first conducted in adults [44]. Barkan [7] first described goniotomy with unsuccessful outcomes in adults and then demonstrated good outcomes in children. Goniotomy became the surgical treatment of choice for children with good outcomes. However, a reasonable cornea clarity was the main prerequisite to perform the surgery to visualize the angle. Subsequently, trabeculotomy was described as an ab-externo technique to rupture the inner wall of Schlemm canal, independently by Burian [8] using the trabeculotome and by Smith using nylon filament [9]. Combined trabeculotomy with trabeculectomy was first described by Maul and colleagues [45], which soon gained popularity because of its higher success rates and faster corneal clearing, which is so important in children to ensure visual rehabilitation and prevent amblyopia.

However, it was a sobering fact that despite the best of surgical technique, many surgical procedures failed. Glaucoma in children could be very refractory to one surgical procedure. Glaucoma drainage devices were introduced as a viable treatment for refractory glaucoma or for glaucomas where the conjunctiva was deemed to be too scarred for a trabeculectomy to succeed. The Baerveldt Glaucoma implant (BGI) and Ahmed Glaucoma Valve implants were introduced in 1990 and 1993, respectively [46]. Recently the Aurolab aqueous drainage implant has been introduced for clinical use by Aurolab, Madurai, India. This implant is a low-cost, nonvalved glaucoma drainage device (GDD) designed as the BGI with a 350 mm^2 plate area, which has shown encouraging results at par with the established implants [47].

Advances in surgical techniques are basically the modifications in the original techniques described years back, some of which are described as follows:

Modifications in goniotomy

a. Coaxial endoscopic goniotomy has been described for cases with corneal edema and was first described in humans by Medow and colleagues in 1997 [48]. It uses an endoscope (EndoOptiks, Little Silver, NJ) with a special blade mounted on the endoscope itself, or one can also use an MVR blade (Visitec, Sarasota, FL) through a separate incision with

anterior chamber maintained by using either a viscoelastic or an anterior chamber maintainer.

b. Other modifications in the goniotomy technique involve the use of an electrosurgical device called Trabectome or Kahook Dual Blade to ablate/excise the inner wall of Schlemm canal, which prevents the closure of the cleft [49].

c. Gonioscopy-assisted transluminal trabeculotomy (GATT) has been described by Dr Davinder Grover in cases where an initial goniotomy cleft is created and an illuminated microcatheter or a prolene suture that is cauterized at the tip are used to pass through the Schlemm canal for 360° treatment of the angle [50].

Modifications in trabeculotomy

A 360° trabeculotomy has been found to have higher success rates with the achievement of lower IOP compared with conventional trabeculotomy by treating greater extent of the angle. It can be performed using either 6–0 prolene suture (introduced by Beck and Lynch) or by an illuminated microcatheter iTrack (iScience Interventional, Menlo Park, CA), which helps with the direct visualization of the illuminating tip [51].

Glaucoma drainage devices

The use of GDDs has increased over the years and are found useful for the failed trabeculectomy cases or multiple failed glaucoma surgeries. It has fewer bleb-related complications, but pediatric eyes are more prone to complications of tube migration, retraction, tube corneal touch, and endophthalmitis compared with adults [47,52]. Small modifications have ensured greater safety in implantation of GDDs in children:

- Tube elongation using angiocatheter or especially available extension devices
- Tube shortening by cutting the longer tubes using lesser invasive methods from within the anterior chamber

Cyclophotocoagulation

This procedure is reserved for cases with poor visual potential or multiple failed surgeries. It is difficult in children, as the location of ciliary processes changes with the globe enlargement due to anatomic changes in a buphthalmic eye and, moreover, ciliary processes regenerate more in pediatric cases. Many developments have been made in the technique in the form of the use of an endoscope for the coagulation of ciliary processes under direct visualization [53].

Using transillumination to localize the site of ciliary processes has been shown to improve the chances of success with this modality.

Despite the rapid strides in the diagnosis and management of childhood glaucoma, there is much to explore in this field. Research continues for the better care of patients with childhood glaucoma in terms of disease control with visual as well as vocational rehabilitation.

Clinics care points

- Childhood glaucoma is a potentially blinding condition unless recognized and treated in time.
- The basis of all childhood glaucomas, whatever may be the cause, is raised IOP due to reduced aqueous outflow.
- Because the infant's eye is elastic, the consequences of this raised IOP includes secondary effects such as globe enlargement, progressive myopia, and corneal changes due to breaks in the Descemet membrane and stromal edema.
- The treatment of childhood glaucoma, especially in infancy is usually surgical.
- Angle surgery is the most commonly performed surgery and includes goniotomy, trabeculotomy performed ab-externo or ab-interno.
- Cases of cloudy corneas may need a trabeculectomy combined with trabeculotomy.
- Refractory childhood glaucomas often require glaucoma drainage devices or cyclophotocoagulation.
- The underlying cause is important to diagnose, as many developmental glaucomas may be associated with other systemic abnormalities.
- Unlike in adult glaucomas, childhood glaucoma cannot be treated by control of raised IOP alone but also requires intensive amblyopia treatment to ensure visual rehabilitation.
- Advances in genetic technology have also opened up techniques such as NextGen sequencing, which allows genotype characterization and opens up avenues for appropriate genetic counseling.

Disclosure
Nothing to declare.

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Systemic Immunomodulatory Therapy in Pediatric Uveitis

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Keywords

Uveitis; Juvenile idiopathic arthritis; Adalimumab; Tocilizumab; Anti-TNF; JAK inhibitor; Biologics

Key points

- A rapid and sustained steroid-free remission should be the target in order to avoid visual complications or loss of vision.
- A multidisciplinary approach is crucial for better management of uveitis.
- Adalimumab is the only biologic that has obtained European Medicines Agency and US Food and Drug Administration authorization for the treatment of childhood uveitis.
- Further agents, including tocilizumab, abatacept, rituximab, and Janus kinase inhibitors, should be considered in patients nonresponsive to second-line or third-line therapies.

Introduction

Uveitis is a disabling inflammatory eye disease that, even though rare in the pediatric age group, accounts for 2% to 14% of all uveitis cases, with an estimated incidence of 4.3 per 100,000 children per year and a prevalence of 28 per 100,000 children per year [1,2]. According to the Standardization of Uveitis Nomenclature (SUN), uveitis can be classified based on laterality, anatomic site involvement, and the clinical course (Table 1) [3].

Table 1 Classification of uveitis according to Standardization of Uveitis Nomenclature

Laterality	Unilateral Bilateral	—
Anatomic classification	Anterior	Inflammation primarily affecting the anterior segment
	Intermediate	Primary site of inflammation is in the middle portion of the globe, including vitreous, peripheral retina, and pars plana
	Posterior	Inflammation of the choroid and the retina and includes retinochoroiditis, retinitis, and neuroretinitis
	Panuveitis	No predominant site of inflammation, but inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid
Time course	Acute	Sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 mo in duration
	Chronic	Persistent uveitis with relapse in <3 mo after discontinuing treatment

Adapted from Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–516; with permission.

The cause of childhood uveitis remains unknown in up to 50% of cases and is defined as idiopathic. However, it may be associated with numerous rheumatologic diseases, the most common being juvenile idiopathic arthritis (JIA). In this condition, 11.6% to 30% of children develop uveitis, usually chronic anterior uveitis [4]. Systemic vasculitis and other autoimmune conditions, for example, sarcoidosis and Behçet disease, may be complicated by uveitis and periodic ophthalmologic evaluation, therefore, may be needed to prevent potential ocular complications [4]. Infections are found to be more frequent in underdeveloped countries, and the main causes are toxoplasmosis and herpes viruses. In developed countries over the past 2 decades, noninfectious uveitis accounts for 90% to 95% of all cases of pediatric uveitis [1]. A multidisciplinary approach, involving pediatric rheumatologists and pediatric ophthalmologists, is crucial in order to determine the optimum diagnostic work-up and therapeutic pathway.

Noninfectious uveitis, if not properly recognized and treated, because of its frequent chronic course, can lead to severe complications, including cataracts, glaucoma, band keratopathy and persistent cystoid macular edema, and legal blindness in up to 60% of patients [4,5]. The development of complications and legal blindness has a severe impact on the quality of life of these children and their families [5].

Thanks to the increasing knowledge about the pathophysiology of autoimmune disease, breakthroughs in the therapeutic field have been achieved, revolutionizing the outcome of numerous diseases, including uveitis. The achievement of inflammation control is crucial to prevent the onset of complications, and a step-by-step approach is the key feature of all international guidelines [2,6–8]. Two randomized controlled trials (RCTs) in the last 3 years have provided strong evidence for the use of adalimumab, an anti–tumor necrosis factor alpha (TNF-α), in combination with methotrexate in childhood uveitis resistant to nonbiologic disease-modifying antirheumatic drugs (DMARDs) [9,10]. Additional studies have provided some evidence for other treatment options, such as anti–interleukin (IL)-6 [11] and alternative therapeutics in patients resistant to these drugs.

This article focuses on analysis of the recent advances in the immunomodulatory treatment strategy for pediatric noninfectious uveitis.

Significance

Current guidelines

Numerous guidelines have been developed in recent years based on current knowledge and expert opinion. They agree on a step-by-step approach and advise that therapy is initiated when the anterior chamber (AC) cell grade is greater than or equal to 0.5 [6–8]. Treatment also is indicated when there is fibrin in the AC and keratic precipitates with corneal edema and loss of visual acuity. The first-line treatment is topical glucocorticoid or systemic corticosteroid based on the severity of disease.

Systemic immunosuppression is required if there is failure to see improvement in inflammation after 3 months of topical treatment or presence of poor prognostic factors such as impaired initial vision, cataract, glaucoma, ocular hypotony, dense vitreous body opacification, and macular edema. The initial second-line treatment is a nonbiologic DMARD, and methotrexate is the first choice for the treatment of uveitis in children. If there is worsening disease or failure to achieve AC cell grade 0 after 3 to 4 months on methotrexate, it is recommended that a biologic drug is added [6–8]. In a recent meta-analysis, Simonini and colleagues [12] found that approximately 30% of children treated with methotrexate failed to achieve disease control and needed the addition of a biologic drug. Strong evidence exists that the first biologic should be the anti–TNF-α adalimumab, which has shown efficacy in 2 RCTs and numerous retrospective and prospective studies [9,10,13].

The situation is more challenging when the patients are resistant to anti–TNF-α. The data currently available are insufficient to recommend a specific treatment of these patients. Options include abatacept, tocilizumab, golimumab, rituximab, and Janus kinase inhibitors. Studies, some currently in progress, will provide further evidence about the use of these new drugs. Fig. 1 shows the treatment algorithm for childhood noninfectious uveitis based on current evidence.

Recent advances in treatment

Immunosuppressive agents

Methotrexate

Methotrexate is considered the first-choice systemic agent for the treatment of pediatric noninfectious uveitis [6–8]. It is a competitive inhibitor of dihydrofolate reductase that leads to the inhibition of RNA transcription and DNA synthesis, especially in B and T lymphocytes. The recommended dosage is 10 to 15 mg/m^2 once a week (orally or subcutaneously). However, a recent retrospective study suggested that high-dose methotrexate (≥15 mg/m^2/wk) was associated with a shorter time to remission on medication compared with low-dose methotrexate (<15 mg/m^2/wk) with comparable side effects [14]. Methotrexate has been shown,

in numerous studies and a meta-analysis, to induce inflammation control in up to 73% of children affected by autoimmune chronic uveitis refractory to steroid therapy [12].

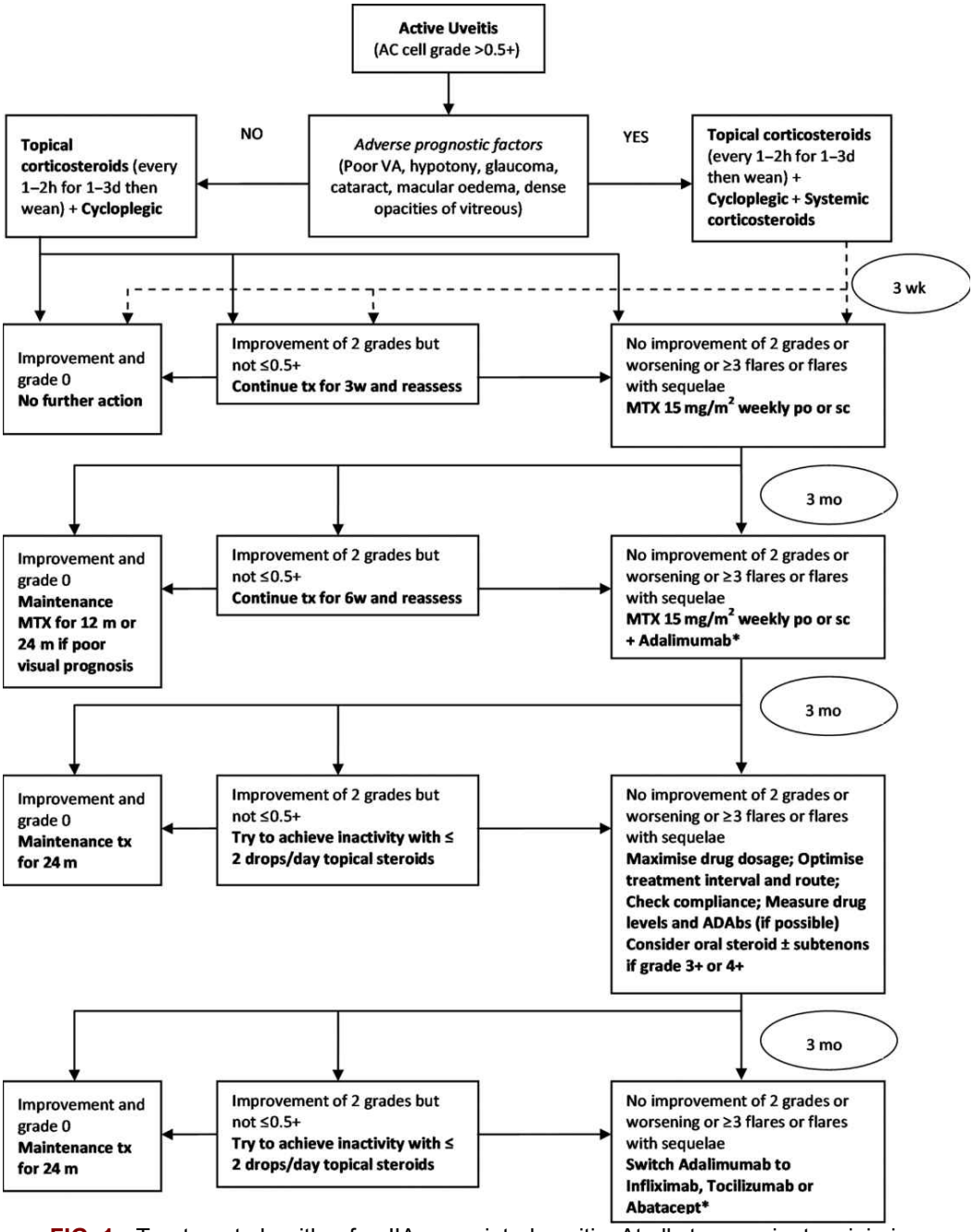

FIG. 1 Treatment algorithm for JIA-associated uveitis. At all stages, aim to minimize topical steroid to less than or equal to 2 drops/d while maintaining AC cell grade less than or equal to 0.5+. [a]Mycophenolate mofetil (MMF) is a potential alternative to a biologic drug if there is active uveitis but no active arthritis. AC, anterior chamber; ADAbs, antidrug antibodies; MTX, methotrexate; po, by mouth; sc, subcutaneous; tx, treatment; VA, visual acuity.
(*Adapted from* Bou R, Adán A, Borrás F et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015 May;35(5):777-85. https://doi.org/10.1007/s00296-015-3231-3 and Heiligenhaus A, Michels H, Schumacher C, Kopp I et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int. 2012 May;32(5):1121-33; with permission.)

Other immunosuppressant therapies

Other nonbiologic DMARDs are available for the treatment of uveitis in childhood, although they seem to be inferior to methotrexate. In the prebiologic era, azathioprine, mycophenolate, and cyclosporine A were considered as second-choice systemic immunosuppressant therapies. However, current guidelines recommend choosing an anti–TNF-α when methotrexate fails to achieve disease control.

Biologic drugs

Anti–tumor necrosis factor alpha

TNF-α is proinflammatory cytokine that plays a pivotal role in the pathogenesis of numerous autoimmune conditions, including uveitis. Several drugs are available that target TNF-α, but not all have the same mechanism of action (Table 2). To date, adalimumab is the only biologic that has been approved for the treatment of pediatric noninfectious uveitis based on the recent evidence provided by 2 RCTs [9,10].

Adalimumab

Adalimumab is a fully humanized monoclonal antibody against TNF-α that is administered by a subcutaneous injection every other week based on the weight of the child (20 mg in those weighing <30 kg or 40 mg in those ≥30 kg). The strongest evidence, previously derived from cohort studies, have been confirmed in the last 3 years by 2 randomized double-blind clinical trials examining the use of adalimumab in the treatment of JIA-associated uveitis [9,10,13,15].

The SYCAMORE trial was a multicenter, double-blind RCT of adalimumab versus placebo that evaluated the efficacy and safety in 90 children with JIA-associated uveitis refractory to topical or systemic steroids and methotrexate [10]. Children were randomized in a 2:1 ratio to receive adalimumab according to body weight or placebo. The addition of adalimumab to methotrexate versus placebo decreased the risk of treatment failure by 75% (hazard ratio of 0.25; 95% confidence interval [CI], 0.12–0.40; P<.0001), and treatment failure was observed in the 27% of patients in the adalimumab group versus 60% in the placebo group. However, at 5-year follow-up in a subset of patients from the trial, the remission did not persist when the drug was withdrawn, but visual acuity continued to be excellent [16].

Another double-blind, placebo-controlled RCT, the Effect of Adalimumab for the Treatment of Uveitis in Juvenile Idiopathic Arthritis (ADJUVITE) trial, included 31 patients with JIA-associated uveitis or idiopathic uveitis with inadequate response to topical corticosteroids and methotrexate [9]. At 2 months, the results confirmed the efficacy of adalimumab compared with placebo. Of the patients treated with adalimumab, 56% (9 out of 16) met the primary outcome

(30% reduction of inflammation on laser flare photometry) compared with 20% (3 out of 15) of those treated with placebo (P = .038) [9]. Both RCTs confirmed a good safety profile of adalimumab [9,10,17].

Table 2 Biologic drugs used in treatment of juvenile idiopathic arthritis–associated uveitis

Target	Drug name	Drug class	Dosage and route	Evidence	References
TNF-α	Etanercept	Dimeric fusion protein	Not recommended for treatment of JIA-U	RCT: no more effective than placebo. Case reports of new uveitis on etanercept	[24–27]
	Infliximab	Chimeric (mouse-human) mAb	6 mg/kg IV initially, then 3–10 mg/kg. Second dose at 2 wk, then every 4–8 wk depending on response	Several case series showing efficacy. Doses up to 20 mg/kg have been reported	[13,15,20,21,25]
	Adalimumab	Fully human mAb	20 mg sc q2w (body weight <30 kg), 40 mg sc q2w (body weight ≥30 kg)	2 RCTs show efficacy when added to methotrexate Meta-analysis	[9,10,13,15,16]
	Golimumab	Fully human mAb	50 mg sc q4w	Case series (n = 3) showing efficacy	[30]
IL-6	Tocilizumab	Humanized mAb	10 mg/kg (body weight <30 kg), 8 mg/kg (body weight >30 kg) IV q4w. 162 mg sc q3w (body weight <30 kg), q2w (body weigh >30 kg)	Single-arm trial showing improvement in 47% with subcutaneous tocilizumab. Two case series (n = 17 and 25) also showing efficacy	[11,31–33]
CD80/86 (CTLA-4)	Abatacept	Fully human fusion protein	10 mg/kg IV at weeks 0, 2, 4, then q4w	Case series (n = 7 and n = 2) showing efficacy. Lack of sustained response in severe uveitis (n = 21)	[35–39]

Target	Drug name	Drug class	Dosage and route	Evidence	References
CD20	Rituximab	Chimeric (mouse-human) mAb	375 mg/m^2 or 750 mg/m^2 IV, 2 doses 2 wk apart	Case series (n = 10 and n = 8 with long-term follow-up) showing efficacy in most patients	[40,41]
JAK 1–2	Baricitinib	Small molecule	2 or 4 mg based on body weight	Case reports	[45] and NCT04088409

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IL, interleukin; IV, intravenous; JAK, Janus Kinase; JIA-U, JIA-associated uveitis; mAb, monoclonal antibody; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; RCT, randomized controlled trial; sc, subcutaneous; TNF, tumor necrosis factor.

Furthermore, in a recent study, Correll and colleagues [18] showed that the escalation to a weekly administration of adalimumab is effective and has a good safety profile in pediatric patients with JIA-associated uveitis with inadequate control on alternate-week dosing. This option might be an option in those patients who lose disease control before changing to a different class of biologic drugs. In a recent meta-analysis evaluating the efficacy of different anti–TNF-α agents in the treatment of noninfectious pediatric uveitis, adalimumab showed its superiority compared with the others, including infliximab [13]. This finding is in keeping with the longitudinal data of the Italian OculaR involvement in CHIldhood rheumatic DisEAses (ORCHIDEA) registry [15].

Based on the RCTs and meta-analysis discussed earlier, adalimumab is the biologic with the strongest level of evidence of efficacy for the treatment of noninfectious uveitis in children when associated with methotrexate.

However, there are patients who fail to respond or are unable to tolerate a specific TNF-α blocker. This particular population might benefit from switching to another anti-TNF, as recently shown in a meta-analysis, where switching to an alternative anti–TNF-α (adalimumab or infliximab) resulted in a favorable effect for intraocular inflammation in 75% of cases (95% CI, 0.51–100) [19].

Other anti–tumor necrosis factor alpha

Infliximab is a chimeric monoclonal antibody that is administered intravenously at a dosage of 5 to 10 mg/kg at weeks 0, 2, and 6 (induction phase), then every 4 to 8 weeks (maintenance phase). Several retrospective studies have documented a significant resolution of ocular inflammation in children with uveitis who failed methotrexate [20–22]. However, discordant data are available about its long-term efficacy, with subsequent possibility of ocular relapse [21–23].

Etanercept is a fusion protein of immunoglobulin (Ig) G1 Fc domain and TNF-α receptor that is administered at 0.4 mg/kg twice a week subcutaneously. In a double-blind RCT, etanercept showed no difference compared with placebo in 12 children with JIA-associated uveitis [24]. Furthermore, several studies have

reported new onset of uveitis or flares while on etanercept [25–27]. Although there is no clear evidence that etanercept causes uveitis, data from national registries show that etanercept is associated with a greater number of uveitis cases than adalimumab or infliximab [28]. However, a recent study seemed to show a protective effect of etanercept on the onset of uveitis, although they highlighted that this is likely explained by confounding, whereby patients in the methotrexate cohort are younger and earlier in the disease course, and therefore at greater risk of developing uveitis compared with etanercept patients [29]. To date, etanercept is not recommended in patients with JIA-associated uveitis.

Golimumab is another human monoclonal anti–TNF-α antibody that may be a viable therapeutic option in cases of JIA-associated uveitis refractory to other TNF inhibitors [30]. However, evidence for its use derives only from small case series.

Non–anti–tumor necrosis factor alpha biologic

Among children with noninfectious uveitis treated with adalimumab, 14% do not achieve inflammation control. Of this group of nonresponders to a first anti-TNF, 25% do not improve on a second anti-TNF [13,19]. The increased knowledge about the pathophysiology of the disease has led to novel targeted therapies. Several studies have shown a good clinical profile of effectiveness and safety for these medications.

Tocilizumab

Tocilizumab is a fully humanized antibody against IL-6, a proinflammatory cytokine involved in several autoimmune diseases, such as JIA. Tocilizumab is administered at 10 mg/kg (body weight <30 kg) or 8 mg/kg (body weight >30 kg) every 4 weeks, intravenously. In patients who failed an anti-TNF, tocilizumab may be a valid option, as shown in case series and in the Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE) trial [11,31–33].

The APTITUDE trial was a phase II, single-arm (adaptive design), open-label study that investigated the efficacy and safety of subcutaneous tocilizumab (162 mg every 3 weeks for body weight <30 kg, or 162 mg every 2 weeks for body weight ≥30 kg) for children with JIA-associated uveitis refractory to anti–TNF-α aged 2 to 18 years [11]. In 33% of patients, a 2-step decrease was observed in AC cell grade at 12 weeks and a further 14% had a 1-step improvement at 24 weeks. Moreover, macular edema, one of the most feared complications of uveitis, was resolved in 75% of patients (3 out of 4) [11]. The primary end point was not met, possibly because the subcutaneous route of administration is linked to a less favorable outcome, as reported by Quesada-Masachs and colleagues [34]. Further investigation will be needed in a comparative study to determine the real difference in efficacy of the two routes of administration.

In 1 case series, 17 patients (mean age 15.3 years, range 7–30 years) with severe and refractory active JIA-associated uveitis were treated with intravenous

tocilizumab [31]. Uveitis inactivity (AC cell grade, 0) was achieved in 5 out of 14 (35.7%) at 6 months, 5 out of 9 (55.6%) at 9 months, and 4 out of 8 (50.0%) at 12 months. The 5 eyes that had macular edema at baseline showed a complete recovery with tocilizumab. Five patients stopped treatment because of lack of efficacy [31].

Calvo-Río and colleagues [33] reported the use of tocilizumab in 25 patients (mean age 18.5 years, range 8–38 years) with JIA-associated uveitis refractory to glucocorticoids, nonbiologic DMARDs, and at least 1 biologic. Improvement in uveitis activity according to the SUN definition was achieved in 68% of children at 3 months, 79.2% (19 out of 24) at 6 months, and 88.2% (15 out of 17) at 12 months. Ocular remission was observed in 19 (76%) patients. Cystoid macular edema improved in all 9 patients with this finding at baseline, with significant reduction in macular thickness at 6 and 12 months. Only 1 patient stopped treatment because of lack of efficacy.

Abatacept

Abatacept is a soluble recombinant protein obtained by the fusion of the extracellular domain of cytotoxic T lymphocyte antigen 4 (CTLA-4) with the IgG1 Fc domain. It selectively binds to an antigen-presenting cell, inhibiting the costimulation signal necessary for T-cell activation. Data regarding the use of abatacept in childhood noninfectious uveitis are still limited. Small case series have reported a decrease in ocular inflammation, frequency of ocular relapse, and need of steroid treatment among patients affected by JIA-associated uveitis treated with intravenous abatacept [35–37]. However, Tappeiner and colleagues [38], in a case series of 21 children affected by severe, longstanding, refractory uveitis, observed a response in ocular inflammation in 11 out of 21 children, but 8 of these 11 relapsed. Furthermore, they showed that a sustained response to abatacept was uncommon in patients with severe and refractory uveitis [38]. Birolo and colleagues [39] reported that 55% of 35 patients with JIA-associated uveitis achieved clinical remission when treated with abatacept. There was no significant difference in remission rate or in frequency of uveitis flare between the group of patients in whom abatacept was used as the first-line biologic versus second-line treatment after an anti-TNF [39].

At the moment, the results of a clinical trial of abatacept for noninfectious uveitis in patients that are 6 years of age or older are still pending release, although the study was finished in 2019 (NCT01279954).

Other drugs

Rituximab is a monoclonal antibody targeting CD20 on B lymphocytes. In small case series, this drug showed a potential role in the treatment of JIA-related uveitis refractory to other therapies [40,41].

Use of the anti–IL-1 agents anakinra and canakinumab was reported in very few cases in specific forms of childhood uveitis, such as Blau syndrome and Behçet

disease [42–44].

Another class of immunomodulatory drugs under investigation for treatment of noninfectious uveitis are the Janus kinase (JAK) inhibitors, such as baricitinib and tofacitinib. They inhibit intracellular tyrosine kinases associated with cytokine receptors and activate the proinflammatory cascade. In a few case series, such as 1 from Miserocchi and colleagues [45], baricitinib has shown ability to control ocular inflammation in adult patients with multidrug-resistant, JIA-associated uveitis. Baricitinib is currently under investigation in an RCT to evaluate its efficacy and safety compared with adalimumab in children with JIA-associated uveitis and ANA-positive, idiopathic uveitis (NCT04088409).

Stopping treatment

Once control of intraocular inflammation is achieved, it is not clear how long the therapy should be maintained. Consensus recommendations suggest continuing treatment for at least 18 to 24 months of inactive disease while not using concomitant topical corticosteroids [4,8]. Furthermore, there is uncertainty about whether to wean immunosuppression gradually, and the order of stopping when more than 1 systemic treatment is being administered.

The early discontinuation of methotrexate, when it is administered as concomitant therapy with adalimumab, might result in the development of antiadalimumab antibodies, as shown in a recent study conducted in 20 patients with JIA-associated uveitis. The development of these antibodies was associated with progressive loss of response to adalimumab monotherapy [46].

The first year after discontinuation of systemic therapy seems to carry the highest risk of uveitis recurrence, as shown in different retrospective studies [47,48]. Moreover, there did not seem to be an association with duration of medication-induced remission. Another study identified a higher probability of remaining in remission after stopping systemic therapy in children with idiopathic rather than JIA-associated uveitis if inactivity was achieved in the first 6 months of systemic therapy and if it was achieved by an anti-TNF treatment [49].

An ongoing, multicenter, randomized international trial is trying to address questions around the feasibility of stopping adalimumab in patients (≥2 years of age) with JIA-associated uveitis controlled for greater than or equal to 12 months [50]. The trial will compare the time to uveitis recurrence between the group who continue adalimumab and the group who receive placebo.

Present relevance and future avenues to consider or to investigate; how this article may change the approach to the subject and conclusion

Noninfectious uveitis in childhood, if not adequately identified and treated, can lead to severe complications and visual loss with significant disability. Prompt and effective treatment following the current evidence-based guidelines is critical. These guidelines have highlighted the importance of earlier use of systemic

immunosuppression with steroid-sparing agents in cases of persisting uveitis activity. Methotrexate should be started early when poor prognostic factors are present at diagnosis of uveitis, followed by adalimumab when disease control is not achieved after 3 months of methotrexate.

As previously discussed, more challenging is the choice of drug when the patient is resistant to methotrexate and adalimumab because comparative superiority studies have not been undertaken. Switching to an alternative anti-TNF agent, such as infliximab, would be a reasonable first step. Tocilizumab might be a valuable option in those patients resistant to anti-TNF that showed macular edema, but further investigations are needed. Data about abatacept and rituximab are derived from small case series and currently are insufficient to provide clear recommendations. JAK inhibitors seem a promising class of drug, and the results of the ongoing trial should provide the evidence necessary to understand whether these treatments are effective in noninfectious uveitis.

A better understanding of the pathophysiology of JIA-associated uveitis will help to produce new targeted therapies. Several ongoing studies are focusing their attention on identifying blood and tear biomarkers that are able to distinguish patients who will develop uveitis and will help to stratify patients with higher risk of severe disease [2,51–53]. This group might benefit from earlier and more aggressive therapy. Future therapeutic options may include drugs targeting IL-17A (secukinumab) and IL-23 (ustekinumab), but studies so far have only included adult patients [54,55].

The results of the ongoing study about the feasibility of stopping biologic drugs will help in the future to identify the right time and right patient in whom to stop the therapy. Results from these and future studies have the potential to guide prediction of patients who will develop ocular disease, and may have implications for more targeted, individualized therapy for patients with JIA-associated uveitis.

Clinics care points

- Prompt diagnosis and treatment are crucial to prevent ocular complications and legal blindness in pediatric uveitis.
- A step-by-step approach is recommended by international guidelines.
- In the presence of poor prognostic factors (poor visual acuity, hypotony, cataract, glaucoma, macular oedema, dense opacities of vitreous) a first-line systemic treatment should be started, for instance methotrexate.
- Systemic treatment should be maintained at a stable dose for a least 18-24 months after the achievement of ocular inactivity, before the systemic therapy is reduced/stopped.
- During the tapering of systemic treatment, more frequent ocular evaluation should be performed.

Disclosure
A.V. Ramanan received Speaker fees/honoraria/consulting for Abbvie, Eli Lilly, Pfizer, Novartis, Roche, SOBI, and UCB. E.S. Sen and I. Maccora have nothing to declare.

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Update on Intravitreal Chemotherapy for Retinoblastoma

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Keywords

Retinoblastoma; Intraocular seeding; Chemotherapy; Intravitreal; Melphalan

Key points

- Intravitreal application of chemotherapy has gained acceptance for management of endophytic disease in retinoblastoma.
- For this purpose most widely used drug is melphalan.
- For safe and effective application of intravitreal chemotherapy, safety precautions have been described.
- Indications for intravitreal chemotherapy in retinoblastoma have been expanding beyond vitreal seeds.
- New drugs are under investigation for intravitreal application to overcome toxic effects of melphalan.

Introduction

Treatment of retinoblastoma has been constantly evolving along with advancements in chemotherapy administration particularly over the last 2 decades. With improving survival rates over time, priorities of clinicians have shifted toward eye salvage and eventually preservation of vision [1]. As of today, the major issues that remain to be resolved without metastatic compromise are relapsing intraocular disease, suboptimal response to systemic chemotherapy, and recognition of high-risk clinical features before development of any distant metastases, in all of which, endophytic retinoblastoma is thought to play a part.

Challenges of endophytic retinoblastoma

Endophytic retinoblastoma describes a growth pattern of retinoblastoma where intraocular seeding is a prominent feature, and tumor growth typically occurs toward the vitreoretinal interface at the tumor apex or tumor base [1]. According to the 3 most popular clinical classifications of the disease, vitreous seeding falls into the highest stage of Vb in Reese-Ellsworth staging, which stratifies intraocular retinoblastoma according to radiosensitivity [2]. The latter and more recent classification systems, International Intraocular Retinoblastoma Classification (IIRC) and International Classification of Retinoblastoma (ICRB) classification schemes, predict ordinal chemosensitivity through groups A to E, where vitreous seeding and endophytic disease are seen in groups C and onward [3,4]. Both IIRC and ICRB systems indicate a reduction in chemosensitivity with increasing extent of vitreous seeding. The reduction of chemosensitivity with presence of subretinal and vitreous seeding also exists with selective ophthalmic arterial infusion of chemotherapy (intraarterial chemotherapy IAC]) in both previously treated and treatment-naïve eyes, where the 2-year ocular survival rates could not exceed 76% and 64%, respectively [5]. More recently, Francis and colleagues reported that the presence of vitreous seeding is a predictor of poor response to second-course ophthalmic artery chemosurgery, which was given after a minimum of 2-month progression-free period in response to the first course [6].

From a histopathological point of view, even though endophytic disease is not considered a high-risk factor or an indication for adjuvant chemotherapy per se, it is important to recognize seeding as a possible reason of unresponsiveness and tumor recurrence [7]. The vitreous cavity is an avascular space, which limits the response of vitreous seeds to intravenous chemotherapy. It also might be that endophytic disease implicitly causes a lag time before significant histopathological risk factors such as choroidal invasion and optic nerve invasion develop, due to its unresponsive nature to conventional chemotherapy. Moreover, in terms of recurrence, long-term risks factors following intravenous chemotherapy include subretinal seeding as well as increasing order of IRCB group, which also designates an increasing order of the extent of seeding [8]. It is also known that histopathological risk factors are more likely to be found in the higher stages of the tumor according to the American Joint Committee on Cancer Tumor, Node, Metastasis classification and in the higher order of IRCB groups, also correlating with more extensive vitreous seeding [9].

Treatment of intraocular seeding

The described chemoresistant nature of intraocular seeding, together with its close association with tumor recurrence and high-risk histopathological risk factors, has led to a more widespread use of a relatively new therapeutic approach: intravitreal application of chemotherapy. As the tumor grows, 4 potential spaces may act as a harbor for intraocular seeding: (1) vitreous cavity, (2) aqueous humor, (3) subretinal space, and (4) retrohyaloid space. Location of seeding is one of the factors that classification of seeding relies on. However, whether seed location plays a role in systemic chemosensitivity, and if vitreous seeding should be handled separately, is not yet established, as IIRC groups subretinal and vitreous seeding as a whole. The only exception is tumors anterior to the vitreous face, which implies group E disease, often necessitating enucleation [3,4]. This concept regarding anterior chamber seeding is being challenged in large part by Munier and colleauges [1], but the impact of location on the overall prognosis remains unclear. The mechanisms for development of seeding in the 4 compartments also differ substantially, according to which, subretinal seeding indicates exophytic growth, whereas the other 3 make up endophytic disease [1]. This review aims to present the most recent developments on intravitreal application of chemotherapy in intraocular seeding of retinoblastoma, which is mainly composed of studies on, but not limited to, vitreous seeding.

Safety of intravitreal injections in eyes with retinoblastoma

The notion that vitreous seeding in retinoblastoma is only amenable to external beam radiotherapy or systemic administration of chemotherapy either by intraarterial or intravenous routes has been gradually abandoned after reports on safety of this procedure regarding inadvertent extraocular spread of the disease. With the overcoming of concerns of extraocular seeding, intravitreal application of chemotherapy has become the most convenient way of achieving the highest concentration of intravitreal chemotherapy (IvitC) with the lowest volume, given the avascular nature of vitreous.

In 2011 Munier and colleagues [10] have reported a meticulous description of the safety profile for IvitC injections. The prerequisite conditions for injection are as listed in Table 1. The additional precautionary measures targeting extraocular spread were an initial paracentesis to achieve transient hypotony and cryoprophylaxis. An anterior chamber paracentesis of 0.1 to 0.15 mL was performed without causing a leakage after the needle was drawn. Triple freeze and thaw cryotherapy was applied at the entry site following intravitreal injection with a 32G needle. The eye was then gently shaken for an even distribution of the drug. After a median follow-up of 13.5 months of 135 injections, no extraocular spread was seen in 30 eyes [10]. Later in 2014, Manjandavida and Shields expanded the contraindications as seen in Table 1 [11].

A comprehensive review of 1304 injections in 304 eyes with retinoblastoma reported only one extraocular spread and a suspect metastatic case where intravitreal injection could not be ruled out as a causative factor, causing a 0.007 prevalence of extraocular disease after a mean follow-up of 72.1 months [14]. The risk was virtually reduced to none when a safety-enhancing procedure was used [14]. In a larger scale multicenter cohort study, no cases of extraocular spread were reported with 3553 injections, which were all reported to be undertaken with a safety precaution, given in 655 patients with a follow-up of at least 6 months [15]. The precautions were at least 2 of the following: hypotony, cryoprophylaxis, irrigation of ocular surface, thorough examination with ultrasound biomicroscopy, and leaving residual subconjunctival chemotherapy at the injection site [15].

Table 1 Eligibility criteria and contraindications for intravitreal chemotherapy

Eligibility criteria defined by Munier et al. [10]	Contraindications defined by Manjandavida and Shields [11]	Prerequisites defined by Munier [12]
A clear view of fundus	Diffuse vitreous seeding	Vitreous hemorrhage and vitritis should be differentiated from seeding
Absence of anterior or posterior chamber invasion	Anterior chamber invasion	Prove viable tumor seeding, observe if necessary
A tumor-free entry site	Ciliary body invasion	Eligibility criteria should be ensured with ultrasound biomicroscopy
No seeding at the entry site	Secondary glaucoma	Primary source of seeding must be addressed either with focal treatments, IAC, or systemic chemotherapy
No retinal detachment at the entry site	High bullous retinal detachment	
Absence of anterior hyaloid detachment [13]	Obscuration of fundus view due to vitreous hemorrhage	

Data from Refs. [10–12]

Real-time qPCR has been used in 22 injections of intravitreal melphalan to test possible RNA reflux following cryotherapy prophylaxis. None of the samples from the cryoprobe or the injection site have tested positive for cone-rod homeobox gene RNA, which was chosen as a potential marker for retinoblastoma cells [16].

There is one recent report on a delayed metastasis in tibia of a patient who had bilateral retinoblastoma in remission and had received 6 intravitreal injections of melphalan during active course of the disease. However, the investigators do not comment on relation of metastasis to intravitreal procedure [17].

Classification of seeding

In his hallmark publication, Munier was the first to propose a classification of vitreous disease, mainly based on clinical observations, on which the growing literature gradually built up [12]. The 3 main morphologic entities of vitreous seeding are dust, sphere, and cloud. In addition to their morphologies, seeds are defined according to the anatomic site they present in, mainly anterior chamber, vitreous, retrohyaloid space, and subretinal space. The first classification according to treatment response has been defined by Munier and colleagues, and it is as listed in Table 2 [13].

Table 2 Types of regression after intravitreal chemotherapy

Regression type	Description
Type 0	Complete disappearance of seeds
Type 1	Calcified or refringent residues
Type II	Amorphous inactive residues
Type III	Combination of type I and II

Data from Munier FL, Gaillard MC, Balmer A, Soliman S, Podilsky G, Moulin AP, Beck-Popovic M. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. Br J Ophthalmol. 2012;96:1078-1083.

Data gathered from the literature on seed classification and its clinical implications are summarized in Table 3. All 3 seed morphologies can show mobility or adherence to the limits of the 4 ocular potential compartments they occur in [12].

Impact of intravitreal injections on patient management

There are several reports that analyze the disease outcomes based on introduction of IvitC in clinical practice:

1. In 2012 Shields and colleagues [22] compared the outcomes of primary IAC treatment according to introduction of IvitC in their clinical practice. Treatment groups before and after 2012 were statistically similar in terms of age, disease extent, presence of vitreous seeds, and number of IAC cycles. The overall need for enucleation in 66 eyes dropped from 44% to 15% after the introduction of IvitC for persistent or recurrent seeding with at least 6 months of follow-up [22]. The reduction was especially valid for eyes classified as group E ICRB; however, the corresponding IIRC group for these patients was not specified in this study.
2. To analyze if IvitC had compensated for the negative effect of vitreous seeding on enucleation rates, Dalvin and colleagues [23] reported their 5-year results of primary IAC in the IvitC era (2012–2017). After a mean follow-up of 27 months, there was no statistically significant difference in enucleation rates in group D and E eyes when patients who received IAC alone were compared with those receiving IAC + IvitC (88% vs 69% for group D, and 58% vs 57% for group E, respectively, $P = .36$, $P = .39$). Again the disease classification was made according to ICRB, but it can be assumed that as a whole, group D and E eyes correspond to the combination of groups D and E in IIRC as well.
3. In order to compare the efficacy and toxicity of IvitC when it is administered with concurrent systemic chemoreduction, or sequential to systemic chemotherapy, Berry and colleagues [24] reviewed 6 eyes of 6 patients who were undergoing integrated treatment of IvitC and intravenous chemoreduction. Given that 4 of 6 eyes were salvaged but all eyes showed toxicity (grade 3 RPE changes in 3 eyes, grade 4 RPE toxicity in 1 eye, and cataract in 2 eyes), they raised concerns regarding the timing of IvitC injections to avoid additional ocular toxicity. By which mechanism systemic chemotherapy enhanced ocular toxicity, however, was not clarified [24].

Table 3 Conceptual data gathered on seed classification

Seed morphology [12,20]	Description [21]	Median age at presentation (mo) [21]	Required treatment [12,20]	Response [12,18,20]	Histopathology [19]	Time to regression [12,20]
Dust/Class 1	Fine particles of cellular infiltration	11	Median 3 injections, median 20 μg melphalan, median total 60 μg melphalan	100% type 0 regression	Viable tumor cells and dispersed macrophages	Median 0.5–0.6 mo
Sphere/Class 2	Larger globular seeds formed by clonal expansion from dusts or sprouting, likely type of seed to be seen in recurrent seeding, also associated with previous IAC	15.5	Median 4–5 injections, median 30 μg melphalan, median total 107–161 μg melphalan	78%–90% type 0 10%–18% types 1 and 2 3% type 3 regression Initial mechanical breakdown is possible	1. Diffusely viable cells OR 2. An outer coat of viable cells with a necrotic core	Median 1.4–1.7 mo
Cloud/Class 3	Massive break-ups from the original tumor, preference for equator-ora serrata location, more likely to be seen in unilateral disease	32	Median 6–8 injections, median 33 μg melphalan, median total 203–229 μg melphalan	55%–69% type 0 32%–45% types 1, 2, and 3 regression Initial mechanical breakdown is possible	An outer coat of viable cells, >90% necrosis, dispersed macrophages	Median 6.6–7.7 mo

Morphologic responses were reported to be similar after intraarterial chemotherapy and intravenous chemotherapy. Similar histomorphology was encountered in primary and secondary seeds.

Data from Berry JL, Bechtold M, Shah S, Zolfaghari E, Reid M, Jubran R, Kim JW. Not all seeds are created equal: seed classification is predictive of outcomes in retinoblastoma. Ophthalmology. 2017;124:1817-1825; and Amram AL, Rico G, Kim JW, Chintagumpala M, Herzog CE, Gombos DS, Chévez-Barrios P. Vitreous seeds in retinoblastoma: clinicopathologic classification and correlation. Ophthalmology. 2017;124:1540-1547.

4. In a retrospective study by Berry and colleagues, 76 naive eyes classified as group D according to IIRC were treated with enucleation or systemic chemoreduction combined with IvitC for recurrent or persistent seeding and were followed-up for a median of 33 months. [25] When primarily enucleated cases were excluded, 39 of 52 (75%) eyes were salvaged, whereas a prior study from the same center reported a cure rate of 47% in group D eyes with chemoreduction alone [26].
5. Specifically addressing clouds, Francis and colleagues reported on their management of this condition with IAC alone or combined with IvitC and periocular chemotherapy between 2006 and 2016 [27]. There is no specific information on randomization of the 2 arms; however, it is thought that the investigators report their findings before and after institution of IvitC in their clinical practice, given the time-span of the study. Combination with IvitC significantly reduced time to regression (14.6 months vs 5.7 months), and 36-month ocular estimates were 83.3% in IAC alone and 100% for the combination group ($P = .16$) [27].

The details of injection protocols of the studies listed earlier and selected large scale studies are depicted in Table 4.

Uses of intravitreal chemotherapy other than for vitreous seeds

With growing interest in use of IvitC for vitreous disease, several other conditions have been reported to benefit from this particular way of targeted chemotherapy, one of which is secondary relapse of retinoblastoma at the optic nerve head (ONH) [33]. In a case series of 6 patients, where in all eyes ONH relapse was derived from the vitreous disease, salvage treatment of IvitC alone or in combination with IAC was applied. Out of 5 eyes receiving IvitC (melphalan), ONH relapse was resolved in 0.8 to 3.9 months and all eyes were salvaged after a median event-free time of 25.1 months and a median of 4.0 injections [33].

In 14 eyes that developed subretinal seeds following primary IAC, Abramson and colleagues used IvitC using melphalan alone or combined with topotecan together with 810 nm diode laser [34]. With none of the eyes receiving concomitant IAC, all of the subretinal seeds were regressed in a mean of 41 days, after a mean of 2 laser sessions and 3 injections per eye, and a mean follow-up time of 17 months [34].

To study whether the indications for IvitC could be expanded to include retinal tumors and subretinal seeds, Abramson and colleagues [35] added IvitC to the treatment regimen at the point where tumors stopped responding to initial IAC or systemic chemotherapy in these conditions. Ninety eight percent of the eyes responded, 5 of 26 retinal tumors with 3 of 27 subretinal seeds showed recurrence, and one eye required enucleation after a mean follow-up of 15 months [35].

Dosage

Although intravitreal melphalan is considered safe in terms of systemic toxicity, clinical reflections of ocular toxicity can occur in various forms, most frequently as findings of retinopathy (see Table 4) [36]. It can vary from signs limited to the injection site to panretinopathy with optic atrophy. The clinical chorioretinal toxicity grading system based on clinical extent was proposed by Munier [12] (Table 5). The highest complication rates in terms of ocular toxicity have been recently reported in cohort of 30 eyes receiving 20 to 33 μg of melphalan per injection [37]. Chorioretinal atrophy was documented in 19 eyes, retinal vascular occlusion in 12, optic atrophy in 6, vitreous hemorrhage in 3, cataract in 8, iris atrophy in 12, and hypotonia/phthisis in 4 eyes. Among those who developed chorioretinal atrophy, even though there was no ordinal sequence, the mean dose of melphalan differed significantly owing to a higher mean dose (>27 μg) in grade 4 and 5 eyes compared with the lower grades of chorioretinal atrophy. The mean cumulative dose was, however, similar among eyes with different grades of retinopathy [37]. Although the investigators have reported a higher prevalence of vascular events than encountered in the studies listed in Table 4, on histopathology, it is now known that melphalan toxicity is not only limited to vascular toxicity but also indicates a direct impact [36].

Table 4 Results of selected studies on intravitreal injections for retinoblastoma

Study, year	Intravitreal drug	Number of injected eyes	Drug dose	Number and frequency and timing of injections	Response of vitreous disease	Ocular survival of IvitC patients	Follow-up time for injection	Side eff
Shields et al. [22] 2016	M ± T	11	20-more than 30 μg M/injection 20–30 μg T/injection	1–6 injections, weekly-biweekly, 0.9–34.5 mo after IAC	NA	None of the eyes were enucleated for active vitreous seeding	NA	NA
Dalvin et al. [23] 2019	M ± T	20	20–188 μg cumulative dose for M 20–160 μg cumulative dose for T	2–14 injections, frequency NA, 0–32 mo after IAC	NA	None of the eyes in IAC + IvitC group was enucleated for recurrence	NA	NA
Berry et al. [18] 2017	M	28	20–40 μg M/injection (median: 25 μg) 25–282.5 μg cumulative dose for M	1–10 injections, weekly follow-up, initiated during chemotherapy cycles 4–6	100% regression	68%	Mean: 33 mo (range: 9–51)	≥gra toxi eyes Cata foca atro infla in 7
Berry et al. [25] 2017	M	22	20–40 μg M/injection (median 25 μg) 25–282.5 μg cumulative dose for M	1–10 injections, weekly follow-up, used for salvage, 0–9 mo after systemic chemotherapy	100% regression	64%	NA	Gra retir in 9, in 8, in 3, 5 in Cata foca atro infla in 5

Table C

Study, year	Intravitreal drug	Number of injected eyes	Drug dose	Number and frequency and timing of injections	Response of vitreous disease	Ocular survival of IvitC patients	Follow-up time for injection	Side effect
Kiratli et al. [28] 2017	M	39	20–40 μg M/injection	1–5 injections, biweekly follow-up, timing relative to intravenous chemotherapy or IAC NA	69.2% regression	56%	Mean: 11.8 mo	Vitreous hemorrhag grade 4–5 retinopath inflammat eye

Study, year	Intravitreal drug	Number of injected eyes	Drug dose	Number and frequency and timing of injections	Response of vitreous disease	Ocular survival of IvitC patients	Follow-up time for injection	Side effect
Kiratli et al. [29] 2020	M ± T	77	25– 40 μg M/injection (median 30 and 36 μg in 2 groups) 40 μg median cumulative dose for M Median 13 μg T/injection 20 μg median cumulative dose for T	Median of 1 injection in both groups, biweekly follow-up, timing relative to intravenous chemotherapy or IAC NA	57% regression	88%	Median: 10 and 7 mo in 2 groups	Vitreou hemorı 8, grad retinop 3, grad grade 5 eyes Posteri synech iris depign in 1 ey
Shields et al. [30] 2016	M ± T	40	20– 40 μg M/injection 20– 25 μg T/injection	1–6 injections for M, 1–5 injections for T, injections every 1–4 wk, 1–73 mo after primary treatment	100% regression	88%	Median: 32 mo	RPE m 13, vitr hemorı 5, retin hemorı 2, optic edema Catara hypoto cornea epithel in 2 ey

Table C

Study, year	Intravitreal drug	Number of injected eyes	Drug dose	Number and frequency and timing of injections	Response of vitreous disease	Ocular survival of IvitC patients	Follow-up time for injection	Side effects
Suzuki et al. [31] 2015	M	264	8– 24 μg M/injection	1–25 injections, frequency or exact timing not indicated	68% complete remission	70%	Median: 124 mo (range: 8–269)	Diffuse chorioretinal atrophy in 2, retinal detachment in 1, extrascleral spread in 1 eye Cataract in 20, iris atrophy in 3 eyes

Study, year	Intravitreal drug	Number of injected eyes	Drug dose	Number and frequency and timing of injections	Response of vitreous disease	Ocular survival of IvitC patients	Follow-up time for injection	Side effects
Francis et al. [32] 2017	M ± T	130	25–30 μg M/injection	Weekly-monthly injections, timing not indicated	NA	2-y estimate: 94.2%	NA	5.3 μV decrement in ERG per injection 8.0 μV decrement in ERG with concomitant IAC ERG decrease marked in dark pigmentation
Munier et al. [13] 2012	M	23	20–30 μg M/injection	2–12 injections, every 7–10 d, exact timing after primary treatment not indicated.	100% remission	87%	Median: 22 mo	Salt-pepper retinopathy in 10, vitreous hemorrhage in 2 eyes

Abbreviations: ERG, electroretinogram; M, melphalan; NA, not available; RPE, retinal pigment epithelium; T, topotecan.

A cohort of 11 eyes receiving a fixed dose of 20 μg melphalan with or without 20 μg topotecan for vitreous seeding in only 1 quadrant developed a relatively lower rate of retinopathy (27%, 3 eyes) with 1 to 12 injections [38]. However, in addition, one eye developed optic atrophy, one submacular hemorrhage/scar, one vascular sheathing, one subretinal fibrosis, 2 sclerosed vessels, and 1 mild vitreous hemorrhage, making the overall prevalence for posterior segment complications higher (5/11) [38]. This finding is also consistent with the fact that underlying mechanisms of melphalan toxicity are the direct impact of the drug and vascular toxicity. This study shows that even moderate doses of melphalan could not rule out the possibility of posterior segment complications in critical anatomic structures.

Table 5 Clinical grading of chorioretinal toxicity following intravitreal melphalan

Grade	Description
Grade 1	Salt and pepper retinopathy <2 clock hours, no posterior than equator
Grade 2	Any retinopathy larger than 2 clock hours, no posterior than equator
Grade 3	Retinopathy exceeds the equator but does not involve macula
Grade 4	Maculopathy is present
Grade 5	Diffuse retinopathy and optic atrophy

Data from Munier FL. Classification and management of seeds in retinoblastoma. Ellsworth Lecture Ghent August 24th 2013. Ophthalmic Genet. 2014;35:193-207.

There is no strict guideline for dose titration for IvitC in retinoblastoma. The enlisted studies in Table 4 are based on results of 20 to 40 μg melphalan per injection. Some centers prefer to inject doses of 20 μg to 30 μg depending on the extent of seeding and inject close to 30 μg if the seeds are recurrent,

and there is dense vitreous seeding or suboptimal response to previous injections [11]. Similarly, some investigators have recommended starting doses of 20 μg and apply dose escalations of 2 to 4 μg up to 30 μg when the patient is older than 2 years, when there is extensive seeding, when seeding is recurrent, or if there is a history of IAC [12]. One consolidation injection is generally recommended, although no established guidelines exist [1]. Others have limited the use of intravitreal melphalan, never to exceed 25 μg following the report on toxicity after 30 μg injections [18,36].

A more reasonable approach regarding dosing involves concerns of intravitreal concentration. In a prominent cohort of 90 consecutive eyes receiving IvitC at a single center, any grade of chorioretinopathy developed in 41%, of more than 90% being composed of grades 1 and 2 [1]. Among grades 1, 2, and 3, the mean melphalan concentration calculated with age-related vitreous volume were similar; however, grade 3 toxicity group fared higher when tumor volume was extracted ($P = .04$), which implies a need for a precise concentration calculation per injection if an eye is to be spared from retinal toxicity especially in an eye bearing a large tumor. The accepted tumoricidal concentration of melphalan is 4 μg/mL, and 5 μg/mL perfusion is shown to be nontoxic to the retina with stable electroretinogram (ERG) findings, whereas 10 and 20 μg/mL are deemed retinotoxic [39,40]. Although the injected volume is assumed to be neglected, the predicted vitreous concentrations with respect to tumor volume and age-adjusted globe volume by Munier and colleagues is as presented in Table 6 [1]. Care should be taken for needle tip positioning because inadvertent retrohyaloid injections in eyes with posterior hyaloid detachment also are reported to be a potential cause of increased toxicity [1]. Still, to what extent retinal function could be put at risk for vitreous remission without causing phthisis is at clinician's discretion and multiple factors including patient preference.

Pharmacokinetics of intravitreal melphalan

Application of a single 15 μg melphalan injection in a rabbit model resulted in a maximum concentration of 7.8 μg/mL immediately [41]. The vitreal concentration was predicted as 4.7 mg/mL at 1 hour and 0.3 mg/mL at 5 hours, in line with the short elimination half-life of the drug from the vitreous (1 hour) [41]. The elimination occurred abiding by zero-order elimination in the first 2 hours and by first-order elimination thereafter [41]. Systemic exposure in the plasma was not observed during the 12-hour study [41]. These results comply with the fact that intravitreal melphalan injections are more likely to cause instant retinal toxicity than long-term cumulative toxicity and are free of systemic adverse events.

Table 6 Predicted vitreous concentrations of melphalan with reference to percentage of tumor volume and age-adjusted globe volume

Tumor volume	Dose (μg)	Vitreous concentration (μg/mL)	
		At 6 mo of age	At 36 mo of age
0%	20	6	*4*
	30	9.5	6.5
	40	**13**	8.2
10%	20	7.5	5
	30	**11**	7
	40	**14**	9
25%	20	9	5.5
	30	**13**	8
	40	**17**	**11**
50%	12	7	5
	20	**13**	8
	30	**19**	**13**

The lower-than-efficient concentrations are expressed with italic text, and potentially toxic concentrations are marked with bold text.

Adapted from Munier FL, Beck-Popovic M, Chantada GL, Cobrinik D, Kivelä TT, Lohmann D, Maeder P, Moll AC, Carcaboso AM, Moulin A, Schaiquevich P, Bergin C, Dyson PJ, Houghton S, Puccinelli F, Vial Y, Gaillard MC, Stathopoulos C. Conservative management of retinoblastoma: Challenging orthodoxy without compromising the state of metastatic grace. "Alive, with good vision and no comorbidity". Prog Retin Eye Res. 2019;73:100764; with permission.

Use of intravitreal topotecan

The current use of topotecan as IvitC is mostly in combination with melphalan as a measure to enhance efficacy (see Table 4) [38]. The use of topotecan alone is limited to a few publications, one of which analyzed 17 consecutive eyes with refractory or recurrent seeding receiving 30 μg/0.15 mL intravitreal injections every 3 weeks [42]. After a mean follow-up of 23.8 months, seed regression was 100% and a glove salvage of 94% was attained. There were no data on adverse events [42]. The use of topotecan as an additive measure to melphalan predicted better ocular survival in both univariate and multivariate regression analyses performed by Kiratli and colleagues (P = .031, .019, respectively) [29]. Retinotoxicity of intravitreal topotecan was analyzed using serial ERG responses following 28 injections of topotecan alone at 20 to 30 μg/injection, and the results were compared with those of melphalan combined with topotecan [43]. The trend in ERG response with topotecan alone resulted in a −1.6 μV decrement per injection; however, the decrease was not statistically significant (P = .72) [43].

Pharmacokinetics of intravitreal topotecan

Pharmacokinetic studies of intravitreal topotecan injection at 5 μg doses resulted in a median maximum vitreous concentration of 5.3 μg/mL, and potentially cytotoxic concentration was maintained up to 16 hours with the least systemic exposure [44]. In vitro studies have shown the need for greater than 19 ng/mL of topotecan for antitumor effect (LC50) [45].

Table 7 Candidate compounds for intravitreal administration that caused greater than or equal to 70% cell death AND are Food and Drug Administration–approved, had adult clinical trials, and had pediatric phase 1/2 studies

Candidate compounds [48]	Biological action
Melphalan	DNA alkylator
Topotecan	Topoisomerase 1 inhibitor
Etoposide	Topoisomerase 2 inhibitor
Digoxin	Na/K ATPase inhibitor
Teniposide	Topoisomerase 2 inhibitor
Romidepsin	Histone deacetylase inhibitor
Gemcitabine	Antimetabolite
Methylene blue	Oxidation-reduction agent

Stability of melphalan and topotecan

In order to attain the efficient dose of 30 μg melphalan, the storage conditions of the drug have been determined [46]. Following dilution of 5 mg/mL of solution to 300 μg/mL with saline, several room conditions were tested. The solutions are advised not to be left at room temperature (25°C) for more than 2 hours and in the refrigerator (5°C) for 3 hours, to achieve effective drug concentration of at least 95%. When kept at −20°C, however, the drug is reported to maintain its concentration for up to 6 months [46].

Table 8 Candidate compounds for intravitreal administration that caused greater than or equal to 90% cell death AND are NOT Food and Drug Administration–approved or do not have adult clinical trials or do not have pediatric phase 1/2 studies

Candidate compounds [48]	Biological action
YM155	Survivin inhibitor
ABT-737	B-cell lymphoma (Bcl)-2 and Bcl-xL protein inhibitor
BIX 01294	Histone methyltransferase G9a inhibitor
UNC0631	Histone methyltransferase G9a inhibitor
ISPINESIB	Kinesin spindle protein inhibitor
ARQ621	Kinesin spindle protein inhibitor
SB743921	Kinesin spindle protein inhibitor
NH125	Eukaryotic elongation factor 2 inhibitor
NSC 319726	P53 reactivator
BAY 11-7085	Nuclear factor kappa-light-chain-enhancer of activated B cells α inhibitor
SBI-0640756	Eukaryotic translation initiation factor 4 gamma 1 inhibitor
STATTIC	Signal transducer and activator of transcription 3 inhibitor

A study with similar methodology was conducted for topotecan [47]. After attaining diluted concentrations of 0.2 mg/mL with saline, it was found that the preparations remained intact following 24 hours at 25°C, 167 days at −20°C, and the following 8 hours after thawing [47].

Future avenues

A remarkable contribution in terms of expanding the repertoire of candidate intravitreal agents for retinoblastoma has recently come from Cancela and colleagues [48]. The investigators have tested a custom library of 2700 variegated medicinal compounds on 2 patient-derived retinoblastoma cell cultures through high-throughput screening essays. A systematic and multidisciplinary prioritization was made to determine novel candidates for intravenous, oral, intraarterial, intrathecal/intraventricular, or intravitreal administration. The candidate drugs for intravitreal use were further excluded if the drug (1) was not available as an injectable solution, (2) had been reported to have vesicant or irritant effects, (3) had been known to have ocular or neurologic toxicity, or (4) was a prodrug. The results of their algorithm and the final candidates are represented in Tables 7 and 8.

As the way moves forward with IvitC, novel drugs targeting different mechanisms come into question in terms of efficacy and toxicity. As in the ideal flow of scientific progression, pharmacokinetic and pharmacodynamic animal studies precede the clinical application of drugs. With developing novel drug delivery systems, synergistic effect with IvitC could be achieved by addressing multiple cellular mechanisms.

Summary

The reintroduction of IvitC in clinical practice has revolutionized the management of vitreous disease, as it was once considered a taboo. The knowledge on IvitC has been accumulating in a logarithmic scale and expanding our understanding of the disease and treatment results ever since. Clinical studies present objective evidence of how IvitC has improved the ocular survival rates together with endophytic disease regression. However, there remain several questions to be answered. One such issue to be clarified is the timing of IvitC. Since 2012 [13], there has been no head-to-head study distinguishing ocular survival or treatment response rates of persistent/refractory or recurrent seeding with primary seeding at presentation. Given that most of the clinical studies of IvitC deal with persistent or recurrent seeding, or timing of IvitC is not clearly indicated, it is of question if ocular survival rates will improve even more with prompt initiation of IvitC concurrent with the systemic approach to the main tumor. A clearly delineated definition of persistent or recurrent seeding also could be helpful in more precise interpretation of data with use of common terminology. The need for a broader comparison of response also exists for persistent and recurrent seeding. And finally, to benefit even more from this safe and effective procedure, the use of IvitC beyond established indications could grow with larger groups of clinical observations, as our experience with IvitC application continues to grow.

Clinics care points

- Intravitreal melphalan is an effective drug for the management of vitreous disease when applied at doses within safety margins.
- Careful case selection and employment of proper technique is important.
- Ocular and systemic complications should be interpreted with caution, as most patients receive concomitant other treatments.
- Precise concentrations are more predictive of toxicity than a fixed dose of injection.
- The indications for use of intravitreal chemotherapy are expanding to include conditions other than vitreous seeds.

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Ophthalmic Pathology & Ocular Oncology

OUTLINE

Applications of Plaque Brachytherapy in Posterior Segment Tumors

A Clinical Review

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Keywords

Brachytherapy; Plaque; Radiation; Retinoblastoma; Melanoma; Choroidal; Hemangioma

Key points

- Benign as well as malignant types of posterior segment tumors can be managed with plaque brachytherapy.
- Benign tumors, such as choroidal hemangioma, retinal capillary hemangioma, and vasoproliferative retinal tumors, have been treated successfully with plaque brachytherapy.
- The American Brachytherapy Society – Ophthalmic Oncology Task Force consensus guidelines are employed for use of plaque brachytherapy for retinoblastoma and choroidal melanoma.
- Pretreatment comparative dosimetry is a foundational element of plaque brachytherapy planning.

Introduction

Ophthalmic oncology is a well-recognized subspecialty of ophthalmology that has transformed from being predominantly surgical to a specialty that encompasses medical and radiation therapy [1,2]. Radiation therapy has become an integral part of ocular tumor management for benign and malignant tumors [3]. It has served to preserve life, vision, and the globe.

Broadly, radiation typically is delivered via teletherapy or brachytherapy. Although external beam radiation therapy (EBRT) most commonly is linear accelerator (LINAC) based, other forms include intensity-modulated radiation therapy, volumetric modulated arc therapy, stereotactic radiosurgery (eg, Gamma Knife), and charge particle irradiation (eg, proton beam therapy). Brachytherapy includes the use of temporary implants (eg, episcleral plaque brachytherapy) or permanent brachytherapy (interstitial or intracavitary placement of radiation source[s]) [1,2,4]. Plaque brachytherapy has been used most commonly on the eye whereas EBRT has been employed to the orbit. [1]

Historical perspective

Brachytherapy has come a long way over the past century. In 1929, Moore [5] successfully treated a "choroidal sarcoma" with radon seeds at the St. Bartholomew's Hospital, London. He was assisted by Stallard [6]in this case, who went on to pioneer cobalt-60(^{60}Co) plaque brachytherapy and published his results in 1966. Around that time, Lommatzsch [7]pioneered solid ruthenium-106 plaques and later published his 20-year experience in 1986. Introduced by Packer and Rotman, it was not until the 1980s when the Collaborative Ocular Melanoma Study (COMS) established iodine-125 (^{125}I) plaque brachytherapy as the most common eye and eye-preserving radiation therapy for choroidal melanoma in North America [8]. More recently, Finger introduced palladium-103 (103Pd) plaques. Finger and colleagues reported their long-term results in 2009 [9].

Ophthalmic brachytherapy plaques too have evolved from cobolt-60 discs (high energy, solid, encapsulated) to ruthenium-106 (^{106}Ru) and strontium-90 (^{90}Sr) plaques (beta-emitting; high-energy, solid shielded plaques with rapid dose fall-off) to iodine-125 and then to palladium-103 seeds (gold shells with low-energy photon seeds). Furthermore, shape modifications, such as the introduction of the notched and slotted plaques, have allowed more posterior segment tumors to be managed with brachytherapy [10] (Fig. 1).

Solid beta-emitting plaques like ruthenium-106 have a longer half-life ($T_{1/2}$ of Ru-106 is 372 days) compared with seeded plaques ($T_{1/2}$ for I-125 is 59.4 days and for Pd-103 is 17 days). The relatively long half-life of Ru-106 plaques allows reuse for multiple patients, making them more affordable [11]. Ruthenium-106 plaques, however, have not been successful in treatment of tumors greater than 5 mm in height and cause more vision loss (due to radiation chorioretinopathy) if used close to the fovea [10]. Along with the evolution of plaques and radionuclide options, the scope of plaque brachytherapy also has broadened [1,4,11]. Table 1 enumerates the posterior segment tumors for which plaque brachytherapy is currently used. These include both malignant and benign conditions. A complete plaque brachytherapy team is composed of an ocular oncology specialist, a medical physicist, and a radiation oncologist [8].

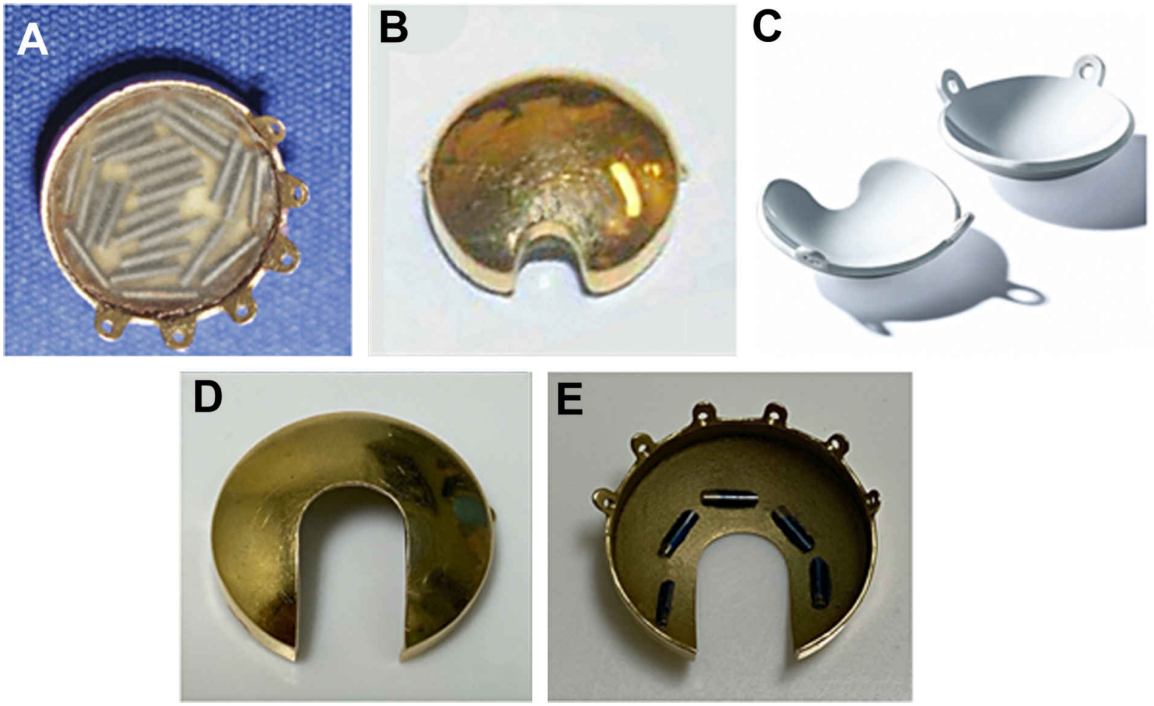

FIG. 1 Various eye plaque brachytherapy plaques. (*A*) COMS plaque with palladium-103 seeds. (*B*) Notched COMS-style plaque with side wall. (*C*) Solid ruthenium-106 plaques. (*D*, *E*) Finger's slotted plaque, demonstrating how palladium-103 seeds can be affixed to surround the slot and thus fill in the slot gap. Note that, in practice, the slot depth is varied to accommodate more or less of the optic nerve sheath into the device.

Choroidal hemangioma

Choroidal hemangioma is an uncommon, benign, vascular hamartoma. Based on morphology, it can be classified into 2 types—circumscribed choroidal hemangioma (CCH) and diffuse choroidal hemangioma (DCH). CCH is nonsyndromic, presents as a solitary lesion, and is not associated with the Sturge-Weber syndrome. Clinically, CCH typically is an orange-red, round to oval mass posterior to the equator. It can have a pigmented surround, involve the macula, and cause an exudative retinal detachment as well as cystoid retinal degeneration. In contrast, DCHs typically are diffuse, presenting as an ill-defined reddish choroidal thickening, and are associated with the Sturge-Weber syndrome [3].

The disease course of a choroidal hemangioma typically is progressive. In untreated patients, a large choroidal hemangioma leads to massive serous retinal detachment and secondary glaucoma. Treatment depends on the type of choroidal hemangioma, tumor size, visual acuity, and associated ocular findings.

Table 1 Current indications of plaque brachytherapy for posterior segment tumors

Benign	Malignant
1. Choroidal hemangioma	1. RB
2. RCH	2. Choroidal melanoma
3. VPTs	

Management of choroidal hemangioma

Small, asymptomatic CCH with no subretinal fluid can be serially monitored for evidence of change prior to intervention. The available treatment options are laser photocoagulation, transpupillary thermotherapy, photodynamic therapy (PDT), plaque brachytherapy, proton beam therapy, and EBRT. Cryotherapy has a limited role in this

condition because of the posterior tumor location and the risk of macular scarring associated permanent vision loss. Laser photocoagulation is the first-line treatment of CCH. The details of laser photocoagulation in treating CCH are beyond the scope of this article (Table 2) [12]. PDT also has its limitations, summarized in Table 2.

Episcleral plaque brachytherapy offers distinct advantages over laser and PDT in the management of choroidal hemangioma. Not only does brachytherapy cause actual tumor regression (up to 80% reduction in tumor height), but also, it has been associated with permanent resolution of the subretinal fluid [3,12–16]. Plaque radiation therapy offers a more localized treatment, with no EBRT-like entry dose through the eyelids, cornea, lens, and the lacrimal system. On the other hand, plaque radiation dose-gradients associated with brachytherapy can significantly affect the relative dose to the fovea and the optic nerve (with associated side effects). Therefore, comparative dosimetry should be employed to contrast plaque, plaque type, and EBRT dose to critical ocular and adnexal structures prior to treatment [8,17].

The first reported use of brachytherapy for the treatment of choroidal hemangioma was with radon seeds in 1960 [13]. The use of ^{60}Co plaques (average tumor apex dose of 40 Gy) for CCH has shown that brachytherapy has been an efficacious and safe treatment of large tumors, lesions involving the macula, and those associated with high serous detachments [14]. Madreperla and colleagues [15] employed ^{106}Ru and ^{125}I plaques (mean tumor apex dose of 50 Gy) for CCH wherein all patients had complete resolution of the subretinal fluid at 1-year follow-up with a gain over pretreatment visual acuity. Aizman and colleagues [12] used ^{103}Pd (mean tumor apex dose of 29 Gy) for CCH cases with 100% resolution of serous detachments and a remarkable reduction in the tumor height.

The common adverse effects of brachytherapy while treating choroidal hemangioma include radiation maculopathy, radiation papillopathy, and cataract. The dose to the fovea and the optic nerve preoperatively can help the clinician in predicting these adverse effects and gauge the visual potential in each case. Also, it has been shown that ^{103}Pd delivers less radiation to the normal ocular structures than ^{125}I (for the same total tumor dose), further minimizing the risk of radiation-induced side effects [9,12].

Management of diffuse choroidal hemangioma

DCHs are, by definition, diffuse. That is, the edges are not defined clearly nor are the sources of exudation. Indications for treatment include exudative retinal detachment, progressive angle closure, and/or iris neovascularization. EBRT typically offers treatment of the entire tumor and has been the treatment of choice. The literature suggests that EBRT can cause side effects, including cataract, radiation optic neuropathy and orbital fat atrophy [13,18]. These side effects, however, are dose dependent. Clearly, EBRT of DCH lesions could benefit from a dose de-escalation study. Prior studies suggest this tumor is exquisitely radiation sensitive. The use of low doses EBRT would be associated with fewer radiation side effects and shorter treatment durations [16].

Table 2 Comparison of treatment modalities employed for choroidal hemangioma

Treatment	Limitations
Laser photocoagulation	• Minimal tumor regression • Chorioretinal scarring leading to visual field defects • Recurrent retinal detachments • Need for multiple sittings • Cannot be used for subfoveal CCH • Cannot be used for CCH with large serous retinal detachments • Multiple sessions typically required extending time that the fovea may be detached risking loss of vision
PDT	• Choroidal ischemia and atrophy leading to visual field defects • May need more than 1 sitting • Cannot be used for large CCH • Cannot be used for anteriorly located CCH • Cannot be used for CCH with large serous retinal detachments •Multiple sessions typically required extending time that the fovea may be detached risking loss of vision
Plaque brachytherapy	• Requires 2 surgical procedures (plaque placement and removal within 3–7 days) • Treats a targeted plaque-size defined area
EBRT	• Relatively diffuse radiation distribution and side effects • Requires LINAC or other relatively expensive capital equipment • 16–20 Gy in 180–200 cGy daily fractions or up to 10 days of treatment

Laser photocoagulation and PDT have a very limited role in DCH management (see Table 2). Plaque brachytherapy has been used for DCH as well, but the available literature currently is limited to isolated case reports or a small case series only [3,16]. ^{125}I and ^{106}Ru, both have been shown to be effective in managing DCH (tumor apex dose of 30 Gy to 35 Gy) [12,16]. The crucial point while planning plaque brachytherapy for DCH is the plaque placement—the plaque should be centered to coincide with the area of maximum tumor thickness, even if it does not cover the entire lesion. The authors use this treatment only for younger patients who cannot have EBRT.

In general, DCH carries a worse prognosis for preserving vision compared with CCH. A large number of cases of unilateral and even

bilateral DCH, however, have been controlled, leaving the patients with more useful vision in their eye. In addition, DCH is associated with the Sturge-Weber syndrome and the Klippel-Trénaunay syndrome. The authors recommend co-management with a neurologist to monitor for central nervous system disease.

Retinal capillary hemangioma

A retinal capillary hemangioma (RCH) is a benign vascular tumor. It is also known as retinal angioma or retinal hemangioblastoma (older terminology). RCH can be classified in several ways. Based on systemic association, RCH can be either isolated or syndromic; based on its location, it can be peripheral or juxtapapillary; and, based on the growth pattern, it can be endophytic (growth toward the vitreous cavity) or exophytic (growth into the subretinal space). RCH is the most common and earliest manifestation of von Hippel-Lindau (VHL) disease [19]. Isolated (or sporadic) RCH typically is unilateral and single, whereas syndromic RCH tends to be bilateral and multiple.

The classic clinical description is that of a well-circumscribed, orange-red, retinal mass with a dilated, tortuous feeder, and a draining blood vessel. The most common location is temporal, anterior to the equator. Leaky tumor vessels lead to fluid accumulation (intraretinal and subretinal) and circinate exudation [3]. Systemic work-up for VHL is mandatory for a patient with RCH.

Although diagnosis of RCH usually is clinical and straightforward, the management poses a challenge, especially in cases where RCH is large or there are multiple tumors. Garg and Finger [20]published a vision outcome–based staging system for RCH. Treatment options have included observation, laser photocoagulation, cryotherapy, PDT, radiation therapy (ie, brachytherapy, proton beam therapy, or EBRT), and vitreoretinal surgery [3,19,21]. The choice of treatment is governed by the size of the tumor, its location, the extent of secondary tumor effects, and the visual potential.

Small RCH lesions measuring less than 500 microns without any vision threatening secondary changes can be observed for change. Laser photocoagulation works best for RCH lesions less than 1.5 mm. Anteriorly located RCH with extensive subretinal fluid respond to cryotherapy. Both treatments may require multiple sessions. Furthermore, laser photocoagulation can cause reactive scarring, which can mask recurrences and heavy cryotherapy can induce proliferative vitreoretinopathy. Enucleation is reserved for blind, painful eyes.

Radiation therapy was first employed for RCH management in 1935 using radon seeds [3]. Currently, plaque brachytherapy of RCH has specific indications, which include large RCH tumors (height >4 mm), RCH with extensive subretinal fluid that precludes the use of laser or

cryotherapy, and indications for globe salvage (when other treatments have failed). Plaque brachytherapy involves a 2-sitting (insertion and removal) surgery with minimal reactive changes. Primary ^{106}Ru brachytherapy (mean tumor apex dose of 126 Gy ± 36 Gy) has been shown to have greater than 90% tumor local control [21]. This same study also concluded that tumor size less than 2.5-disc diameter in the absence of exudative retinal detachment carries a favorable outcome after brachytherapy [21]. Primary and adjuvant ^{125}I brachytherapy (mean tumor apex dose of 35 Gy) also had been used for RCH, albeit in a very small sample size [19]. The authors could not find long-term studies, however, on the efficacy and safety of plaque brachytherapy for treating RCH.

Juxtapapillary RCH carries a worse prognosis for vision. Observation is preferred for asymptomatic cases because treatment typically is associated with a decrease in visual acuity due to damage to the optic nerve or major retinal vasculature [19]. A dose de-escalation study would be of benefit for this benign vascular tumor, considering that arteriovenous malformations are treated with total doses of 20 Gy in a single fraction.

Vasoproliferative retinal tumors

Vasoproliferative retinal tumor (VPT) is a rare, benign intraocular tumor arising from the retinal vasculature, with variable glial proliferation. It also is referred to as a vasoproliferative tumor of the ocular fundus [22]. VPT can be either primary (idiopathic, more common) or secondary (retinitis pigmentosa, Coats disease, pars planitis, toxoplasmosis, familial exudative vitreoretinopathy, post–retinal detachment surgery, aniridia, and retinopathy of prematurity) [22]. VPTs typically are inferotemporal, single, yellow-red, dome-shaped masses with nontortuous, near-normal caliber retinal feeder vessels. Their far peripheral retinal location offers a therapeutic advantage for plaque brachytherapy. Secondary VPTs tend to be multifocal. Although benign and peripherally located, VPT can cause severe visual disability because of macular edema, preretinal gliosis, and vitreous hemorrhage. Secondary neovascular glaucoma can compromise globe salvage. In general, primary VPT carries a better prognosis than secondary VPT. VPT needs to be clinically differentiated from RCH of VHL disease.

There is no standard treatment protocol for VPT. With the aim of preservation of visual acuity, treatment often is guided by tumor height (or tumor size) and secondary tumor effects. Treatment options include observation, cryotherapy, laser photocoagulation, PDT, plaque brachytherapy, and surgery [3,22–25]. A small VPT lesion that does not affect visual acuity can be observed for growth and exudation. Cryotherapy is an economical, noninvasive modality; however, it requires multiple sessions, especially if the tumor height is greater than 2 mm [3]. Furthermore, an increase in subretinal fluid/exudation or vitreous hemorrhage can occur after heavy cryotherapy for larger lesions. Laser photocoagulation and PDT are used sparingly because of peripheral tumor location. Laser photocoagulation can lead to vitreous hemorrhage precluding further tumor management and a decrease in visual acuity. Enucleation is reserved for painful blind eyes.

Plaque brachytherapy has been used both as primary therapy and adjuvant therapy in the management of large VPT (tumor height >2 mm) [22,23,26]. Primary ^{106}Ru plaque brachytherapy (mean tumor apex dose of 108 Gy) has been reported to effect a 100% tumor regression with zero radiation maculopathy or papillopathy [23]. Primary ^{125}I plaque brachytherapy (mean tumor apex dose of 40 Gy) shows excellent local

control with a 97% regression rate and complete resolution of exudative retinal detachment in more than two-thirds of cases [26]. The absence of posterior segment radiation side effects is attributed to a low total radiation dose as well as to the remote tumor location (distance from the source to the fovea and optic nerve), which decreases the radiation dose to those structures. Recently, ^{106}Ru and ^{125}I have been used as adjuvant therapy (mean tumor apex dose <50 Gy) with good results [25]. The adverse effects of plaque brachytherapy for VPT include cataract and epiretinal gliosis [25].

Retinoblastoma

Retinoblastoma (RB) is the most common malignant intraocular tumor in children. The tumor is associated with high mortality rates in the developing world [27]. The primary goal of RB therapy is life salvage in advanced cases [28]. Globe and vision salvage are secondary goals [29,30].

Plaque brachytherapy has specific indications in the treatment of RB. Brachytherapy was first used for RB in 1929 where radon seeds were employed [31]. Salient points from the American Brachytherapy Society – Ophthalmic Oncology Task Force (ABS-OOTF) consensus guidelines for use of plaque brachytherapy for RB include [8]

- Plaque brachytherapy is not a common primary treatment of RB.
- Plaque brachytherapy is used more often as secondary or adjunctive therapy for unilateral, small, anterior, residual tumors after failed chemoreduction and focal therapies, for tumors situated in visually critical areas such as the macula (where focal therapy can compromise visual potential), and for recurrent tumors with underlying chorioretinal atrophy in the tumor bed (poor laser/cryotherapy uptake).
- Plaque brachytherapy is not used when there is anterior segment involvement and if the tumor is juxtapapillary in location.
- Plaque brachytherapy is thought to avoid EBRT-induced orbital dysplasia of the bones as well as the EBRT-related risk of secondary cancers (children with a germline mutation).
- Radionuclides, including ^{125}I, ^{106}Ru, ^{103}Pd, and ^{90}Sr, can be used. Generally, ^{125}I or ^{103}Pd is used in North America, ^{125}I or ^{106}Ru in Europe, ^{106}Ru in Japan, and ^{90}Sr in Russia [32,33].
- Comparative radiation dosimetry should be performed between locally available radionuclides plaques. The parameters include radiation dose to the tumor apex, sclera, lens, optic nerve, fovea, and the opposite eyewall. The aim is to deliver the therapeutic radiation dose to the tumor with the least amount of radiation exposure to normal intraocular tissues.
- RB tumors less than 15 mm in maximum basal dimension and less than 10 mm in height are eligible for plaque brachytherapy. The permissible tumor height for ^{90}Sr and ^{106}Ru brachytherapy is

lower, at 3 mm and 5 mm, respectively. Vitreous seeds, when present, should be within 2 mm from the edge of the tumor.
- A tumor apex dose of 40 Gy to 50 Gy is recommended with ^{125}I and ^{103}Pd. The dose is higher with ^{106}Ru and ^{90}Sr (80–90 Gy) [31,34].
- Unilateral tumors located anterior to the equator are the primary indications for primary plaque brachytherapy.

Radiation complications include cataract, radiation vasculopathy of the macula and optic nerve, uveitis, neovascular glaucoma, scleral thinning, vitreous hemorrhage, and retinal detachment. Such complications are more likely if a child has received or is receiving concurrent sensitizing chemotherapy [1].

Choroidal melanoma

Choroidal melanoma is the most common malignant intraocular tumor in adults [35]. By far the most common type of uveal melanoma (approximately 90%), choroidal melanoma typically presents as a melanotic, dome-shaped choroidal mass with orange pigment (lipofuscin) and subretinal fluid. Less commonly, it can be mushroom-shaped, amelanotic, or diffuse. Tumor staging should be performed according to the American Joint Cancer Committee *AJCC Cancer Staging Manual* (8th ed) for choroidal melanoma [36].

Management options typically include observation, radiation therapy (plaque brachytherapy or proton beam irradiation), and surgery (enucleation or exenteration). The choice of therapy has been dictated by the tumor size, staging, location, and availability of eye and vision-sparing radiation therapy techniques. Traditionally, select small melanoma tumors were observed for change prior to treatment at minimal risk [8,36,37]. Medium-sized melanoma were treated with plaque brachytherapy and large melanoma were either radiated or the eye was enucleated.

The ABS-OOTF consensus guidelines for treating choroidal melanoma are as follows [8]:

- A clinical diagnosis is sufficient for treatment and histopathologic confirmation is not mandatory.
- Plaque brachytherapy can be used for AJCC stages T1, T2, T3, and T4a-d tumors.
- Contraindications to plaque brachytherapy include AJCC T4e stage tumors with extraocular extension, painful blind eyes, no perception of light, and patient preference for enucleation. Also, certain tumor dimensions are not amenable to brachytherapy.
- There is no consensus for treating small AJCC T1-staged tumors. Generally, tumor height less than 2 mm with no subretinal fluid and no orange pigment can be observed for growth prior to treatment.
- All patients with uveal melanoma should undergo systemic evaluation for metastatic disease before any ocular treatment.
- Metastatic uveal melanoma is not an absolute contraindication to plaque brachytherapy, considering that irradiation can prevent loss of vision and reduce the chances of secondary glaucoma.

- Radionuclides used for choroidal melanoma include ^{125}I, ^{106}Ru, ^{103}Pd, and ^{90}Sr.
- The preferred radionuclide should be chosen after preoperative comparative dosimetry between locally available sources. Such parameters include radiation dose to the tumor apex, sclera, lens, optic nerve, fovea, and the opposite eyewall. The aim is to deliver therapeutic radiation dose to the tumor with the least amount of radiation exposure to normal intraocular tissues.
- Although tumor apex doses of 70 Gy to 100 Gy were recommended, higher tumor apex doses typically are used with Ru-106 plaques (for uveal melanoma <5 mm in height) [38].
- The duration of brachytherapy typically is 5 days to 7 days. The duration may be shorter, however, depending on the tumor height and choice of radionuclide.
- The maximum tumor height cut-off for ^{106}Ru plaques in uveal melanoma is 6 mm. Also, commercially available ^{106}Ru plaques are no larger than 20 mm in diameter. Treatment margins should exceed the tumor edges by 2 mm to 3 mm.
- With I-125 or Pd-103 plaques, patients with uveal melanoma greater than 14 mm in height or greater than 20 mm in basal dimension are typically recommended to undergo enucleation.
- Regardless of the tumor dimensions or chosen source of radiation, a 2-mm to 3-mm tumor-free safe margin all around is desirable during episcleral plaque placement (Fig. 2).

Local tumor control rates as high as 99.7% have been reported after ^{103}Pd plaque brachytherapy [39,40]. Cases of juxtapapillary and circumpapillary melanoma have been treated with Finger's slotted plaques to a local control rate of 98.2%. This is an improvement over what has been reported by Sagoo and colleagues (80%) [41]. With slotted eye plaques, it now is possible to treat choroidal melanoma that extends within 1.5 mm of the optic disc, those touching the optic disc and even those overlying the optic disc [9,10,42,43].

Following plaque brachytherapy, choroidal melanoma decreases in size but does not typically disappear [35]. Regression features include decreased tumor height, reduced intrinsic vascularity, and increased pigmentation. Tumor-associated drusenoid pigment epithelial detachments typically disappear after brachytherapy [43].

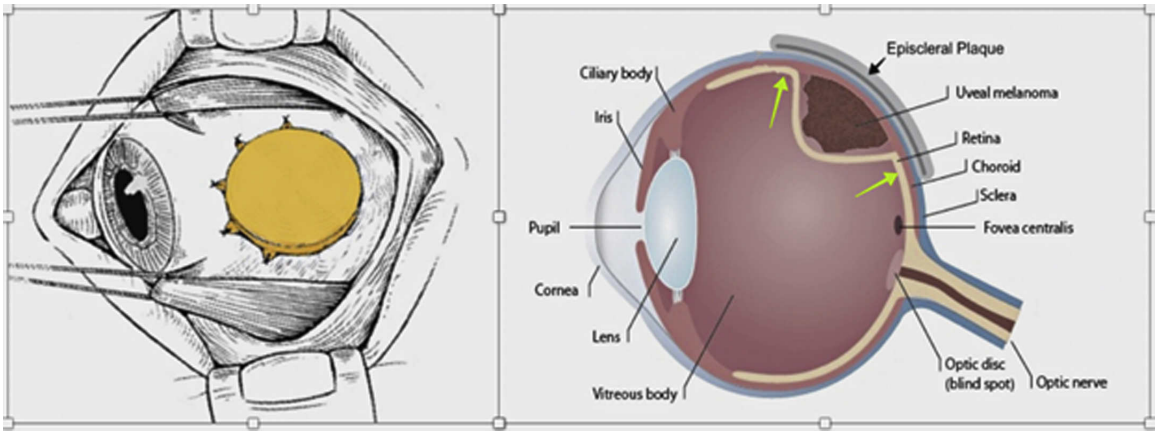

FIG. 2 (*Left*) Diagram showing COMS plaque sutured episclerally over a choroidal melanoma. (*Right*) Sagittal view showing plaque placement over the tumor with tumor-free margins (*arrows*).

Complications of plaque brachytherapy are dose-related radiation retinopathy, radiation papillopathy/optic neuropathy, cataract formation, neovascular glaucoma, vitreous hemorrhage, scleral thinning, strabismus, diplopia, and dry eye [44].

Limitations of plaque brachytherapy

As with any treatment modality, plaque brachytherapy has its own set of limitations. First, it is a surgical modality that requires suturing the plaque to the sclera as well as plaque removal, usually performed days later, in the operating room. Second, it can be offered only by ophthalmic oncology specialty centers, because it requires a multidisciplinary team consisting of an ocular oncologist, a radiation oncologist, and a medical physicist. The cost of plaques, LINACs, lasers, PDT dye, cryotherapy machines, operating rooms, anesthesia, disposables, drugs, and radiation sources are too complex to be discussed in this article.

Future avenues

Pretreatment comparative dosimetry is a foundational element of plaque brachytherapy planning and patient safety [8]. Comparison of intraocular radiation dose distribution among the locally available radionuclides allows the ophthalmic oncologist to have a better understanding of the amount of radiation that will be delivered to visually critical structures, namely macula, optic nerve head, and lens. Typically, comparative dosimetry reduces the chance of local treatment failure and radiation-associated complications [8,45].

Dose de-escalation studies would allow for a better understanding of what minimum radiation doses are required to control each tumor. Such reductions in tumor dose would, in turn, reduce the radiation dose to critical intraocular structures, and the total radiation dose delivered to the eye and thus improve outcomes. Even the current recommended dose for treating a choroidal melanoma is 85 Gy (ABS-OOTF guidelines) was based on prior phase I clinical studies rather than prospective medical evidence [8].

Methods for dose de-escalation

1. Choice of radionuclide: comparative intraocular dose distribution assessments allow for selection of the most favorable radionuclide for local control and side-effect reduction [45]. The authors suggest centers examine the dose delivered to the tumor apex, tumor base, inner sclera, lens, fovea, optic nerve, and the opposite eye wall (organ dose).
2. Plaque design alteration: using seed-guide inserts or grooves within the plaque tends to collimate the radiation, thus reducing the side-scatter penumbra [46]. Note that such modifications reduce the dose not only lateral to the targeted zone, but also, to the borders of the tumor and the free margins.
3. Actual reduction in prescribed radiation dose: reductions in the tumor apex dose have been used for treatment of large choroidal melanoma [17,18]. There is a need, however, for a large prospective evidence-based study or registry to collect enough statistically significant information on which minimum apical radiation doses

are effective for each form of radiation used for local control for intraocular tumors.

Clinics care points

- Use of plaque brachytherapy for a CCH causes appreciable tumor regression with permanent resolution of the subretinal fluid.
- For DCH, the goal is to center the plaque to the area of maximum tumor height. The plaque may or may not cover the entire lesion.
- Plaque brachytherapy finds specific indications in the management of RCH. These include large tumors, tumors with extensive subretinal fluid, and globe salvage.
- VPTs of more than 2 mm height have been treated with plaque brachytherapy when used as primary or adjuvant therapy.
- Plaque brachytherapy is not a common primary treatment of RB and is used more often as secondary or adjunctive therapy.
- Plaque brachytherapy has been used for treating choroidal melanoma tumors belonging to AJCC stages T1, T2, T3, and T4a-d.

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Intraocular Tumors—Advances in Ophthalmic Pathology

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Keywords

Retinoblastoma; Malignant melanoma of the choroid; Primary vitreoretinal lymphoma; Pathology; Vitreous biopsy; Immunohistochemistry; Molecular biology

Key points

- Retinoblastoma is the most common primary intraocular tumor in children. Pathologists play an important role in the confirmation of clinical diagnosis and establishing the high-risk features that are predictive of metastasis or local recurrence. They play a key role in the prognostication of the disease.
- Malignant melanoma is the most common primary intraocular malignancy in adults. Prognosis depends on the cell type and invasion of the tumor beyond the sclera.
- Primary vitreoretinal lymphoma, a rare B-cell intraocular malignancy, usually occurs in adults, with or without primary central nervous system lymphoma. Cytopathology of the vitreous and immunohistochemistry clinches the diagnosis.

Retinoblastoma

Retinoblastoma is the most common primary intraocular tumor in childhood, affecting children between birth and 5 years of age. It may be either sporadic or hereditary. Retinoblastomas constitute 3% of all pediatric cancers. They occur as a result of the inactivation of the RB1 gene, known as the tumor suppressor gene. The incidence of retinoblastoma accounts for 15,000 to 20,000 live births corresponding to approximately 9000 new cases every year [1]. The mutation of this disease is based on Knudson's 2-hit hypothesis, proposed in 1971 [1,2]. This states that 2 chromosomal mutations are required for developing retinoblastoma. The initial hit is a germline mutation that is inherited and found in all cells in hereditary retinoblastoma. The second hit is in the somatic retinal cells, leading to the development of retinoblastoma. MYCN gene has been seen in young retinoblastoma patients with a fairly large tumor.

Retinoblastomas present most commonly as a white reflex known as leukocoria (Fig. 1). They are classified as endophytic (extend from the inner retinal layers anteriorly into the vitreous cavity), exophytic (originate from the outer retinal layers and grow into the choroid and sclera) (Fig. 2), or mixed [1,2].

Treatment strategies aim at saving the life of the child followed by globe and vision salvage.

Recent advances to chemotherapy are the emergence of intra-arterial and intravitreal chemotherapy [2].

Pathology

Fresh specimens can be trephined from the enucleated globe for genetic study and should be done before the specimen is put in formalin. After the eye is enucleated (International Classification of Intraocular Retinoblastoma groups D and E), the specimen is processed after 48 hours of fixation. The eyeball is grossly examined for any tumor dissemination from the external coat of the eyeball. The presence or absence gross thickening of the optic nerve is noted. The eyeball then is subjected to transillumination in a dark room to know the position of the intraocular tumor. The cut end of the optic nerve is submitted separately. Subsequently, sectioning of the eyeball is made. According to the recent guidelines, central calotte and 3 lateral calotte are made in the bread loaf technique (Fig. 3).

On sectioning, the retinoblastoma eye shows several characteristic findings, which are chalky white masses, often friable (Fig. 4), and can be present with different growth patterns: exophytic, endophytic, mixed, and diffuse. Tumors can extend to the uvea, epibulbar structures, and the optic nerve and are grossly visible in advanced cases. Choroidal invasion can be grossly visible.

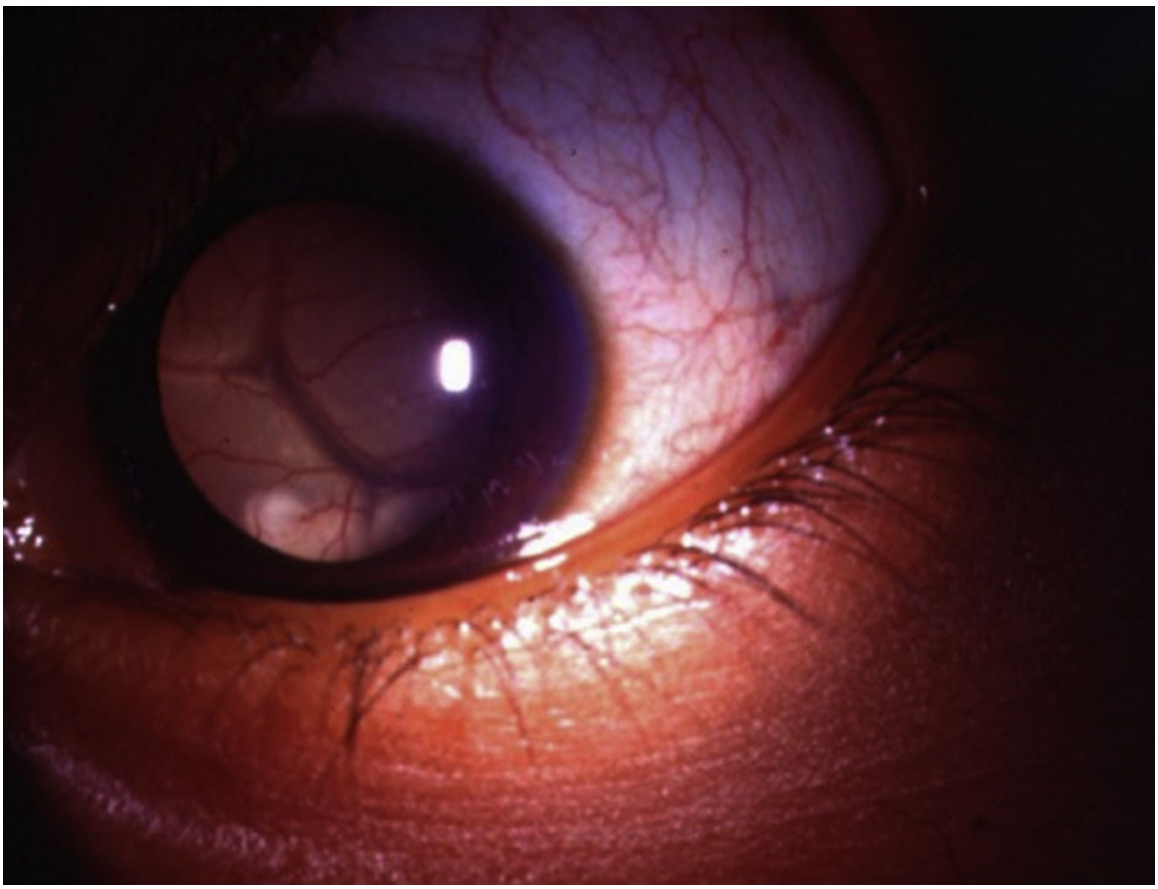

FIG. 1 Slit lamp photograph of leukocoria in a 2-year-old child with retinoblastoma.

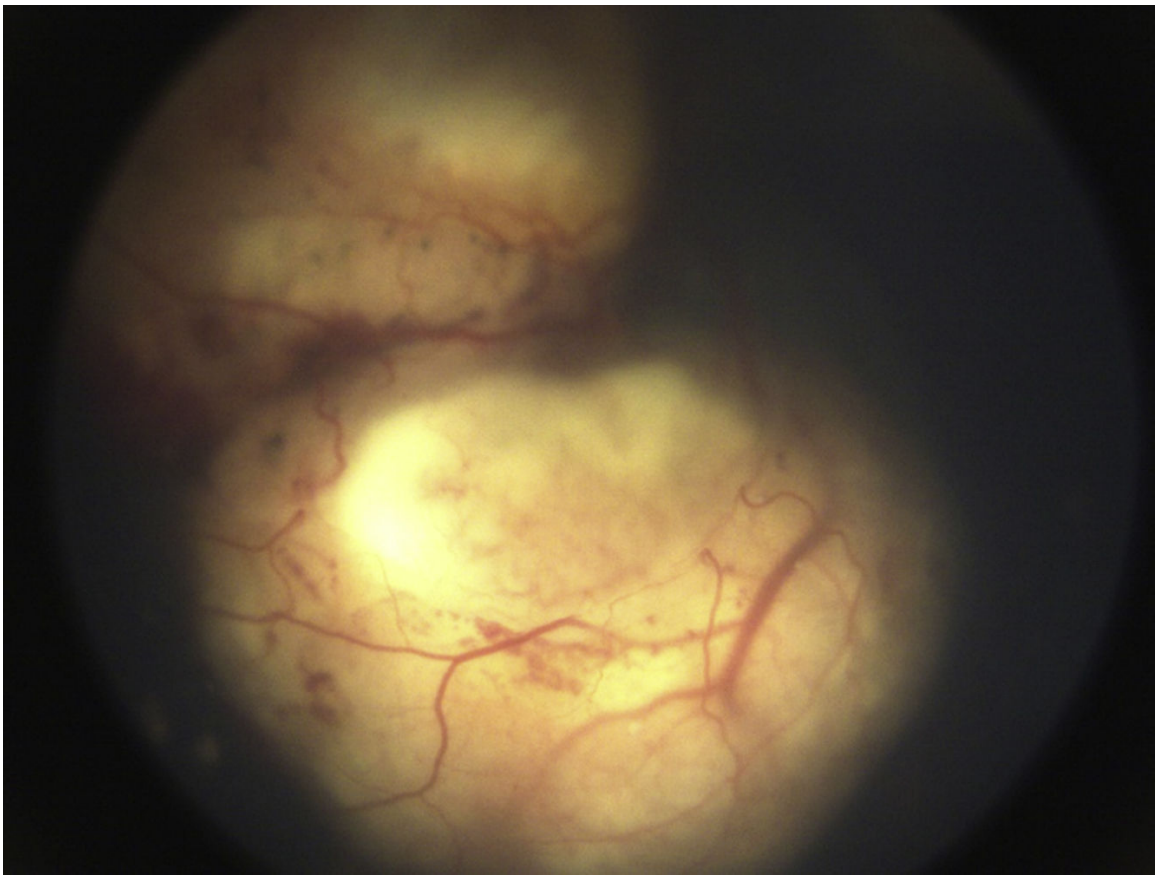

FIG. 2 Fundus photograph showing exophytic masses of retinoblastoma.

On microscopic examination, low power shows a basophilic mass with lightly eosinophilic areas indicating necrosis and multiple dense basophilic foci suggestive of calcification (Fig. 5).

High power shows that 2 different types of cellular characteristics: poorly differentiated and well differentiated. Poorly differentiated characteristics show small to medium-sized round cells with hyperchromatic nuclei and scanty cytoplasm and well-differentiated rosettes and fleurettes.

Rosettes are of 2 types. They are Flexner-Wintersteiner and Homer Wright rosettes.

The Flexner-Wintersteiner type is highly specific for retinoblastoma. It is formed by the cuboidal cells arranged around a clear central lumen (Fig. 6).

Homer Wright rosettes are less common and also can be seen in neuroblastoma and medulloepithelioma. Tumor cells are arranged radially around a central core of neural fibers in contrast to the clear lumen in Flexner-Wintersteiner type (Fig. 7) [3]. Third true rosettes have been found

in retinoblastomas which differ from Flexner-Wintersteiner and Homer Wright rosettes. Retinoblastoma cells are seen in the central empty lumen and these rosettes are larger than conventional Flexner Wintersteiner and Homer Wright rosettes [4].

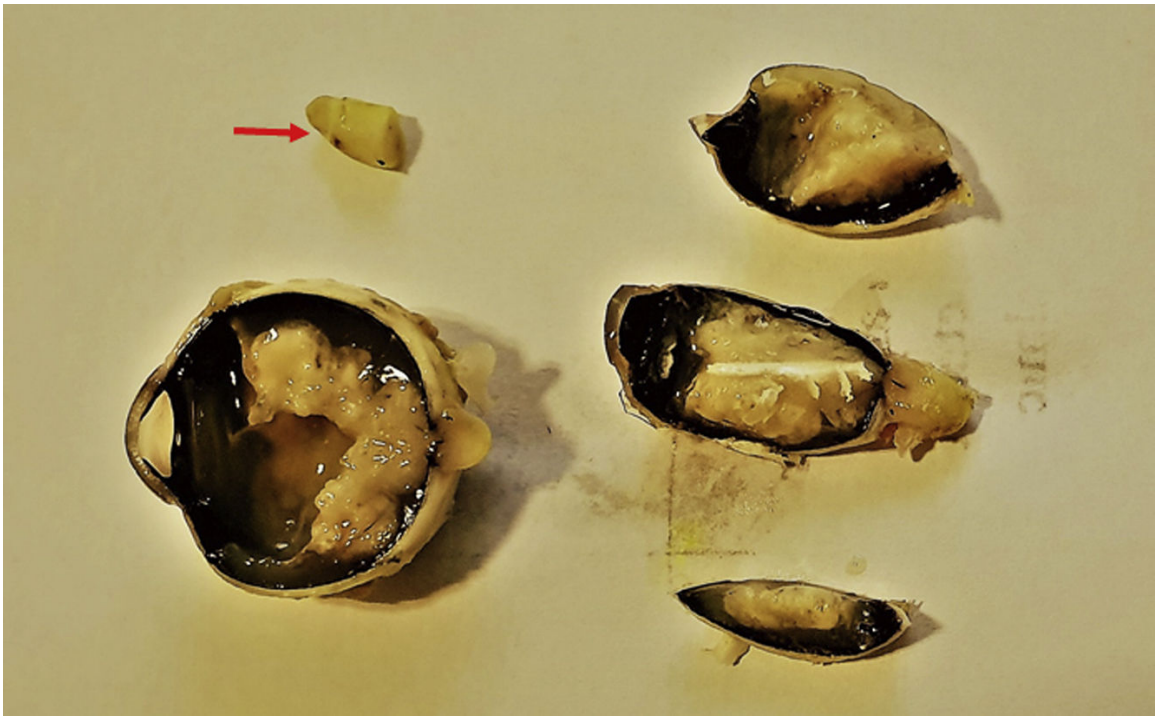

FIG. 3 Bread loaf section of an enucleated globe of retinoblastoma. Cut end of the surgical margin of the optic nerve is shown by an arrow.

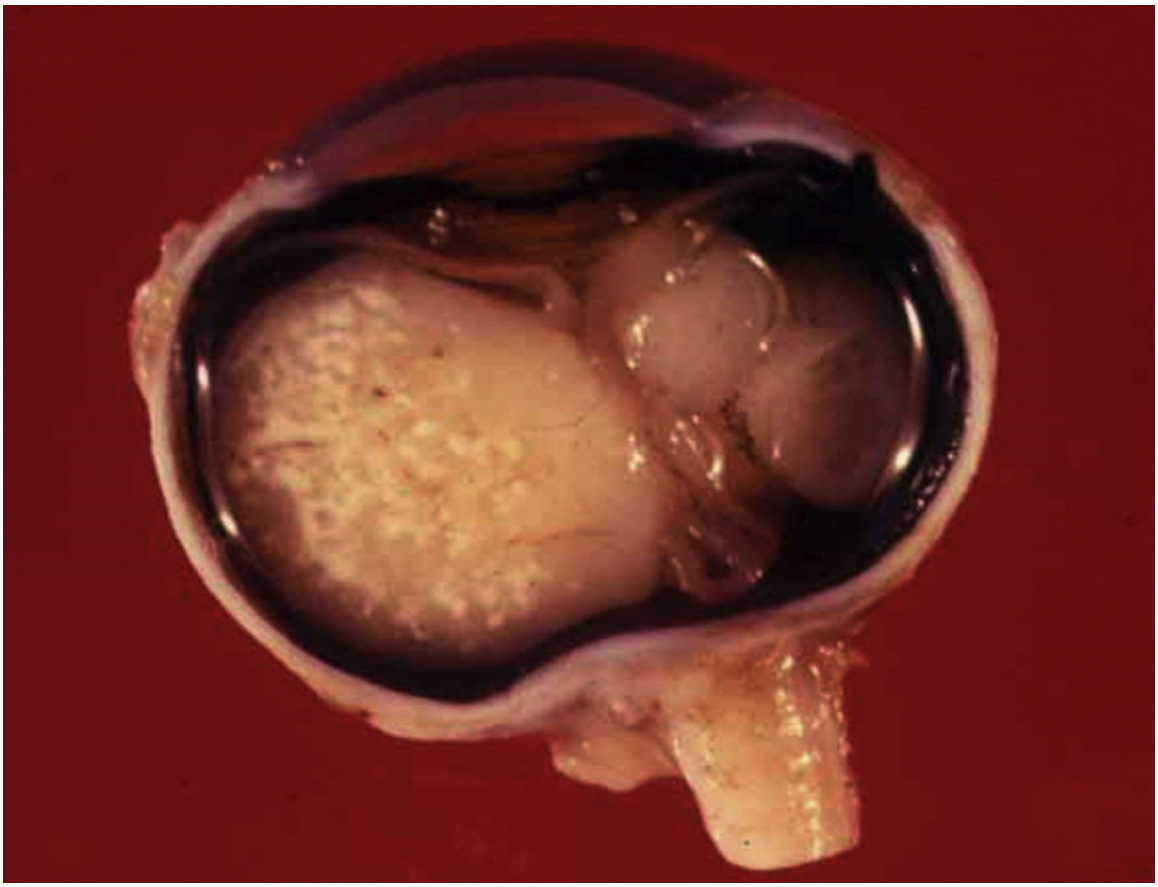

FIG. 4 Cut section of an enucleated globe showing chalky white tumor mass in a case of retinoblastoma.

Fleurettes are uncommon in retinoblastoma. They have been documented as flower bouquet–like aggregates of tumor cells with bulbous eosinophilic processes projecting through the fenestrated membrane.

Other pathologic features are areas of necrosis and calcification, endothelial hyperplasia around blood vessels within the tumor, DNA clumping around blood vessels within the tumor, neovascularization of the iris, and extension of tumor cells into the anterior chamber, iris, choroid, optic nerve, and orbital tissue. Tumor seeding may be seen in the vitreous cavity (Fig. 8). Apart from iris and ciliary body invasion by tumor cells, massive choroidal invasion or choroidal invasion of 3 mm or more (Fig. 9), postlaminar optic nerve invasion, and invasion of the surgical end of the optic nerve (Fig. 10) constitute high-risk histopathologic features that are indications for treatment with adjuvant chemotherapy after enucleation [5].

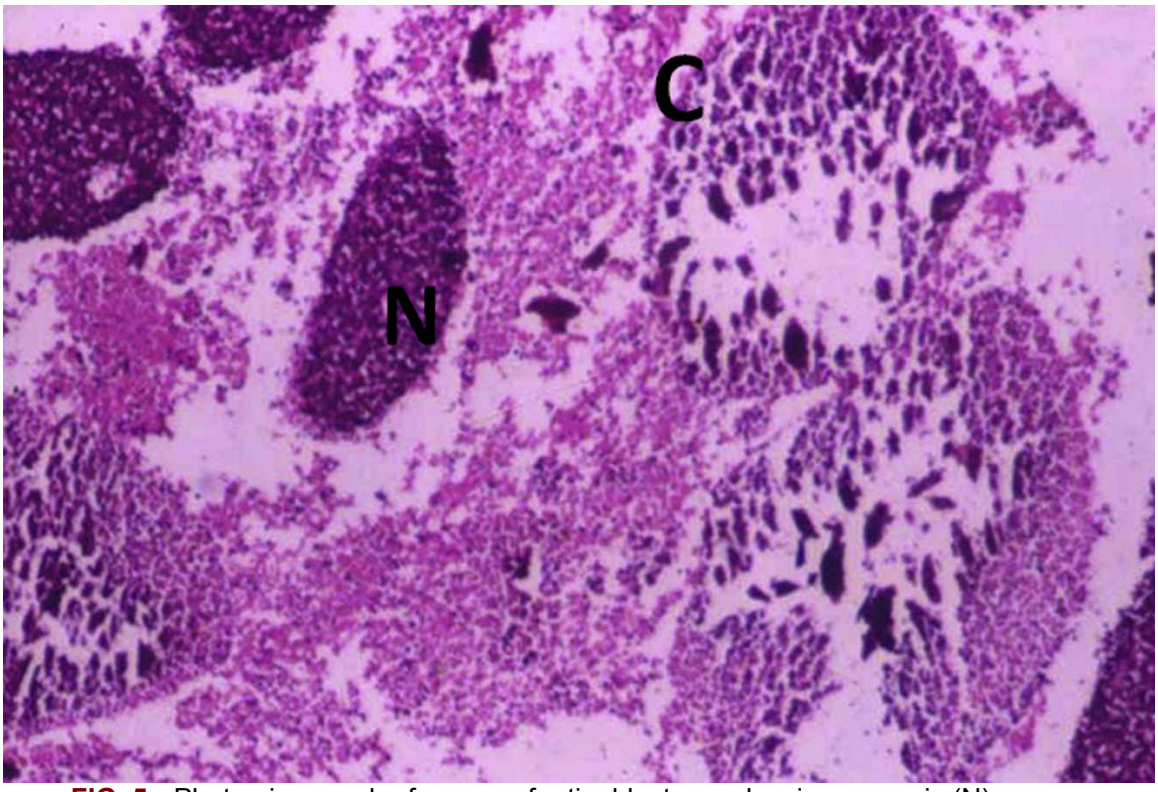

FIG. 5 Photomicrograph of a case of retinoblastoma showing necrosis (N) of the tumor with calcification (C) (hematoxylin-eosin, ×100).

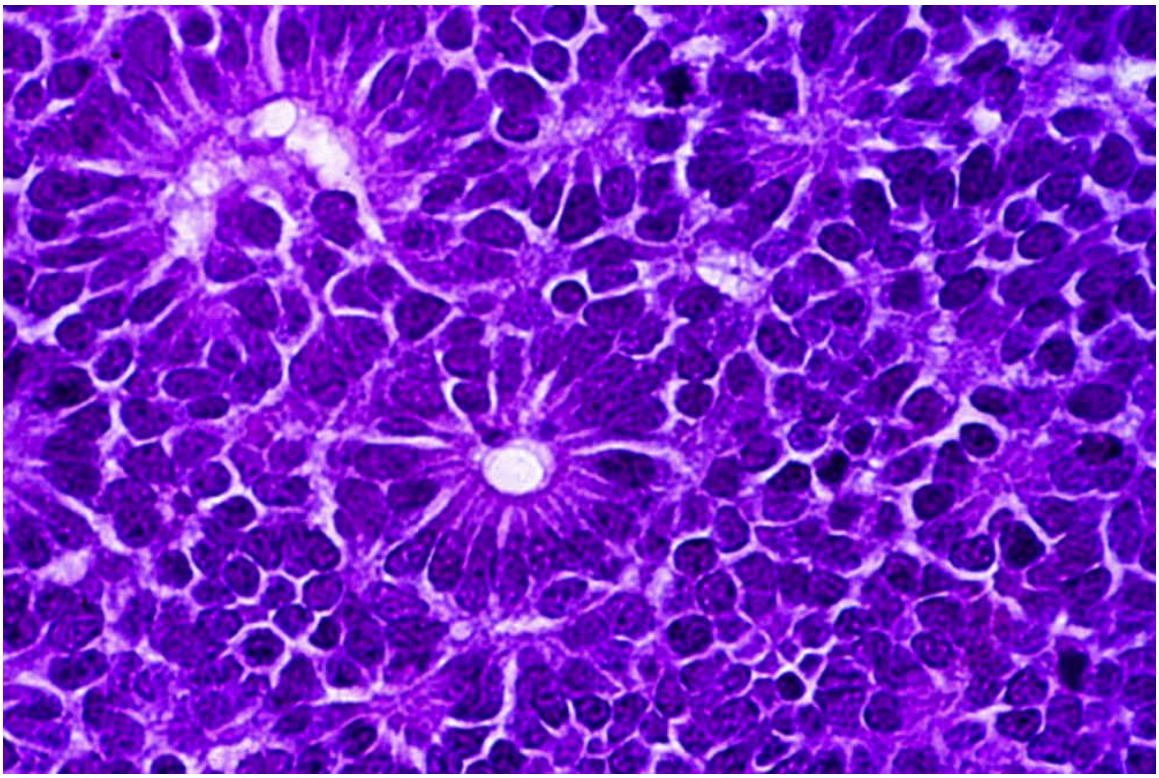

FIG. 6 Photomicrograph of a case of well differentiated retinoblastoma showing Flexner-Wintersteiner rosettes, showing tumor cells arranged around a central clear lumen (hematoxylin-eosin, ×400).

Mendoza and colleagues [6] described increasing grade of anaplasia found to be associated with decreased overall survival and increased risk of metastasis. Histopathologic features that were associated with anaplasia included optic nerve invasion, choroidal invasion, and anterior segment invasion. Multivariate analysis considering high-risk histopathology and anaplasia grading predictors of distant metastasis and death showed that high-risk histopathology was statistically significant as an independent predictor but anaplasia was not. In the absence of high-risk features, severe anaplasia identified an additional risk of metastasis. They concluded that adjuvant therapy may be needed in these situations even in the absence of high-risk histologic features [6]. Classification and staging systems for retinoblastoma have evolved over the years. The recent TNM classification based on the American Joint Committee on Cancer *American Joint Committee on Cancer Staging Manual* (8th edition) has included "H", which is a hereditary factor and is unique to this cancer [7].

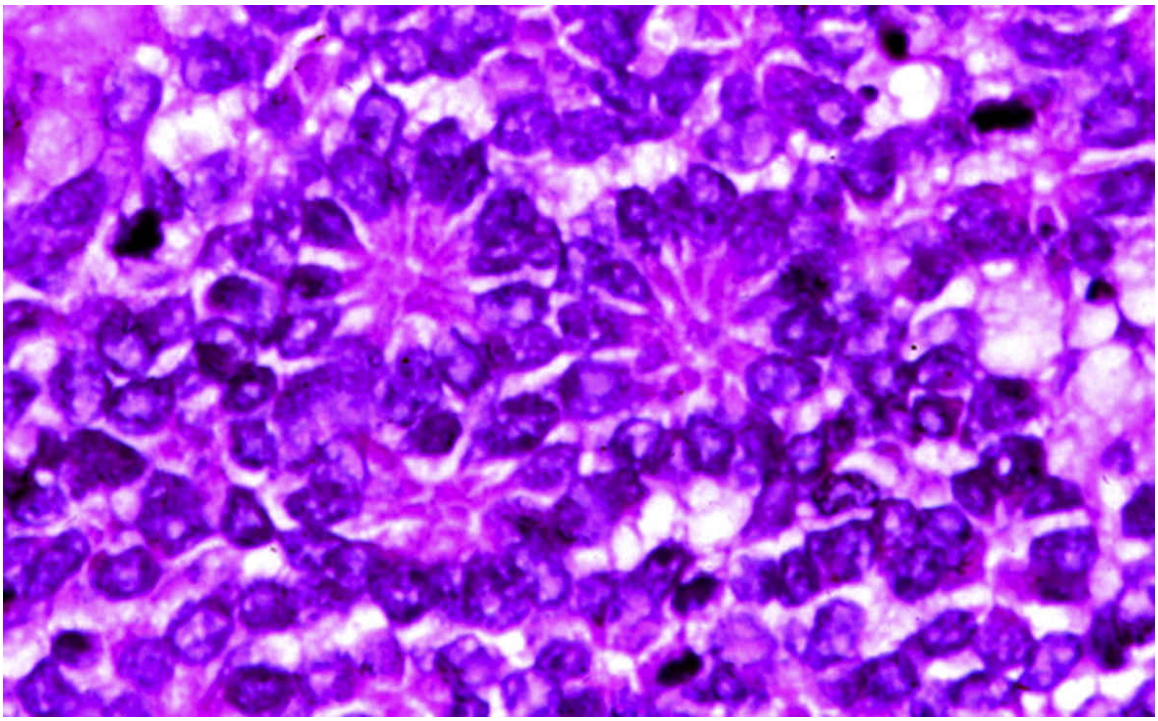

FIG. 7 Homer Wright rosettes—tumor cells arranged around a central core of neural fibrilins (hematoxylin-eosin, ×400).

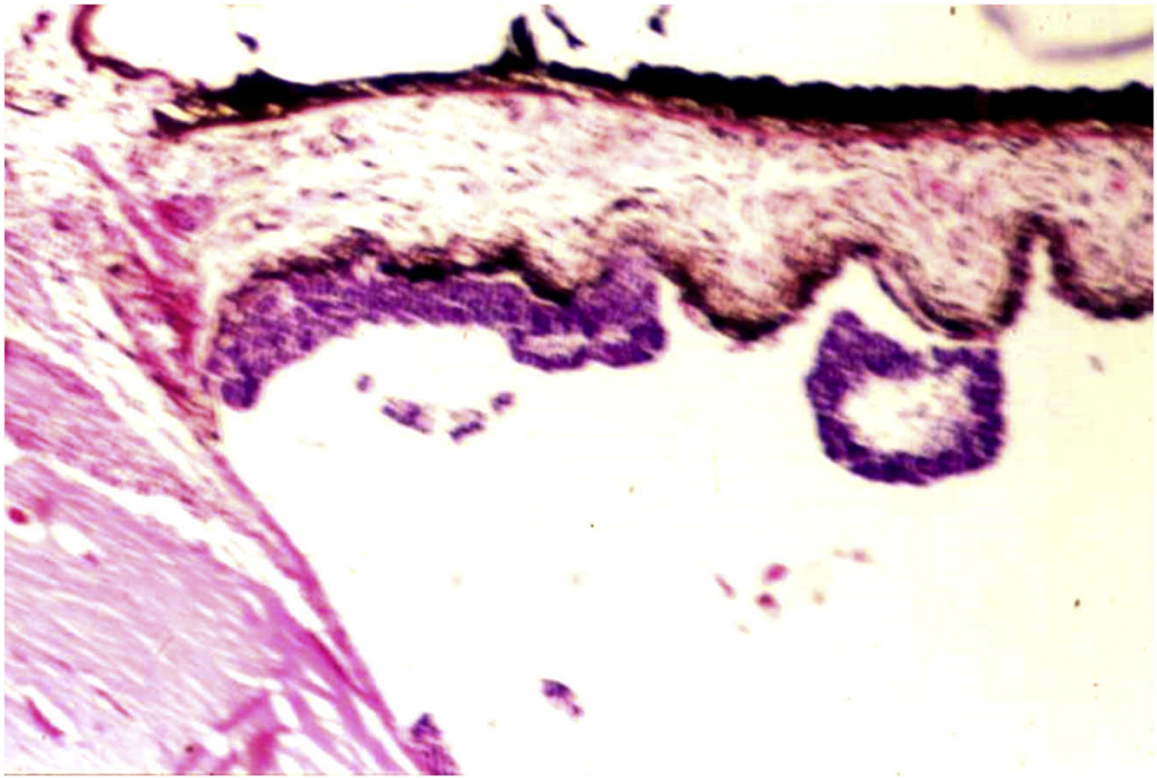

FIG. 8 Photomicrograph showing vitreous seeds in a case of retinoblastoma (hematoxylin eosin, ×200).

Molecular Pathology

Recent molecular pathologic study of retinoblastoma points toward various molecular markers in the prognostication of retinoblastoma. CDC25 phosphatase, PLK3, BCL-2, P53, and BAX have shown expression in tumor samples indicating the prognosis of this childhood cancer. FOXO3a can have a translational role for newer chemotherapeutic agents. Noninvasive diagnosis of retinoblastoma using cell-free DNA has been correlated in aqueous samples of retinoblastoma [8].

Uveal melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults [9]. It represents 5% of all melanomas [2].The mean age of presentation is at 50 years to 60 years. Uveal melanoma can be familial. Melanoma most commonly affects the choroid (90%), followed by the iris and the ciliary body. It is characterized by uncontrolled clonal cellular proliferation occurring as a result of numerous genetic and epigenetic aberrations. This tumor usually presents as a pigmented mass (Fig. 11) in the ciliary body or choroid and can lead to metastasis and death. Host factors are said to be the strongest risk factor. Sunlight exposure is uncertain, but acute or intense exposure to UV rays might increase the risk of development of uveal melanoma [9]. Although several chromosomal abnormalities have been linked to the disease, two proved and reliable predictors of the disease are the gain of 6p and loss of one copy of chromosome3. The gain of chromosome 6p occurs mainly in nonmetastasizing tumors with a good prognosis, and the latter most frequently predicts a poor prognosis with metastasis [10].

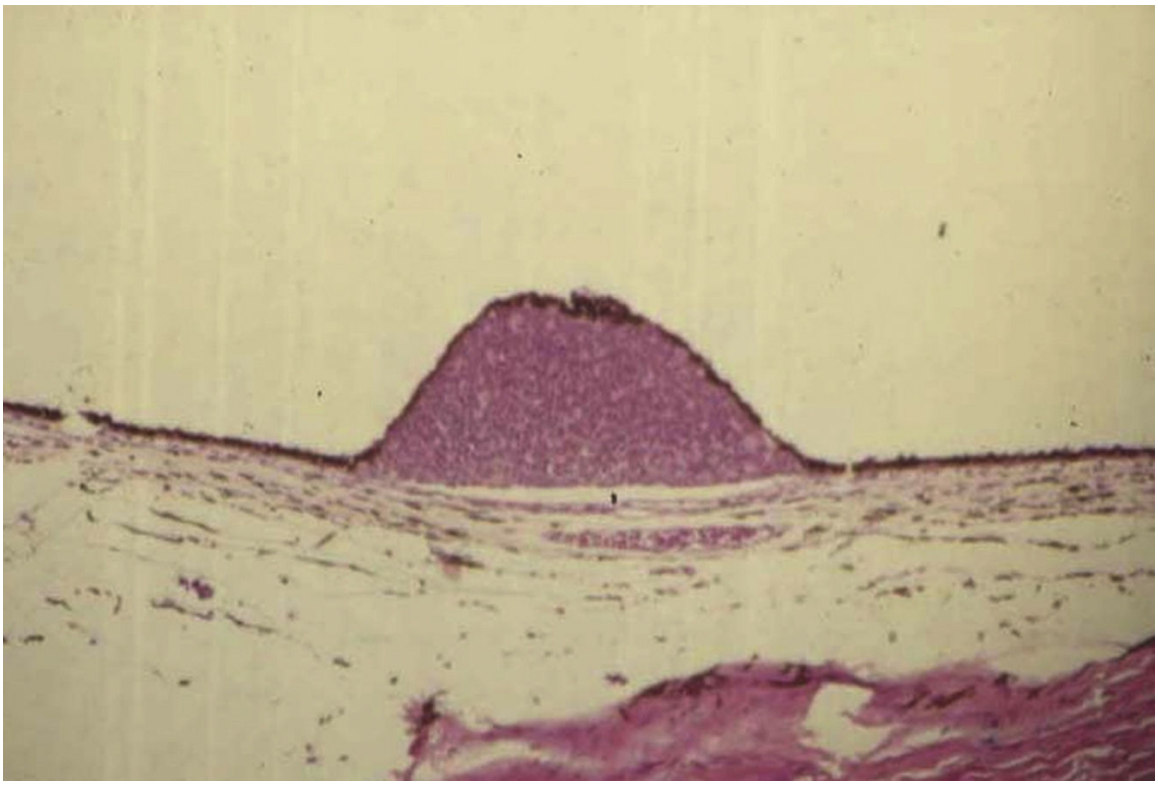

FIG. 9 .Photomicrograph showing superficial choroidal invasion of retinoblastoma tumor cells (hematoxylin-eosin, ×200).

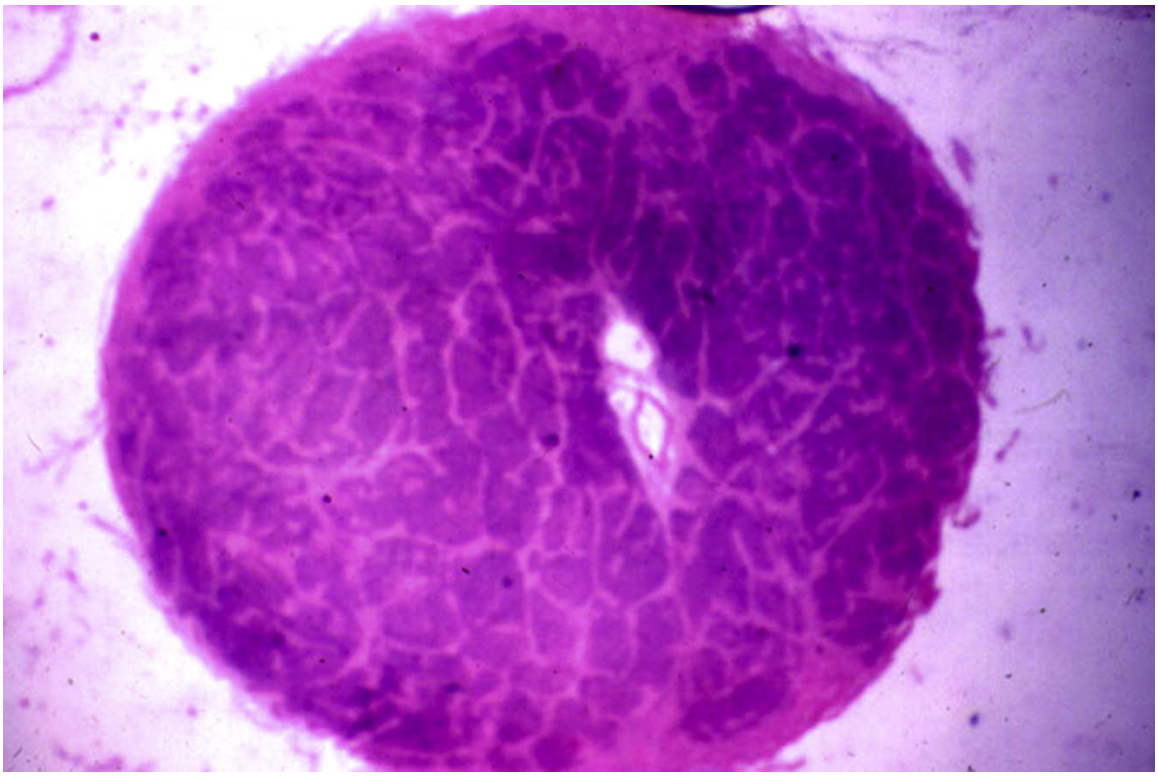

FIG. 10 Photomicrograph showing cut end of the optic nerve showing tumor cells in a case of retinoblastoma (hematoxylin-eosin, ×200).

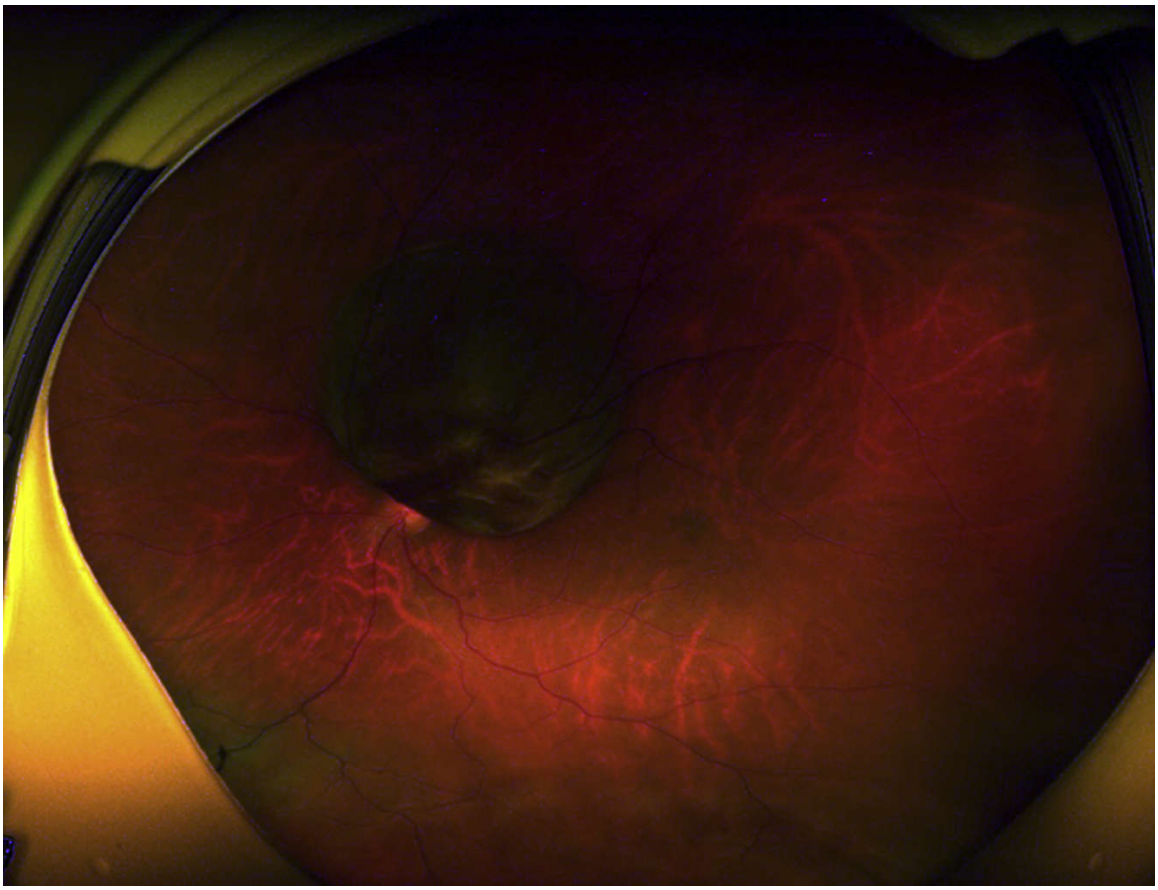

FIG. 11 Optos showing a pigmented tumor mass of a case of malignant melanoma of choroid.
(*Courtesy of* G Suguneswari, MD, Chennai, IN).

With the advent of multimodal imaging, early detection of these tumors is possible. The most important modality of diagnosis in uveal melanoma is indirect ophthalmoscopy. Studies have shown analysis of tumor size, tumor location, and patient age at presentation is important significant factors with the tumor thickness playing an important role. According to the clinical presentation, several treatment options are available, such as observation, transpupillary thermotherapy, plaque radiotherapy, tumor excision, and enucleation [2]. Uveal melanoma can be very small, medium-sized, large, or extra-large. Ring melanoma has a poor prognosis because they are detected late. Sometimes, suspicious choroidal nevus can be converted into frank melanoma. Clinical risk factors are (1) tumor thickness greater than 2 mm; (2) posterior tumor margin touching the optic disc; (3) sudden visual symptoms; (4) orange pigment on the tumor; and (5) presence of subretinal fluid.

Pathology

The tumor appears as a pigmented mass (Fig. 12) and can arise from the choroid, ciliary body, or both. Ciliary body tumors have a poorer prognosis. Two types of growth patterns are noted: focal and diffuse. Focal tumors are rare and oval in shape and are early tumors confined to the uvea. As the tumor grows, it can rupture through the Bruch membrane and produce a collar button or mushroom-shaped mass. The diffuse type is rare and involves the larger area of the choroid and is known to be more aggressive, frequently resulting in extrascleral extension. Clinically, it macrophages laden with lipofuscin pigments corresponding to orange pigmentation. Secondary retinal detachment most commonly is associated [3].

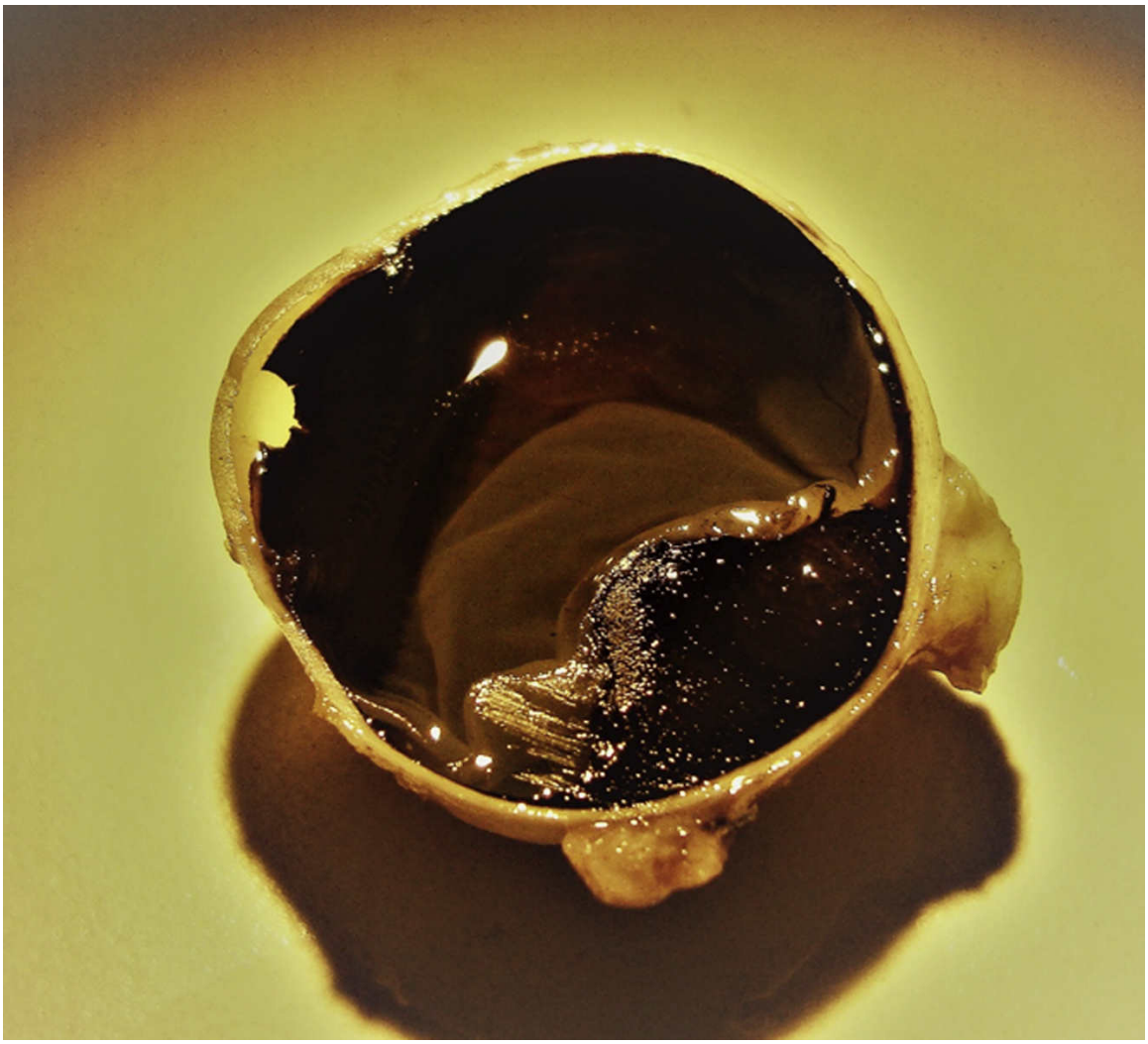

FIG. 12 Cut section of the globe showing a pigmented tumor mass arising from the choroid in a case of malignant melanoma of the choroid.

Callender's cytologic classification describes 4 histologic cell types: spindle A, spindle B including the fascicular variant (Fig. 13), epithelioid (Fig. 14), mixed cell type.

Spindle A cell melanomas are spindle in shape with scanty cytoplasm. The cells have a long and narrow nucleus and poorly defined nucleolus. The tumor cells may show cohesiveness.

Spindle B melanomas are spindle, with less cytoplasm seen. The nucleus is oval and round with well-defined nucleolus. They may show cohesiveness [3].

Epithelioid tumor cells are larger with a pleomorphic polygonal shape. The nuclei, as well as nucleoli, are larger and may be multiple.

Cytoplasmic features are abundant. Typically, a loss of cohesiveness occurs.

The TNM classification system for uveal melanoma is based on the size of the tumor and the extent of the systemic metastasis. The most recent TNM classification system for uveal melanoma has been published in the 8th edition of the *AJCC Cancer Staging Manual* [11].

Prognosis of choroidal melanoma depends on (1) Wilder staining for reticulum formation in the tumor; (2) variation of tumoral pigmentation; (3) tumor size (larger tumors have poorer prognosis); (4) types of cells (spindle cell has a good prognosis and epithelioid cells have a worse prognosis); (5) nucleolar areas; (6) lymphocytic infiltration of tumor; (7) vascular pattern; (8) adjoining structure involvement; and (9) evidence of distant metastasis.

Genetics

Driver mutation of choroidal melanoma indicates initiation, progression, and distant metastasis. Gene expression profile using 12 gene classifiers has proved better management in choroidal melanoma. Preferentially expressed antigen in melanoma (PRAME) is an important prognostic biomarker that can indicate the evidence and risk of metastasis. PRAME-specific T cells nowadays provide immunotherapy in metastatic uveal melanoma in some advanced cancer management. The mutated gene also can be seen as expressed in BAPI, GNAQ, GNA11, EIF1AX, or SF3B1.

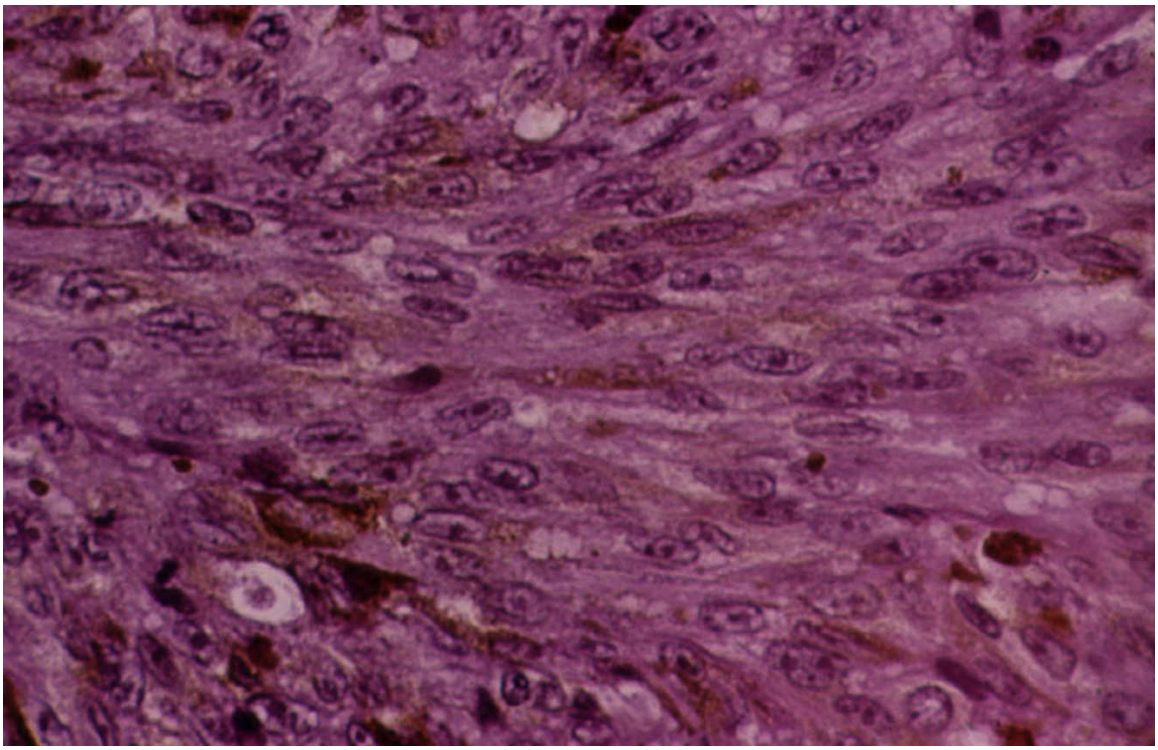

FIG. 13 Photomicrograph showing spindle A and spindle B cells in a case of malignant melanoma of the choroid (hematoxylin-eosin, ×400).

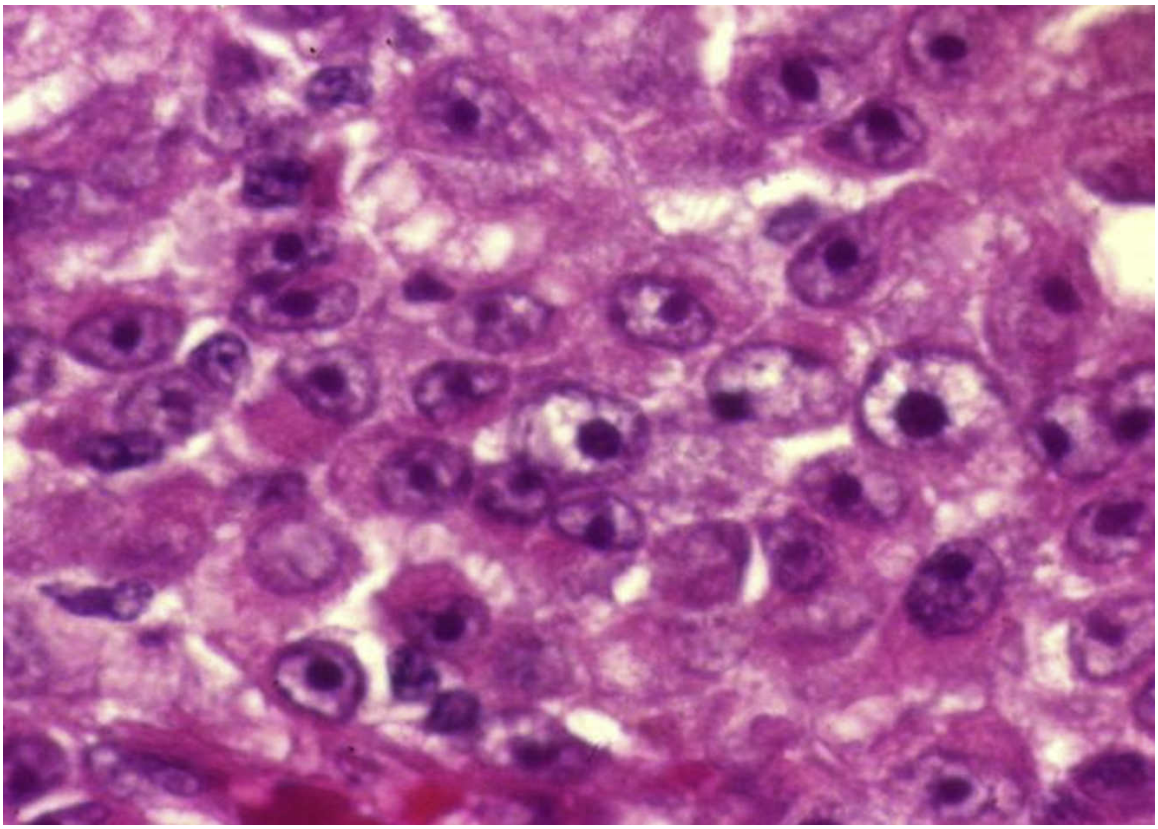

FIG. 14 Photomicrograph showing epithelioid cells in a case of malignant melanoma of the choroid (hematoxylin-eosin, ×400).

Primary vitreoretinal lymphoma

Primary vitreoretinal or intraocular lymphoma is a rare ocular malignancy where the lymphoma cells occur initially within the eyes (vitreous cavity and retina), sometimes with initial involvement of the disease in the brain or cerebrospinal fluid. They are described mainly as diffuse large B-cell lymphomas [12]. Very rarely, they are associated with T-cell lymphoma as secondary features of mycosis fungoides or Sézary syndrome. The mean age of presentation is in the fifth and sixth decades of life. One-third of these patients are said to have concurrent primary central nervous system lymphoma (PCNSL) at presentation, and 42% to 92% develop PCNSL within 8 months to 29 months [13].

Diagnosis remains challenging because it can present as a masquerade. Anterior segment finding includes corneal deposits, mild anterior chamber flare, and sometimes pseudohypopyon. Posterior segment findings show typical flat orange-yellow subretinal lesion, which can be focal or multifocal (Fig. 15). Although advanced multimodal imaging is available to aid in the diagnosis, vitreous biopsy remains the hallmark procedure in the diagnosis [13].

Management and follow-up of these patients require a joint association between oncologists and ophthalmologists. Regular systemic examination with magnetic resonance imaging and ocular examination is mandatory. Local treatment by intravitreal methotrexate and rituximab (CD20) have been tried in these patients along with systemic/local radiotherapy or chemotherapy.

Cytology and immunohistochemistry

Analysis for vitreous biopsy involves assessing the cytologic findings, immunohistochemistry, and flow cytometry. Cytologic studies in the vitreous fluid are the first line of invasive investigation for diagnosis of primary intraocular lymphoma. The specimens can be obtained by fine-needle vitreous aspiration or by pars plana vitrectomy. It should be known to the clinician that a vitreous specimen as a modality of investigation is known for containing a small number of pathologic cells and sometimes with reactive cellular infiltration in a necrotic background. Cytologic evaluation for lymphoma has a positive predictive value of 99% to 100% and a negative predictive value of 61% to 81%. Preparation of vitreous specimens requires some additional procedure, including immediate

cytospin (approximately 10–12 thousand rpm for 5 minutes to 10 minutes), and then a centrifuged deposit smear is made. The smear on the slide is fixed with 95% alcohol for 1 minute to 2 minutes. After fixation, the slide is stained by hematoxylin-eosin stain or Giemsa stain. In some advanced centers, these fluid specimens are fixed in Cytolyt.

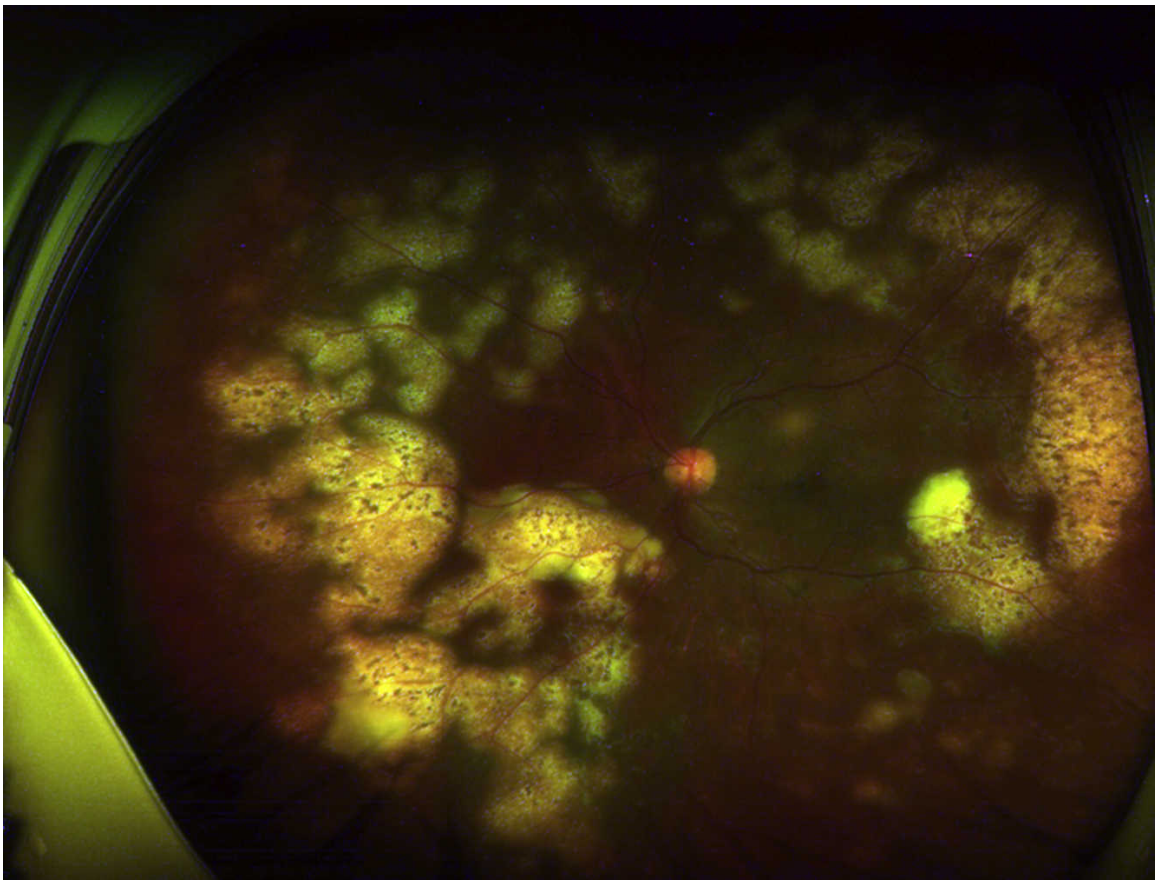

FIG. 15 Optos photograph showing multiple choroidal infiltrates with leopard skin appearance.

Morphologically, the typical lymphoma cells are large B-cell lymphoid cells with scanty basophilic cytoplasm, elevated nucleus cytoplasmic ratio, and hypersegmented round, oval, or bean-shaped nuclei with a coarse chromatin pattern and prominent nucleoli. There may be some macrophages scattered around the atypical lymphocytes in the necrotic background. Because a possibility of fragility of neoplastic lymphocytes exists, cytology may contain many lytic cells (Fig. 16).

Immunocytochemistry is done by identifying the cell surface markers on the lymphomatous cells. This technique is helpful especially when

cytology turns out scanty.

The rate of diagnosis increased from 30% (using cytology alone) to 70% by immunohistochemistry. Both techniques target monoclonal populations in Primary Intraocular Lymphoma (PIOL). There is an expression of pan–B-cell markers, such as CD20 positive (Fig. 17), CD79a positive, BCL-2 positive/negative, BCL-6 positive/negative, Oct 2 positive, BOB.1 positive, multiple myeloma protein 1 positive, CD10 positive/negative, and MIB1 (often positive in more than 60% of a case of primary intraocular lymphoma) and PAX5 positive [12]. In comparison to primary choroidal lymphoma, MIB1 is approximately 5% to 15% positive. These features suggest that PVRL are derived from lymphoid cells at a late stage of B-cell differentiation in the germinal center. Another feature that is observed is high cellular proliferation and apoptosis, confirmed by the presence of a lytic cellular background in the vitrectomy specimens.

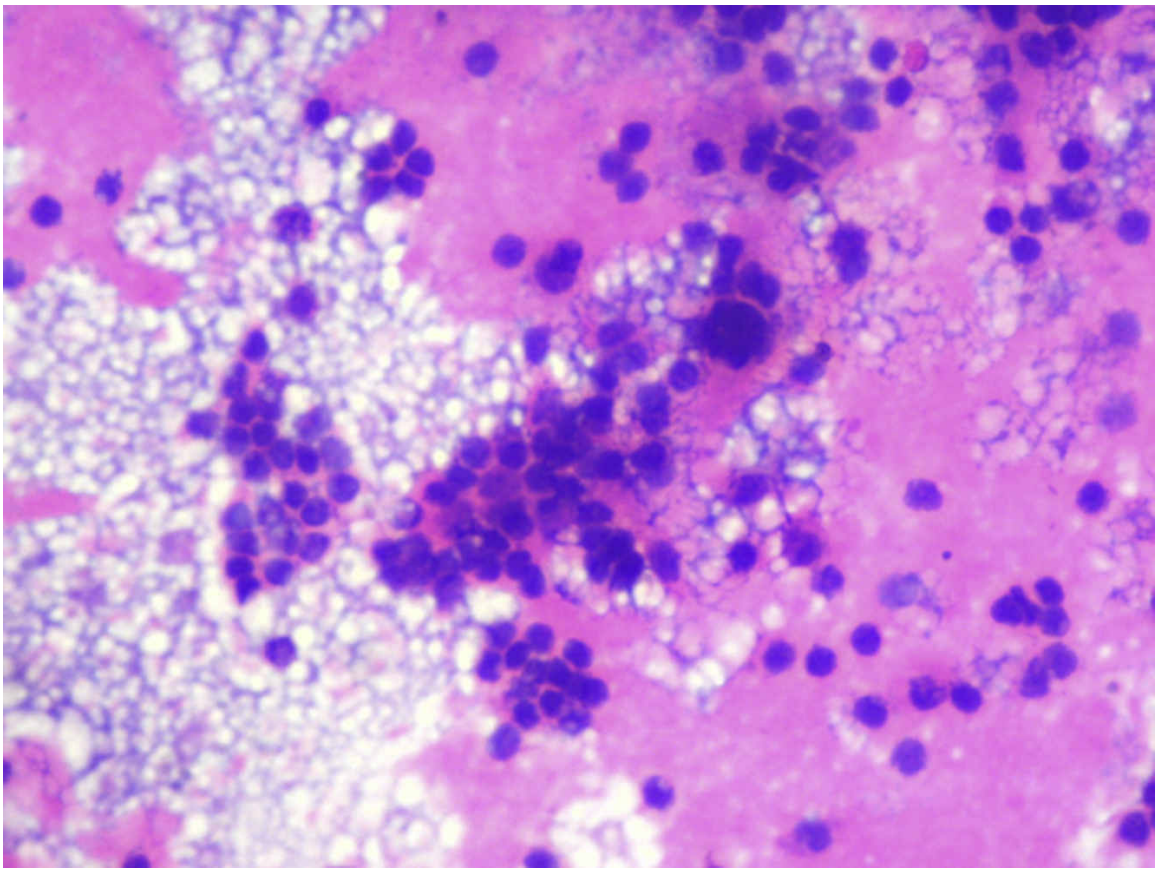

FIG. 16 Cytopathology of vitreous aspirate showing pleomorphic malignant lymphoma cells with high nuclear cytoplasmic ratio in a necrotic background (hematoxylin-eosin, ×200).

Molecular features

Researchers have detected high frequencies of mutations in MYD88, the gene encoding myeloid differentiation factor 88 (MYD88). The MYD88 gene is located in chromosome 3p22 and is involved in Toll-like receptors and interleukin (IL)-1 (IL-1R) signaling pathway [14]. Polymerase chain reaction–based assays are useful in determining etiology in ocular fluids and have been used for the diagnosis of PVRL. Polymerase chain reaction examining the monoclonality of the heavy and light chain of B-cell lymphoma can be demonstrated. CDR3 polymorphism in the variable region of the immunoglobulin gene can be seen. BCL-6 protein in primary intraocular lymphoma with central nervous system involvement is a predictor of poor prognosis. Translocation of t (14; 18) might be associated with clinical aggressiveness of the intraocular lymphoma [15].

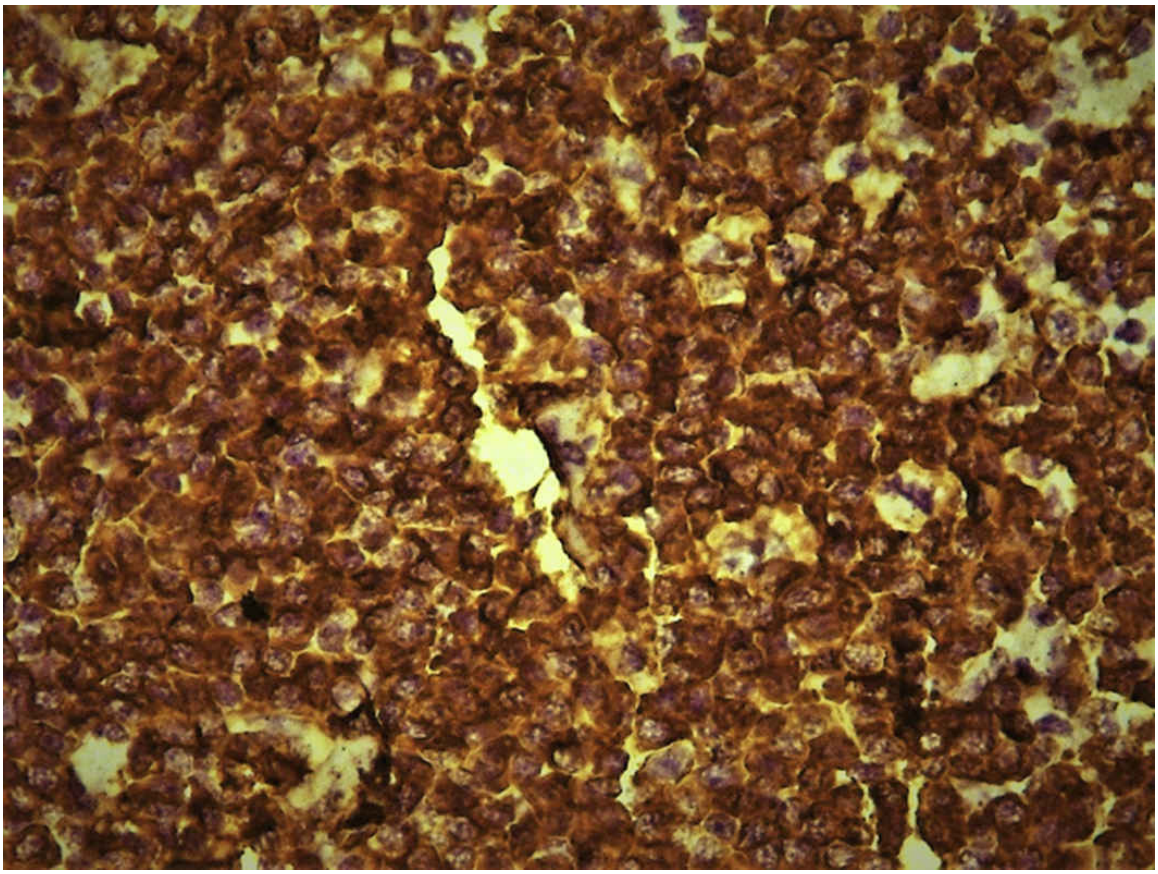

FIG. 17 Immunohistochemical staining with pan–B-cell marker (CD0) showing intense positivity of the tumor cells (CD20, ×200).

Summary

With the current advancement in the treatment strategies for retinoblastoma weighed toward globe and vision salvage, a better understanding of pathobiology and recent advances in molecular biology and genetics may help prevent long-term morbidity.

Melanoma of the choroid is a common tumor in adults. Chromosome in situ hybridization and microsatellite analysis help with a better understanding of the pathogenesis of a tumor and its prognosis. An understanding of the molecular landscape of the tumor has helped in developing a treatment that can target the pathways involved in the disease. With this advancement, the progression of the disease may be able to be prevented in the near future.

Vitreoretinal lymphoma often poses a diagnostic and therapeutic challenge. Vitreous IL analysis (IL-6/IL-10 ratio) and mutated gene detection (MYD88 L265P) recently have proved of high reliability. Therefore, referral to a hospital with an expert cytopathologist is required for better assessment and management of patients affected by this malignancy.

Clinics care points

- Histopathology and immunohistochemistry of specimens of intraocular tumors can guide clinicians to confirm the diagnosis. In retinoblastoma, histopathology features, such as retrolaminar optic nerve invasion, massive choroidal invasion, and scleral and orbital tissue invasion, suggest the need for additional chemotherapy.
- Uveal melanoma arises most commonly from the choroid (90%), followed by the ciliary body (5%) and iris (5%). Tumor size is the best indicator of the prognosis of the disease. Histopathology and gene profiling also aid in the prognostication of the disease.
- Primary vitreoretinal lymphoma often presents as a masquerade syndrome. Vitreous biopsy is the preferred method of diagnosis. Undiluted samples are to be taken, and it is important to send the specimen within an hour of collection for best results. The need to communicate to pathologist prior to biopsy is very important.

Acknowledgments

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Disclosure

Nil financial interests by any of the authors.

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Adenoid Cystic Carcinoma of the Lacrimal Gland

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Adenoid cystic carcinoma; Lacrimal gland; Pathology; Immunohistochemistry; Treatment approach

Key points

- Despite the rarity of lacrimal gland adenoid cystic carcinoma (LGACC), it is the most common malignant epithelial cancer of the lacrimal gland, with a low survival rate.
- In selected cases, the combined approach of globe-sparing surgery with adjuvant radiotherapy is considered to have a favorable visual and functional outcome with good local control rates.
- Future randomized clinical trials are crucial to determine the outcomes between conservative and radical surgical protocols.
- The therapeutic strategy of LGACC relies on a strong multidisciplinary collaboration between an orbital surgeon, radiotherapist, pathologist, and oncologist.

Introduction

Head and neck adenoid cystic carcinomas (ACCs) arise most commonly from the secretory epithelial cells of the salivary glands; however, sporadically, ACC can occur in other exocrine glands of the body, for example, breast, lacrimal glands, nasal passages, tracheobronchial tree, prostate, cervix, and vulva [1]. The tumor occurs in all age groups, children included, but it has a slightly higher frequency in middle-aged patients (50s–60s). Lacrimal gland tumors are a very rare oncological entity that represent an incidence of 1 case per 1,000,000 persons per year and constitute approximately one-quarter of orbital space–occupying lesions with the majority being benign. These lesions are of epithelial origin in more than half of cases and of lymphoid origin in one-third of cases. Lacrimal gland ACC (LGACC) constitutes between 32% and 66% of the epithelial lacrimal gland malignancies and approximately 1.6% of all space-occupying orbital lesions. Despite the rarity of this disease, it is the most common malignant epithelial cancer of the lacrimal gland [2–4]. LGACCs are high-grade, slowly progressive, and aggressive tumors associated with a high mortality due to perineural invasion and dissemination not only to the regional lymphatic system but also to brain, lung, liver, and bones [5].The 5-year survival rate is less than 50% and median overall survival only 7.6 years, due to early local, distant metastatic disease and delayed patient presentation [4]. The main factors related to locoregional recurrence or distant metastases are tumor size, TNM stage, perineural invasion, invasion of large trunk, incomplete resection, and lack of postoperative radiotherapy (RT) [6]. Currently, there is no standardized protocol for the management of LGACC and consensus regarding the optimal approach because of the rarity of the tumor. As a result, the effect of local resection, RT, or exenteration on the patient outcome still is unclear. The rarity of this tumor, lack of prospective studies, and the still debatable therapeutic approaches emphasize this article's significance in understanding the disease behavior by reviewing the most relevant studies from the past decade's literature.

Significance (in-depth analysis)

Signs and symptoms

The median age for patients with LGACC is 40 years and the main clinical signs according to the tumor expansion at the time of diagnosis are superior temporal eyelid swelling with concurrent downward and medial globe displacement, ptosis, proptosis, and restriction of eye movements. Due to perineural invasion, pain and/or dysesthesia are the cardinal symptoms, followed by headaches, decreased visual acuity, and diplopia in some cases [7,8].

Staging

According to the eighth edition of the American Joint Committee on Cancer (AJCC) *AJCC Cancer Staging Manual* classification, primary tumor (T), lymph nodes (N), and metastasis (M) were subsequently defined (Table 1):

Studies have revealed that the AJCC classification might be able to guide the treatment planning and to help predict its outcome. Thus, patients with a disease stage under T3 at the time of presentation are associated with a more favorable outcome in contrast to patients with an advanced disease stage over T3 [9,10].

Histopathology

For a correct and complete assessment of LGACC and specific therapeutic management, incisional biopsy or fine-needle aspiration if done in order to determine the histopathologic tumor type. LGACC consists of a dual population of small hyperchromatic differentiated ductal and modified myoepithelial cells. Regarding the growth pattern, 3 histologic forms have been described. The most common type is the cribriform pattern, followed by the tubular form, whereas the solid (basaloid) pattern is among the rarest and the most infiltrative form with a low survival rate. The cribriform type is known for the Swiss cheese aspect, given by islands of basaloid cells that surround cystlike spaces. Solid tumors also can present central necrosis as well as anaplastic and nuclear pleomorphic cells. With respect to mitosis, tubular LGACC and cribriform LGACC have low mitotic activity, specifically 2.9/10 high-power fields, whereas tumors with

solid pattern evidence a higher mitotic activity with a median of 10.1 mitotic figures/10 high-power fields [8]. Immunohistochemical staining of luminal cells reveals positivity against CK 8/18, CD117, and AE1/AE3, whereas myoepithelial cells demonstrate positivity against CK 5/6, S-100, calponin, and p63. The recently described aggressive undifferentiated ACCs usually show an abrupt demarcation between areas of low-grade and high-grade carcinoma and present a higher proliferative rate, a high Ki67 positivity rate, and high incidence of p53 staining in high-grade areas compared with the low-grade ones [11].

Table 1 TNM staging

Primary tumor	T0	No evidence of primary tumor
	T1	Tumors with a size <2 cm with or without invasion of the soft orbital tissue moreover
	T1a	Absence of periosteal/bone involvement
	T1b	Presence of periosteal involvement
	T1c	Both periosteal and bone involvement
	T2	Tumors with a size between 2 cm and 4 cm
	T2a	Absence of periosteal/bone involvement
	T2b	Presence of periosteal involvement
	T2c	Both periosteal and bone involvement
	T3	Tumors greater in size than 4 cm
	T3a	Absence of periosteal/bone involvement
	T3b	Presence of periosteal involvement
	T3c	Both periosteal and bone involvement
	T4	Tumor extension into adjacent structures
	T4a	Tumors with size <2 cm
	T4b	Tumors with a size between 2 cm and 4 cm
	T4c	Tumors with size >4 cm
Regional lymph nodes	Nx	No assessment of regional lymph nodes
	N0	No involvement of regional lymph nodes
	N1	Presence of regional lymph nodes metastasis
Metastasis	M0	Absence of distant metastasis
	M1	Presence of distant metastasis

Adapted from AJCC Cancer Staging Manual. 8th ed. Springer International Publishing; 2017: 1032.

Imaging

Imaging is crucial in assessing a lacrimal mass because in many cases the presenting symptoms are nonspecific. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) scans to evaluate a suspected LGACC due to its ability to detect perineural spread; however,

bone assessment is superior on CT. On CT, the mass appears hyperdense with homogeneous enhancement and poorly demarcated margins extending along the orbital lateral wall up until the orbital apex, depending on the tumor size. Adjacent bone destruction and foci of calcification are common in large tumors. On MRI, the lesion is described as a well-defined nodular irregular mass that can infiltrate the adjacent orbital tissues and enhances moderately intense after contrast administration (Fig. 1). On T1-weighted images, the tumor has a hypointense signal to orbital fat, whereas on T2-weighted images it becomes hyperintense to fat with areas of central necrosis in some cases, giving a patchy aspect (Fig. 2). Foci of calcification appear as hypointense areas [8,12]. Contrast-enhanced T1-weighted images can reveal areas of cystic changes surrounded by a heterogeneous enhanced mass [13]. Additionally, MRI is helpful in demonstrating micro-serrations along the lesion border and in detecting perineural invasion or dura penetration. A study conducted by Williams and colleagues [14] reported evidence on imaging of bone involvement in 87.5% of patients who underwent both MRI and CT. A preoperative imaging assessment of the lacrimal fossa with positive bone invasion might indicate a more extended surgical approach with bony wall removal [14]. Recent studies have shown the utility of diffusion-weighted imaging in differentiating benign from malignant orbital tumors through measuring the apparent diffusion coefficient. Due to the hypercellularity of malignant lacrimal tumors, the diffusion of water protons is restricted; therefore, the mean apparent diffusion coefficient values are lower than in benign lacrimal tumors. Larger studies are fundamental, however, in order to raise the accuracy of diffusion-weighted imaging in discriminating the malignant tumors from the benign ones [15].

Treatment approach

Controversy remains regarding the appropriate local therapy for LGACC. The rare nature of this malignancy is the reason for a lack of prospective randomized trials on different forms of treatment. As a result, clinical practice patterns are based mostly on anecdotal experience. Although the most common surgical treatment is orbital exenteration followed by various forms of postoperative RT, recent studies on eye-sparing surgery with adjuvant RT reported good local control similar to orbital exenteration and a good long-term survival in patients with early-stage

tumors and locally advanced LGACC [16,17]. Management strategies include orbital exenteration, globe-sparing resection followed by plaque brachytherapy, proton beam RT, neutron radiation and concurrent systemic or neoadjuvant intra-arterial chemotherapy, however, without any clear conclusion [18].

At first, in the early 30s, RT alone without surgery was recommended for ACC. Over time, it became evident that RT alone was ineffective as a curative treatment modality for ACC [19]. Later, the eye-sparing procedures with complete tumor excision (without RT) became more common. Because this approach was not effective in controlling local recurrence, radical orbital exenteration (without RT) with bone removal was selected in some patients despite the high mortality and low survival rates of 20% [20–25].

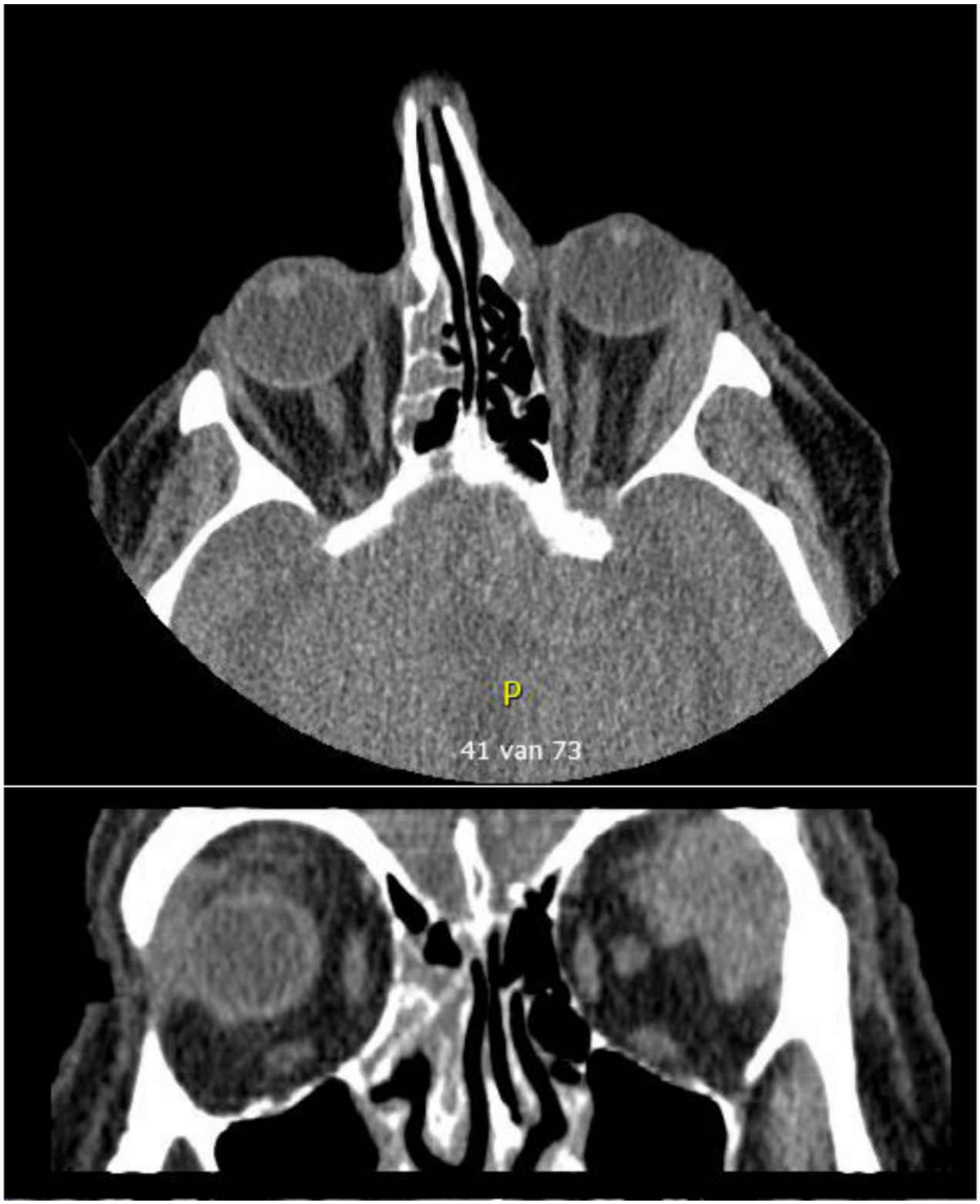

FIG. 1 Axial (*upper*) and coronal (*lower*) CT scans in a 78-year-old male patient with left intraorbital soft tissue mass at the level of lacrimal gland with both extraconal and intraconal components with irregular margin. The mass cannot be delimited from the lacrimal gland, superior rectus, lateral rectus, and superior oblique muscles.

Historically, orbital exenteration with or without removal of the bony walls of the lacrimal gland fossa has been viewed as the most common

“standard” surgical approach, despite the uncertain evidence of survival benefit. This most likely was because of concern regarding toxicity from adjuvant high-dose radiation when delivered in close proximity to the sensitive components of the eye. With more experience, it was evident that the radical surgical approach did not reduce rates of recurrence, metastasis, and mortality but decreased patient quality of life due to functional disability and disfigurement [2,26]. Thus, the idea of adjuvant RT treatment began to gain more interest.

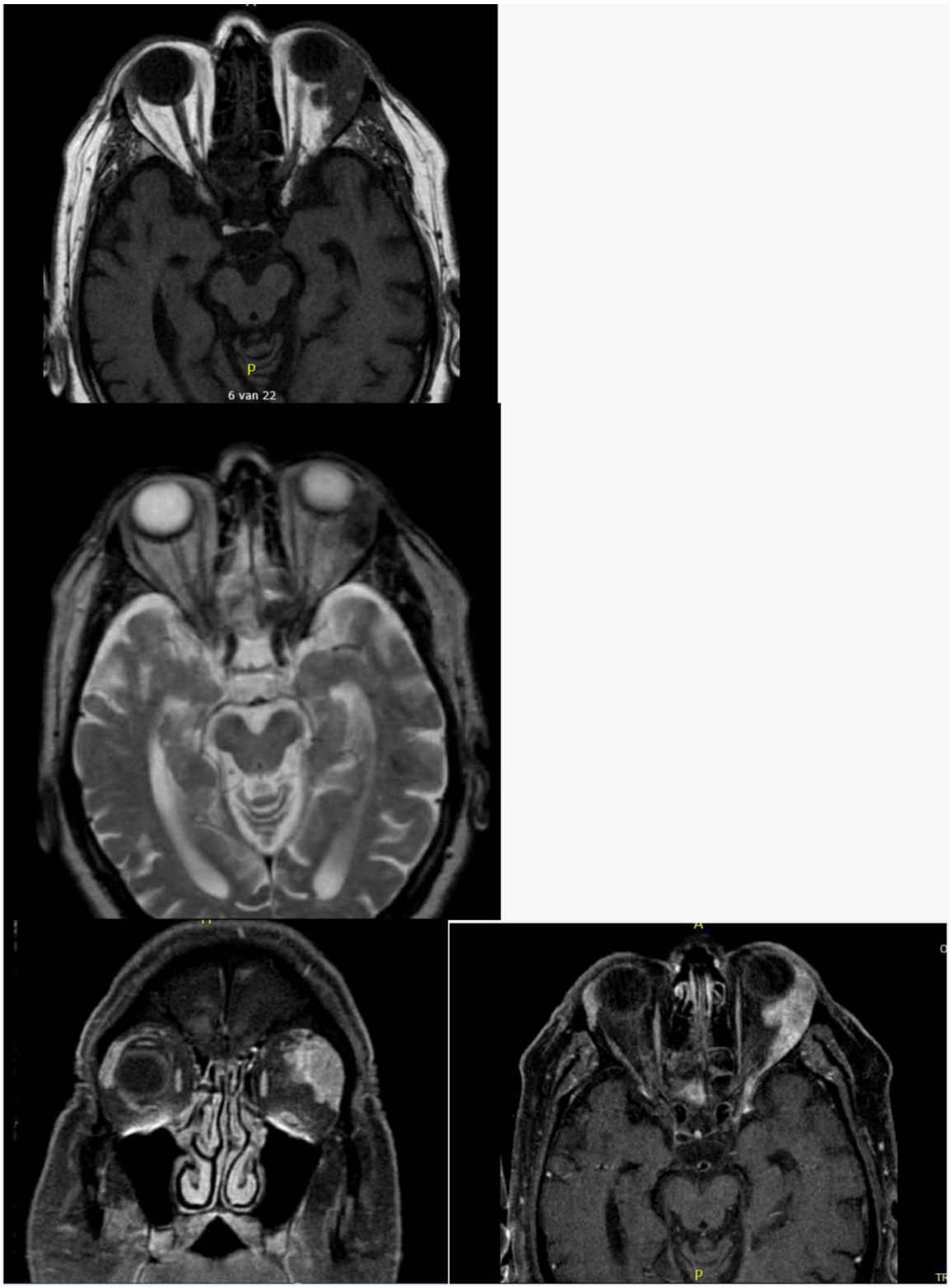

FIG. 2 MRI in the same patient (T1W [*upper*]; T2W [*middle*], T1W with contrast [(*bottom* (*left/right*))]). T1w, T1 weighted image. Undelineated soft tissue mass at the level of the lacrimal gland with and isointense signal on T1W sequence and a hypointense signal on T2W images. Intense and

inhomogeneously enhancement after contrast. Enhancement is present up until the orbital apex but no signs of perineural extension or intracranial metastasis are noted.

In the mid-1980s, Lee and colleagues [27] embraced the eye-sparing procedure with en bloc excisional biopsy via anterolateral orbitotomy in cases of small, localized tumor. Wright and colleagues [28] reported that disease-free survival may not be improved after cranio-orbital resection in patients with clinically and radiologically localized tumors, and extensive surgery does not appear to have an impact on the risk of distant metastasis and mortality.

Recent literature on LGACC focuses on eye-sparing local excision followed by radiation therapy. Adjuvant high-dose radiation therapy is initiated 4 weeks to 6 weeks after surgical tumor resection due to the very high incidence of perineural invasion. A retrospective cohort analysis reported favorable outcomes of eye-sparing tumor excision combined with adjuvant RT or chemoradiotherapy for 37 patients with lacrimal gland carcinoma, specifically 32 patients were tumor-free, 3 patients presented distant metastasis, and 1 patient died after treatment. The 5-year recurrence-free survival rate was worse in patients who were not treated with adjuvant RT compared with those who underwent RT [16,17]. Moreover, Han and colleagues [29] presented their cohort results of 9/10 patients treated with eye-sparing surgery followed by adjuvant RT without any local recurrence during their study period, and the only patient with local recurrence was treated successfully with orbital exenteration.

These studies support the point of view that in LGACC patients, eye-sparing surgery with adjuvant RT is associated with a favorable visual and functional outcome and the postoperative adjuvant RT seems to improve local control rates. The treatment of a patient with LGACC is approached stepwise by a multidisciplinary team consisting of an orbital surgeon, radiation oncologist, radiologist, and oncologist. Patients are considered eligible for the combined approach of eye-sparing surgery with RT when the tumor is considered grossly resectable without sacrifice of the eye or extraocular muscles. Nonetheless, the risks of local recurrence and secondary exenteration are acknowledged and agreed on by the patient.

Several reports suggest that tumor size affects prognosis in patients with LGACC. A multi-institutional study of 53 LGACC patients concluded that the sixth edition of the *AJCC Cancer Staging Manual* T factor (which is

dictated mostly by tumor size at presentation) correlated with prognosis. This report found that tumors categorized as T3 or higher were associated with significantly higher risks of local recurrence, lymph node metastasis, distant metastases, and lower disease-free survival rate than tumors with tumors below T3. Thus, this report concludes that patients with T1 or T2 tumors might be suitable candidates for less invasive surgical treatment. In cases of lacrimal gland carcinomas, no more than 2.5 cm in dimension, gross total tumor excision (eye sparing) followed by radiation therapy can be considered [10].

Adjuvant RT is the standard of care after surgery for local control. Various types of RT have been reported, including external beam radiation (EBRT) therapy, proton beam therapy (PBT), and plaque brachytherapy. Being the most affordable and accessible, EBRT is the most common technique. The median total dose is 60 Gy (59.4 Gy to approximately 70 Gy) with daily fractions ranging from 2.0 Gy to 2.3 Gy. Based on small series, plaque RT appears to be a reasonable alternative to external beam irradiation. In contrast to EBRT, plaque RT can be completed in 4 days rather than 4 weeks to 5 weeks. It does, however, require a surgical procedure, usually with local anesthesia. The surgical placement sometimes can be difficult because of scar tissue from the previous orbital surgery [30]. Another treatment approach is intensity-modulated radiation therapy (IMRT), which uses multiple small photon or proton beams of varying intensities to irradiate the tumor mass precisely. The radiation intensity of each beam is controlled, and the beam shape changes throughout each treatment. The goal of IMRT is to conform the radiation dose to the target and to avoid or reduce exposure of healthy tissue to limit the side effects of treatment. Investigators showed high control rates and low side effects by using IMRT in head neck ACC [31,32]. PBT is considered another local RT treatment choice for ACC after primary excision. Linton and colleagues' [33] and Lesueur and colleagues' [34] reports emphasize that PBT is a safe and efficient treatment and should be considered an adjuvant irradiation modality for patients with LGACC after conservative or radical surgery [33,34].

New therapeutic options, such as intra-arterial neoadjuvant chemotherapy (IANC) consist of chemotherapy administered before any definitive surgical procedure in patients without evidence of metastatic disease but at high risk for such. The rationale of the neoadjuvant regional treatment is to administer a high concentration of a chemotherapeutic agent to the lacrimal gland tumor through the vascular system, prior to

surgical excision of the tumor, in order to enhance tumor cell apoptosis [35]. Thanks to the drug's intra-arterial route delivery, its concentration is considerably higher than that with intravenous delivery. The higher drug concentration increases its cytotoxic effect while preserving the therapeutic levels for chemotherapy to the systemic circulation. The authors demonstrated that IANC was effective in achieving preoperative cytoreduction by down-staging the disease and enhancing the ability to resect the entire lesion for local disease control. Controversy still remains, however, regarding the optimal local therapy for lacrimal gland. The reluctance of many orbital surgeons and oncologists to integrate IANC into the primary treatment is based on the lack of long-term survival data, chemotoxicity, and the desire to preserve the globe. In addition, fewer data are available regarding systemic therapy in the locally advanced setting, with less than 10% of patients receiving any type of chemotherapy in the largest series to date. The only evidence to support such practice comes from case reports and is insufficient to recommend the routine use of adjuvant chemotherapy for LGACC. Furthermore, adjuvant chemotherapy has not been shown to bring additional benefits in other types of head and neck cancer [36–38].

Future avenues

Guidelines defining therapeutic approaches are lacking, due to the rarity of these tumors. Surgery followed by postoperative RT in a majority of cases seems to be the mainstay of treatment to date, although there is not yet consensus on the type of surgery and postoperative RT. Several studies have shown equal survival outcome for patients treated with eye-sparing surgery compared with exenteration. Some investigators have pleaded for postoperative EBRT with photons or protons after eye-sparing surgery, whereas others advocate brachytherapy or neoadjuvant plus adjuvant intracarotid chemotherapy with cisplatin and doxorubicin in combination with exenteration and postoperative RT.

Due to morphologic and embryologic similarities, lacrimal gland tumors are treated analogously to salivary gland tumors. Lacrimal and salivary gland tumors have been treated bimodally with carbon ion RT (CIRT) in combination with IMRT or with CIRT alone based on prior experiences with high linear energy transfer RT for malignant salivary gland tumors. This approach is well known for more accurate tumor targeting due to superior dose distribution compared with photons or protons and increased biological effectiveness as well as better preservation of surrounding tissue and less toxicity. Although superior results for CIRT in the treatment of malignant salivary gland tumors of the head and neck have been shown in recent years, for lacrimal gland tumors this remains challenging, possibly due to histopathologic differences and locoregional challenges regarding surrounding organs at risk. Further studies are necessary in order to determine the outcome of this treatment approach with regard to recurrence rate and late toxicity [39].

Because approximately 50% of LGACCs have oncological mutations (such as MYB-NFIB fusion gene transcript abnormalities), gene-targeted therapies might represent an alternative option in the future [40]. Despite efforts, no viable agent targeting MYB was efficient. There is evidence, however, that targeted agents against receptor tyrosine kinases (sunitinib and dovitinib), epidermal growth factor receptor (cetuximab), and histone-deacetylases (vorinostat) may extend survival rates and have limited responses against the tumor in a small proportion of patients. There is hope that current or future studies of targeted agents may reveal clinically relevant antitumor activity to locally and systemically control the disease by preventing metastatic spread [41].

Summary

Today, more orbital malignancies, such as ACC, are discovered at an earlier stage by orbital imaging studies, which allow for eye-sparing, near-total surgical excision. In cases of patients who have only minor residual tumor and good visual function of the affected eye, attempts at further excision, orbital exenteration, or external beam irradiation may be undesirable, particularly because there is no firm evidence that they improve prognosis. There is no doubt that orbital exenteration can cause functional and psychological disability for patients. Consequently, patients often are inclined to refuse such radical surgery despite the possible risk to life. At this time, there is debate about the treatment of LGACC with regard to the survival benefit, but this review suggests that, in selected patients with lacrimal gland carcinoma, an eye-sparing approach with surgery and adjuvant RT or concurrent chemoradiotherapy may be both safe and effective while preserving cosmesis and visual function. This approach has gained traction in the recent years due to the positive impact on the quality of life of patients. Eye-sparing surgery followed by RT, however, is appropriate only for patients with less than T3 tumors, whereas patients with greater than or equal to T3 tumors have a surgical indication of orbital exenteration with bone removal and RT [29]. Various publications have reported that the ocular toxicity profile after eye-sparing surgery and RT was reasonable with good visual acuity (<20/40). Radiation retinopathy and keratitis were the most serious adverse events. Close follow-up after surgery should be undertaken to evaluate both local recurrence and radiation-related complications.

The global strategy to cure lacrimal ACC has yet to be determined. If a patient proceeds with preservative surgery and adjuvant RT, the irradiation modality and the role of IANC can be discussed. Future clinical trials with longer follow-up time, however, are fundamental to better understand the risks of locoregional recurrence and ocular adverse events associated with eye-sparing multimodality treatment of LGACC and to validate the safety and efficacy of eye-sparing approach over radical orbital exenteration.

Clinics care points

- Orbital exenteration followed by various forms of postoperative RT.
- Radical orbital exenteration (without RT) with bone removal.
- Targeted agents against receptor tyrosine kinases (sunitinib and dovitinib).

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Cataract & Refractive Surgery

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Micro-Invasive Glaucoma Surgery

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Keywords

MIGS; Micro-invasive glaucoma surgery; Minimally invasive glaucoma surgery; Techniques; Updates; Glaucoma

Key points

- Relevance of MIGS: Micro-invasive Glaucoma surgery has filled a gap in care in the management of glaucoma, allowing for earlier surgical intervention in a safe and effective manner.
- MIGS Approaches and Devices: MIGS devices and techniques have different tissue targets within the eye. Some MIGS bypass or incise the trabecular meshwork. Other devices stent open the canal of Schlemm, while others divert the flow of aqueous to the subconjunctival or suprachoroidal spaces. Cycloablative procedures also are used to lower the intraocular pressure.
- Literature Update: Recent long-term data for specific devices, randomized clinical trials, and head-to-head comparative studies are summarized.

Introduction

Glaucoma is a chronically progressive optic neuropathy resulting in characteristic irreversible visual field depression. It is estimated that glaucoma affects almost 80 million individuals worldwide, and this number may increase to 111.8 million by 2040 [1,2]. Glaucoma currently is the leading cause of irreversible blindness worldwide. The mainstay of glaucoma treatment is lowering intraocular pressure (IOP), the only major modifiable risk factor shown to slow down progression of the disease [3]. IOP reduction can be achieved with medications, which are often the most used treatment modality, lasers, and surgery. Poor adherence to medications poses an increased risk for visual loss in patients with glaucoma, especially for those on multiple eyedrops [4]. In addition, some patients show progression of their glaucomatous disease despite good medication adherence.

Before the twenty-first century, the glaucoma specialist's surgical armamentarium was mostly restricted to invasive filtering trabeculectomies and tube shunt procedures, which are wrought with serious short and long-term complications that have been well-documented, and often result in failure [5]. With advancements in glaucoma surgical techniques, the role for procedural intervention earlier in the disease course is becoming increasingly common. Micro-invasive Glaucoma Surgery (MIGS) is an approach to glaucoma surgical management that affords patients with good efficacy, a high safety profile, relatively shorter surgical times, and rapid surgical recovery. MIGS are deemed less invasive and safer than traditional glaucoma filtering procedures. At a minimum, a modest reduction of IOP is the goal, and this is achieved with minimal tissue disruption often by enhancing the eye's existing anatomy [6]. There are many approaches, but generally, there is less or no conjunctival disturbance compared with traditional filtering procedures. MIGS can be performed either as a standalone procedure, or in combination with cataract surgery.

Since they have become commercially available, MIGS have increasingly filled a gap in care for patients with glaucoma. These techniques have become a standard of care for patients with glaucoma and IOP–related issues for comprehensive ophthalmologists and glaucoma specialists alike. Novel technologies and techniques provide for unique treatment modalities alternative to traditional filtering surgeries. Updated studies on

MIGS are constantly emerging, allowing for better data on efficacy and real-world clinical and surgical practice.

Within this article, we provide a summary of the MIGS devices and techniques available and discuss the advances and updated research in this field. We detail the devices used, pathways targeted, short and long-term efficacies where applicable, and safety profiles. We offer summaries of current research, including studies that compare techniques head-to-head, and discuss future avenues in MIGS care.

Significance and current relevance

Traditional glaucoma filtering procedures have been the mainstay for glaucoma surgical management for decades. At the turn of the twenty-first century, a novel approach to glaucoma surgical management emerged: MIGS. The cardinal features of MIGS are that they are minimally invasive to the target tissue, demonstrate a modest reduction of IOP with minimal tissue disruption, provide a good safety profile, and allow for a relatively rapid recovery [6]. A vast array of patients with glaucoma can benefit from MIGS (Table 1).

There are a wide array of procedures and devices that are considered MIGS, and their mechanistic targets differ in how they achieve IOP reduction. The main mechanisms by which MIGS lower IOP are improving trabecular outflow through the Schlemm canal, creating an alternate outflow pathway in the subconjunctival space, enhancing uveoscleral outflow in the suprachoroidal space, and ciliary body destructive procedures (Table 2).

Table 1 Micro-invasive glaucoma surgery candidates

Open-angle glaucoma • **Mild** • **Moderate** • **Severe** **Angle closure** • **Select cases and devices**	Medication toxicities/Intolerance/Allergy
	On intraocular pressure–lowering therapy and will be undergoing cataract extraction
	Insufficient intraocular pressure control with laser/medications
	Medication burden/Noncompliance

Most aqueous humor drainage occurs via 2 pathways: the conventional trabecular outflow pathway and the unconventional uveoscleral pathway. It has been well-established that most aqueous outflow resistance is at the level of the juxtacanalicular trabecular meshwork, especially in older patients [7]. Thus, most of the commercially available MIGS devices aim to lower resistance at the level of the trabecular meshwork, either by removing a portion of the trabecular meshwork or bypassing it completely to allow aqueous to access the Schlemm canal and the collector channels. The nasal quadrant is the most common surgical target in MIGS, given its easy access from the temporal clear corneal incision of cataract surgery,

and this coincides with the highest concentration area of collector channels.

Table 2 Different Micro-invasive glaucoma surgery categories and devices/techniques

Schlemm Canal/Increase Trabecular Outflow		
Stenting	**Cutting**	**Dilating**
iStent Micro-Bypass (Glaukos) **IStent *inject* (Glaukos)** **IStent inject W (Glaukos)** **Hydrus Microstent (Ivantis)**	Excimer Laser Trabeculostomy Gonioscopy-assisted transluminal trabeculotomy (GATT) Kahook Dual Blade (New World Medical) TRAB 360 Trabeculotomy (SightSciences Inc) Trabectome (NeoMedix Inc)	Ab interno canaloplasty (ABiC) VISCO360 Viscosurgical System
	OMNI	

Subconjunctival **CyPass Micro-Stent (recalled)** **XEN Gel stent (Allergan)** **PRESERFLO MicroShunt (Santen)**
Suprachoroidal **IStent SUPRA (Glaukos)** **MINIject (ISTAR medical)** **CyPass MicroStent (Alcon): Recalled**
Cycloablative **EndoCyclophotocoagulation (ECP)** **High-Intensity Focused Ultrasound cyclocoagulation** **Micropulse diode laser**

We provide a review of select MIGS devices and procedures and updates on their use and efficacy. First, we discuss trabecular stenting procedures. The 2 commercially available devices approved for implantation at the time of cataract surgery in the United States are the iStent Trabecular Micro-bypass stent and the Hydrus Microshunt. These enhance the flow of aqueous through the Schlemm canal and the collector channels by helping to bypass resistance at the level of the trabecular meshwork.

IStent trabecular micro-bypass stent

The iStent Micro-bypass Stent (Glaukos Corporation, San Clemente, CA) was first implanted in the United States in 2005 and received Food and Drug Administration (FDA) approval in 2012 [8]. It was designed to create a permanent conduit for aqueous to pass directly from the anterior chamber into the Schlemm canal. The device is made of heparin-coated, non-ferromagnetic titanium. In its first-generation design, the device has an inlet or "snorkel" that connects to the implanted portion of the implant at a 90-degree angle. The implanted portion is pointed to facilitate canal entry [9]. Three retention arches help to stabilize the device in the angle. The device's dimensions are 1 mm × 0.33 mm × 120 μm.

The second-generation iStent, known as the "iStent inject," was developed such that 2 stents are injected into the Schlemm canal. It received FDA approval in 2018. The device is made of heparin-coated titanium, just as the first generation. The design is smaller and consists of an apical head that connects to a thinner thorax and a terminal wider flange. The device is 360 μm in length × 230 μm in diameter. The apical head is inserted directly into the Schlemm canal. A slightly larger variant to the iStent, known as the "iStent inject W" has also been made commercially available, and its wider dimensions are thought to aid with surgical placement.

In the United States, the iStent is approved for implantation in mild-to-moderate open-angle glaucoma in combination with cataract surgery, but is approved as a standalone procedure in Europe. The ideal surgical candidate is a patient who has stable mild-to-moderate open-angle glaucoma or who is somewhat uncontrolled. As with other trabecular devices, the iStent's IOP-lowering capability is limited by the episcleral venous pressure, thus after implantation, IOP would likely be no less than 8 to 9 mm Hg [7,10].

In 2011, the iStent Study Group published outcomes in IOP reduction in patients receiving first-generation iStent at the time of cataract extraction versus cataract extraction alone. The primary endpoint was an unmedicated IOP ≤21 mm Hg at 1 year. This endpoint was seen in 72% of the iStent group and 50% of the control group. In addition, the iStent group demonstrated a significant reduction in the number of hypotensive medications required to achieve equivalent IOP reduction compared with cataract extraction alone [11]. Years later, it was proposed that implanting 2 iStents would be at least as efficacious as the IOP-lowering effects of

being on 2 anti-ocular hypertensive medications. This was further studied in the iStent *inject* Study Group. At the time of cataract extraction, the treatment group received 2 iStent *inject* implants versus the controls, who only underwent phacoemulsification. The primary endpoint of the study was ≥20% reduction in unmedicated diurnal IOP by 24 months. This was demonstrated more frequently in the treatment group than controls [12].

Hydrus microstent

The Hydrus Microstent (Ivantis Inc., Irvine, CA), received FDA approval in 2018. The device is 8 mm in length and 290 μm in diameter; 7 mm of the device is scaffolded into the angle at a curvature consistent with the natural architecture of the Schlemm canal, and this portion contains 3 windows. The inlet, which is 1 mm, resides in the anterior chamber. The device spans approximately 3 clock hours of the angle. It scaffolds the Schlemm canal to help keep it patent and bypasses the trabecular meshwork by way of stenting. The device is made of nitinol, which is a nickel-titanium alloy that has demonstrated excellent biocompatibility and has been used in vascular stenting [13]. The single-use Hydrus inserter is used to place the device. The trabecular meshwork is pierced with the distal sharp tip of the device and then dialed into the angle for approximately 3 clock hours. The inlet is then nudged into the angle so only approximately 1 mm is protruding into the anterior chamber. This can be achieved with a second instrument such as a Sinski or even the irrigation and aspiration handpiece (Fig. 1).

The HORIZON study, published in 2019, demonstrated superior efficacy in the reduction of IOP for the Hydrus Microstent when implanted at the time of cataract surgery compared with cataract surgery alone up to 24 months after implantation. This study was a multicenter, single-masked randomized controlled trial in patients who had cataracts and mild-to-moderate primary open-angle glaucoma (POAG) on 1 to 4 topical glaucoma medications. The primary endpoint was a reduction in unmedicated mean diurnal IOP by 20% or more. This was achieved in 77.3% of the Hydrus Microstent group and 57.8% of controls at 24 months. The secondary endpoint was change in mean diurnal IOP from baseline at 24 months, which favored the Hydrus group. Twenty-four-month unmedicated mean diurnal IOP was reduced by 7.6 ± 4.1 mm Hg and 5.3 ± 3.9 mm Hg in the Hydrus and control groups, respectively. In addition, the device was deemed to be safe, as no serious adverse events occurred in relation to its implantation and no significant differences in safety were noted between the 2 groups [13].

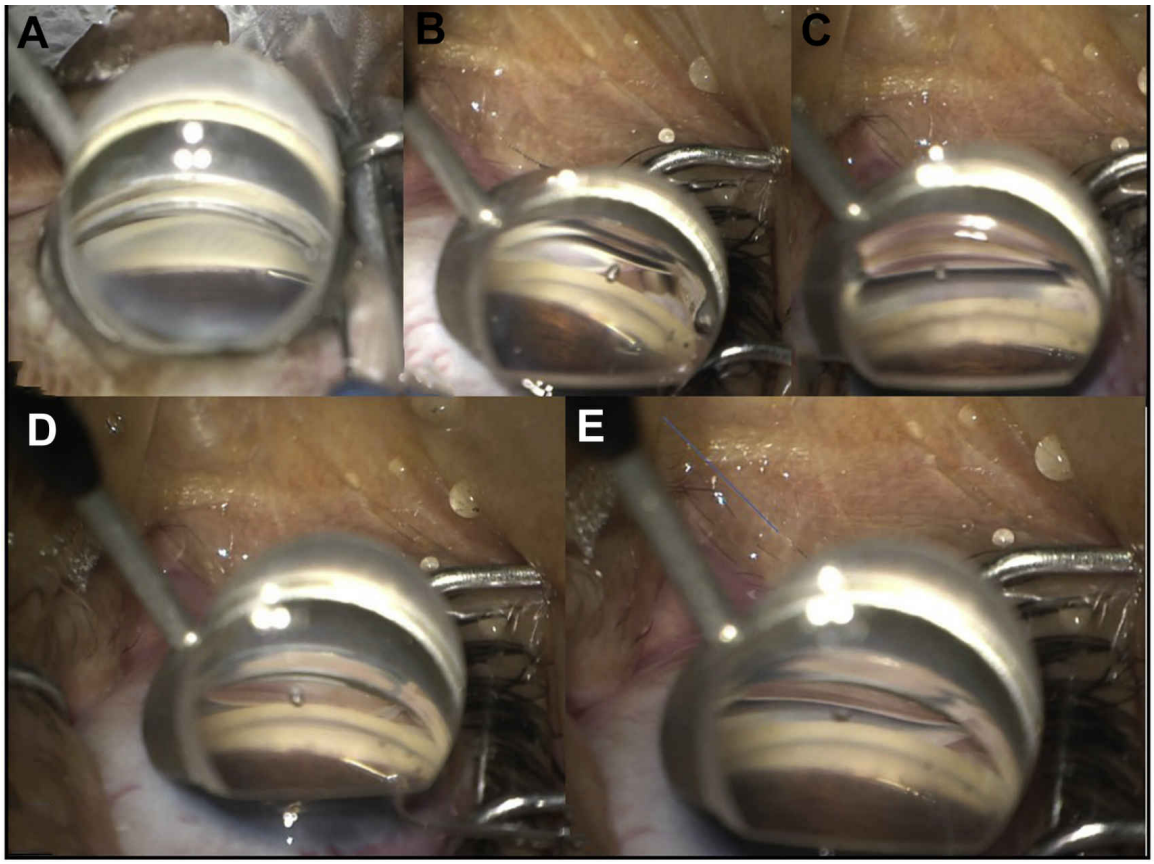

FIG. 1 Hydrus Microstent implantation into the Schlemm Canal; various stages. (*A*) Initial placement by engaging device into trabecular meshwork. (*B*, *C*) Device advancement into the Schlemm Canal. (*D*) Device deployed from injector (used Sinskey to advance to final position). (*E*) Final position of implant.

Three-year data from the HORIZON trial showed promising long-term efficacy and safety. At the 3-year mark, patients in the Hydrus group had stable IOP compared with controls. Seventy-three percent of Hydrus patients and 48% of controls were medication-free. Hydrus eyes also were more likely to demonstrate an IOP of ≤18 mm Hg without medication compared with controls (56.2% vs 34.6%). No difference was seen in endothelial cell density between the 2 groups, and no significant differences in safety were noted between the 2 groups [14].

Other studies have demonstrated the efficacy of the Hydrus Microstent finding it to be superior in lowering IOP in patients with POAG compared with selective laser trabeculoplasty and canaloplasty [15].

Recently, the 5-year HORIZON data were presented at the American Glaucoma Society 2021 virtual conference. The results redemonstrated the safety and efficacy of the Hydrus, with no significant long-term differences

noted compared with cataract extraction alone. A sustained decrease existed in IOP and use of hypotensive medications, and subjects were 2.8 times less likely to have repeat glaucoma surgery. There was 20% to 30% improvement in being medication-free compared with control group. No evidence occurred of statistically significant endothelial cell density difference between Hydrus and controls [16].

Another recent randomized clinical trial, the COMPARE study, performed a head-to-head comparison of the Hydrus and iStent implants as standalone treatment for mild-to-moderate open-angle glaucoma. Subjects were divided into 2 different treatment arms, either receiving 1 Hydrus Microstent, or 2 iStent Trabecular Micro-bypass devices, and were followed for 12 months. The study looked at several different parameters: IOPs, number of medications, and need for repeat glaucoma surgeries. At 12 months, the Hydrus group demonstrated a higher success in subjects attaining medication freedom, and also had greater rates of complete surgical success. In eyes that remained medication-free, the Hydrus group achieved an IOP of ≤18 mm Hg at a rate of 30.1% versus 9.3% of the iStent group. Two patients in the iStent group required further glaucoma surgery, and none in the Hydrus group. At 12 months, the Hydrus group had an elimination of 1.6 medications and the iStent group had an elimination of 1.0 medications compared with preoperative levels. A ≥2-line decrease in best corrected visual acuity occurred in 2 eyes in the Hydrus group and 1 eye in the iStent group. Compared with prior single-center studies looking at standalone insertion of 2 iStent devices, data from the COMPARE trial demonstrated less of a pressure reduction effect. Prior studies demonstrated an average IOP of approximately 13 to 14 mm Hg with and without medications at 12 months, whereas IOP was shown to be higher on average at 12 months in the COMPARE trial [17].

The next set of MIGS to be discussed mainly involve incising the trabecular meshwork to remove the level of resistance of aqueous flow. Removing the trabecular meshwork allows the aqueous to access the collector channels more easily and with less resistance. The various trabecular meshwork removal MIGS vary in their techniques and in the amount of tissue excised. Unlike the implantable devices mentioned previously, the indications for usage in the United States are broader, therefore they can be used to treat forms of glaucoma other than mild-to-moderate POAG.

Goniotomy-assisted trabeculotomy

Goniotomy-Assisted Transluminal Trabeculotomy (GATT) is a technique in which an Ab interno approach is used to incise and remove the trabecular meshwork, thus improving flow into the Schlemm canal and the collector channels. The surgical technique involves making a nasal incision in the trabecular meshwork under direct gonioscopic visualization followed by advancement of an illuminated microcatheter (iTRACK; Ellex iScience Inc., Fremont, CA) or Prolene suture circumferentially 360° around the Schlemm canal. After complete advancement, the distal end is grasped and pulled, while holding tension on the proximal end, creating a full-thickness excision of the trabecular meshwork. The first data on GATT were released in 2014. The study was a retrospective review of patients with documented various forms of open-angle glaucoma, and GATT was performed both as a standalone and in combination with cataract surgery. Results for patients with POAG at 12 months demonstrated an IOP reduction of 11.1 ± 6.1 mm Hg (average of 39.8% decrease in IOP from baseline) and subjects were on approximately 1 less hypotensive medication. For subjects with other forms of open-angle glaucoma, results also were promising with a reduction of IOP by 19.9 ± 10.2 mm Hg at 12 months, and patients required 1.9 fewer hypotensive medications at this time frame. Treatment failure, which was deemed to be an IOP of 21 mm Hg or more at 2 consecutive visits, was seen in 9% of patients, and these patients required further glaucoma surgery [18]. Twenty-four-month follow-up data on GATT, released in 2018, redemonstrated efficacy of the procedure. For subjects with POAG, there was a 37.3% reduction in IOP at 24 months. For patients with other forms of open-angle glaucoma, there was an average reduction of 49.8% from baseline. Interestingly, in the subgroup of patients who underwent GATT at the time of cataract extraction, a higher rate of failure was noted and reoperation occurred after 24 months [19]. Two other studies by Grover and colleagues [20,21] have demonstrated efficacy of GATT in other forms of glaucoma, including eyes that have had previous incisional surgeries, primary congenital glaucoma, and juvenile open-angle glaucoma.

In 2021, a retrospective comparative cohort study was performed comparing trabeculectomy with mitomycin-c versus GATT in patients with open-angle glaucoma. The study included patients with different forms of open-angle glaucoma, including POAG, pseudoexfoliative, and uveitic with uncontrolled IOP despite maximal medication therapy.

Success within this study was defined as a ≥30% reduction in IOP from baseline and absolute IOP of ≤18 mm Hg. At 18 months, subjects in the augmented trabeculectomy group displayed greater IOP reduction than those in the GATT group, with a 16.9 mm Hg reduction in the trabeculectomy group and a 11.6 mm Hg reduction in the GATT group. The average IOP at 18 months was approximately 12.4 mm Hg in the Trabeculectomy group and 15.2 mm Hg in the GATT group, which has implications for patients requiring extreme IOP reduction to control their disease. Given the parameters for success within this study, the probability of success was not statistically significantly different between the 2 groups. Also, the overall GATT success rate within this study echoes those previously reported in Grover's original studies. Within this study, as has been well-established previously, hypotony was the most common complication in post-trabeculectomy subjects, and hyphema was the most common complication of GATT [18,20]. This study also found that GATT is at least or more effective in lowering the IOP compared with other commonly performed MIGS procedures [22].

Trab360 trabeculotomy

The Trab360 (SightSciences) microsurgical device has a similar mechanistic surgical action compared with GATT. This device can be used in patients with open-angle glaucoma. The trabeculotomy is achieved through a disposable, nonpowered injector device, which consists of a cannula, from which a flexible nylon-like suture is injected into the Schlemm canal. The suture is advanced for 180° then pulled out of the angle, incising the trabecular meshwork, and repeated for the untreated 180° [23] (Fig. 2).

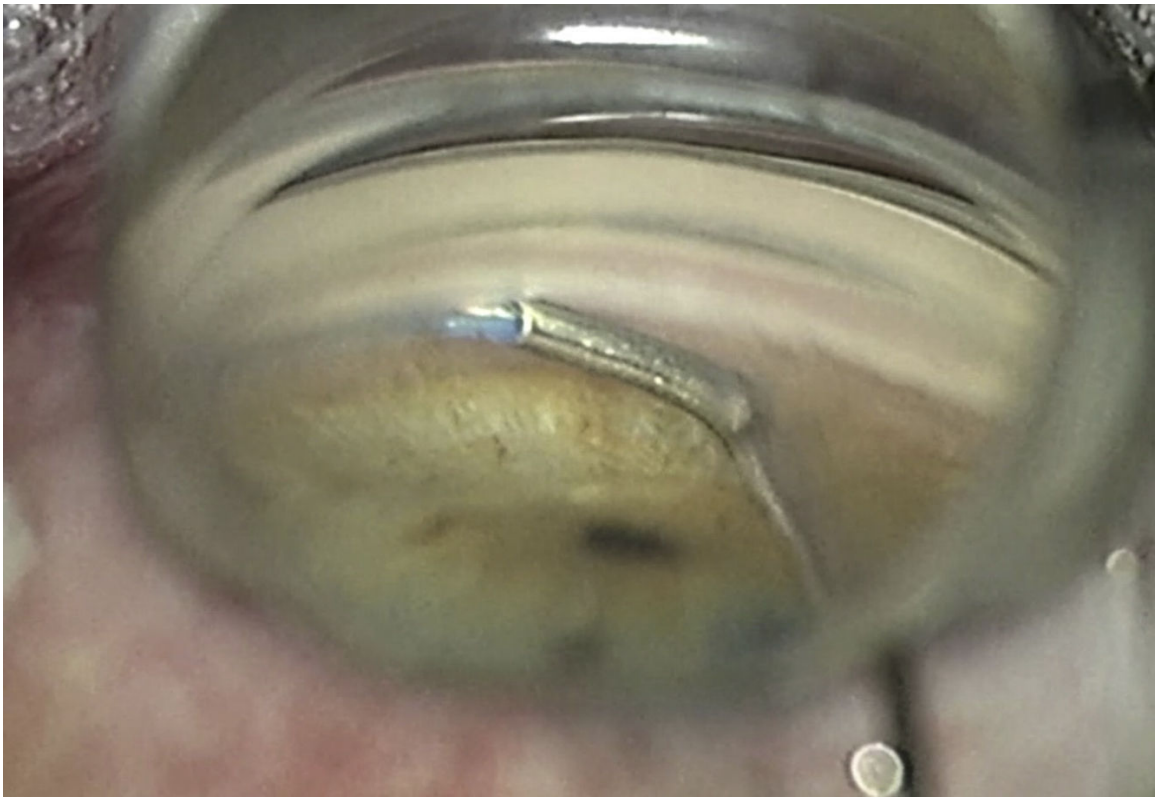

FIG. 2 Trab360 insertion.

Trabectome

The Trabectome (Neomedix Corporation, Tustin, CA) received FDA approval in 2004 for Ab interno trabeculectomy (AIT). This device combines bipolar electrocautery (550 kHz electrode) with irrigation and aspiration and is used to ablate 30° to 180° of the trabecular meshwork. According to a meta-analysis of AIT, most cases in the literature were reported on individuals with POAG followed by pseudoexfoliative open-angle glaucoma and various other secondary open-angle glaucoma subtypes. Generally, success was defined as a final IOP of ≤21 mm Hg or a >20% decrease in IOP from baseline without further surgical intervention. Average success was deemed to occur more frequently among the studies analyzed in cases of combined phaco-AIT compared with standalone AIT. Information obtained from the Trabectome database, which has the longest available data, demonstrated success rates of 85% for phaco-AIT at 5 years and 56% for standalone AIT at 7.5 years. Seven percent of these cases required further surgical intervention. Similar to GATT, AIT does not reliably result in an IOP in the low teens, and thus may not be a substitute for more invasive filtration surgery in eyes requiring this level of IOP control. Overall, AIT lowers IOP by approximately 36% to approximately 16 mm Hg on 1 less hypotensive medication. At 2 years, average success rate is approximately 66% per the previously mentioned criteria. Similar to other trabecular-excising MIGS, hyphema is the most common complication, but generally otherwise has a good safety profile. Currently, there are no randomized controlled trials in the medical literature on AIT [24].

Kahook dual blade

The Kahook Dual Blade (KDB; New World Medical Inc, Rancho Cucamonga, CA) was FDA approved in 2015 for use in combination with cataract extraction and as a standalone MIGS procedure. It can be used in open and closed angles and can also be used for goniosynechialysis. This single-use device has a distal tip with 2 cutting edges. It is advanced through a clear corneal incision and is used to incise and cleave approximately 3 to 4 clock hours of trabecular meshwork, removing a strip of trabecular meshwork, thus theoretically reducing the risk of scarring and failure (Fig. 3).

A prospective, interventional case series looked at the efficacy of KDB in combination with cataract surgery in the treatment of open-angle glaucoma. The average reduction in IOP was 26.2% with a reduction in medication usage of 50% from baseline at 12 months. The procedure was deemed to be safe with no sight-threatening complications. The most common adverse event observed was intraoperative hyphema, as with other trabecular-incising MIGS procedures [25].

The efficacy of KDB has been studied in comparison to and in combination with other MIGS procedures, including iStent and ECP [26,27]. A small retrospective study published in 2021 demonstrated that both iStent and KDB goniotomy were safe and have IOP-lowering effects, with goniotomy showing a slightly advantageous IOP reduction [26]. Izquierdo and colleagues [27] compared eyes undergoing phacoemulsification with ECP versus phacoemulsification with goniotomy and ECP and found that the tri-modal treatment was safe and more effective in reducing IOP than that of the phacoemulsification with ECP alone.

Ab interno canaloplasty

Ab interno canaloplasty (AbiC) is a minimally invasive glaucoma technique in which an illuminated microcatheter (iTrack; Ellex iScience, Inc.) accesses the anterior chamber angle through a clear corneal incision, and is used to catheterize the Schlemm canal for 360°. Following this, viscoelastic is used to dilate the canal and its proximal collector channels. It has been proposed that this technique can help patients achieve IOP in the low-to-mid teens. It is thought that the Viscodilation of the Schlemm canal and the collector channels allows for some restoration of the natural anatomic function of the angle, thus contributing to the efficacy of the procedure. AbiC can be performed in various forms of open-angle glaucoma including pseudoexfoliation, pigmentary, and in pediatric and congenital cases. Potential complications include hyphema, Descemet membrane detachment, cataract formation, IOP spikes, and hypotony [28]. The Visco360 and Omni360 devices also are used to perform AbiC and are discussed as follows.

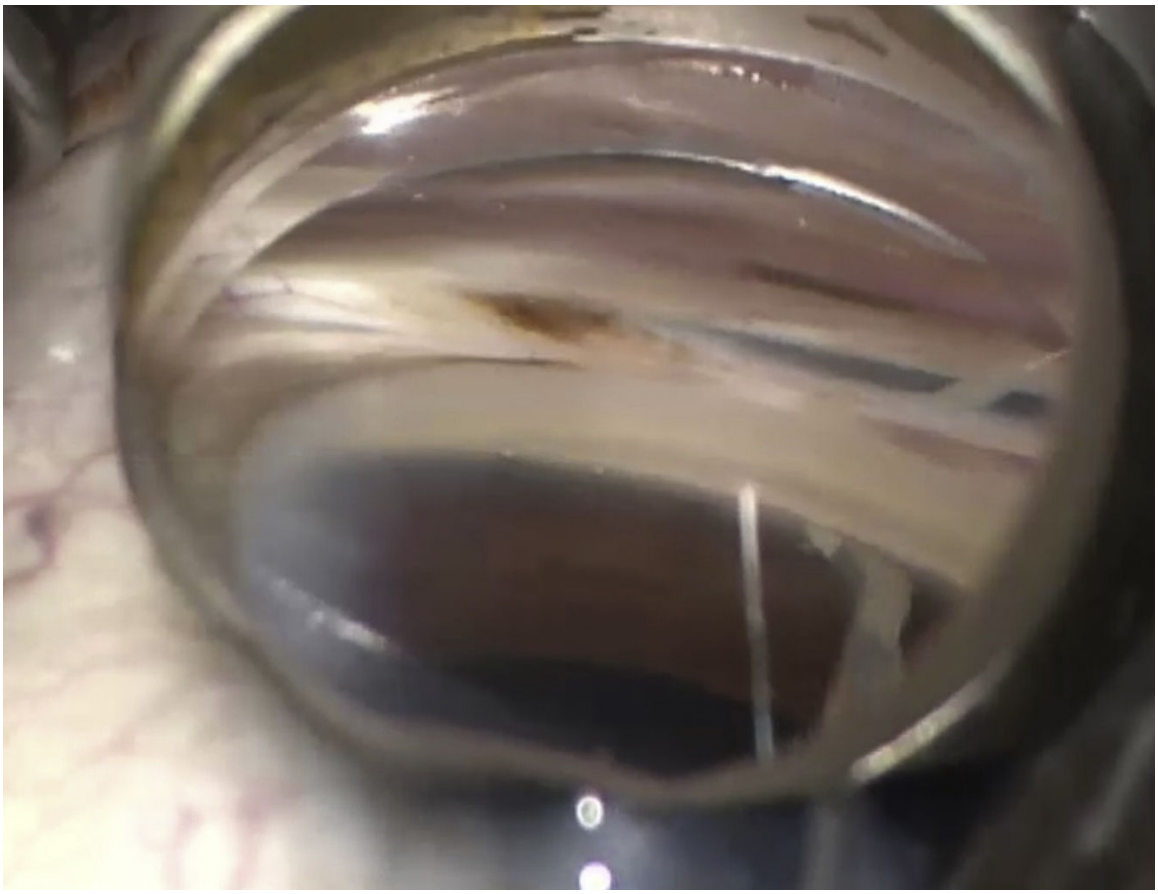

FIG. 3 Kahook dual blade goniotomy.
(*Courtesy of* New World Medical, Inc.)

Visco360 and OMNI

Similar to the technique described previously for AbiC, the Visco 360 device can be used to catheterize and Viscodilate the Schlemm canal. This single-use device has a distal tip that incises the trabecular meshwork allowing a microcatheter to advance 180° through the canal. Then, viscoelastic is inserted into the Schlemm canal. This is then repeated for the remaining 180° [29].

The OMNI system uses the same handpiece as the Visco 360 but is unique in that it combines the techniques of the Visco360 and Trab360. After the device is used to catheterize and Viscodilate 180° of the Schlemm canal, a trabeculotomy is performed. This is then repeated for the remaining 180°. This technique targets 3 main mechanisms of resistance to flow: excision of the trabecular meshwork, which helps to overcome the resistance to aqueous flow, and Viscodilation of the Schlemm canal, and dilation of the collector channels. The Omni system has been shown to reduce IOP by an average of approximately 35% from baseline and can reduce medications by 25% to 50% according to retrospective studies. A recent prospective case series published in the *European Journal of Ophthalmology* in 2021 further investigated the effects of OMNI in patients with mild-to-moderate open-angle glaucoma as a standalone procedure and in combination with cataract extraction. This study found an IOP reduction of approximately 35% and reduction of approximately 2 medications compared with preoperative baseline at 12 months. Hyphema was the most common complication [29].

Both Visco 360 and Omni can be performed for the treatment of open-angle glaucoma and ocular hypertension. They can be performed in combination with cataract surgery or as standalone.

The next 2 devices that are discussed work by forming a subconjunctival bleb to divert aqueous and lower IOP. These techniques can be used in cases of more advanced disease contrary to the devices that target the trabecular outflow and the Schlemm canal.

XEN gel stent

The XEN Gel stent (Allergan, an AbbVie company, Irvine, CA) received FDA approval in 2016 as a subconjunctival stent allowing aqueous to flow from the anterior chamber to the subconjunctival space. The device is a 6-mm hydrophilic tube with an inner tube ostium of 45 μm (most commonly used size). The material is biocompatible and in contrast to the silicone material used in tube shunts, is thought to induce less of an inflammatory reaction, thus contributing to less scarring. The tube channels through sclera, allowing for controlled flow of aqueous from the anterior chamber to the subconjunctival space. The original FDA trial for the XEN described an Ab interno approach, but it has become commonplace for the Xen to be placed both Ab interno and Ab externo depending on surgeon preference and patient selection. Some noted complications with both approaches are hypotony, choroidal effusion, and loss of Snellen visual acuity. It has been reported that the Ab externo approach has similar safety and efficacy to Ab interno approach [30].

Preserflo

The PRESERFLO Microshunt (Santen Inc., Miami, FL) is a subconjunctival MIGS device that is awaiting FDA approval. It was previously known as the InnFocus MicroShunt. The device is 8.5 mm in length with a 79-μm lumen. It is composed of an inert and biocompatible material. It is designed to be placed from an Ab externo approach and is used in conjunction with 0.4 mg/mL of Mitomycin-C. The procedure involves making a 6- to 8-mm conjunctival peritomy to form a fornix-based subconjunctival and tenon's flap in the superotemporal quadrant. Mitomycin-C then is injected underneath the flap for approximately 3 minutes and washed out. Then, 3 mm posterior to the limbus, a triangular scleral pocket is made. A 25 to 27g needle then is used to transect the sclera in this area to enter the anterior chamber. Forceps then are used to insert the shunt into the anterior chamber. The fins of the shunt are tucked into the scleral pocket. The distal end is observed for droplet formation. The conjunctiva and tenons are closed [31].

A recent single-center, nonrandomized, single-armed interventional clinical study evaluated the safety and efficacy of the device in patients with POAG up to 5 years. Subjects achieved a mean IOP reduction of 46.7% from baseline and 61.1% of subjects were medication-free. Adverse events associated with PRESERFLO Microshunt placement were similar to that of prior 3-year data and included device to iris touch, transient hypotony, flat anterior chamber, hyphema, and bleb-related complications. No cases of chronic hypotony or endophthalmitis were noted [31].

Summary

MIGS has allowed for a renaissance in glaucoma management. A wide range of techniques and devices give the glaucoma surgeon a diverse armamentarium to deal with this complex and often recalcitrant disease process. The paradigm of glaucoma treatment is prevention, as we are all too familiar with its irreversible and blinding effects. Delaying the need for medications helps with delaying glaucoma-disease progression. Adherence to therapy is a known issue for many patients and accelerates optic nerve damage. Patient quality of life can be adversely affected by medications, which can place a large cost burden and often result in ocular surface irritation. Offering MIGS to patients earlier in their disease course can lower their medication burden and allow eye surgeons to get ahead of disease progression.

In the past, the necessity of MIGS in combination with cataract surgery has been called into question, but data from randomized clinical trials have continued to support the use of MIGS in combination with cataract surgery, showing significant decreases in IOP that are sustained.

Traditional glaucoma surgeries require very close postoperative management, are more prone to severe adverse outcomes, and require longer operative times. These features limit their use for many comprehensive ophthalmologists. MIGS has many benefits for surgeons and patients alike. Techniques are relatively straightforward, allowing both comprehensive ophthalmologists and glaucoma specialists to offer surgical intervention to more patients. Outcomes are safe and effective, surgical times are relatively short, and patients often have immediate improvements in IOP in the early postoperative period in addition to similar visual acuity outcomes when combined with cataract surgery.

With the recall of certain MIGS devices, such as the Cypass Micro-stent, due to accelerated endothelial cell loss, evaluating the safety of other MIGS devices is an important goal for the glaucoma community. Thankfully, no other commercially available MIGS devices have been shown to contribute to accelerated endothelial cell loss compared with cataract surgery alone. Accelerated endothelial cell loss has been associated with tube shunts and trabeculectomies in prior studies [32,33].

Current available research and data on the various available MIGS techniques and devices argues for their safety, effectiveness, and role in the management of glaucoma. Further investigational studies, specifically randomized clinical trials, are needed to further substantiate the safety

and efficacy of various MIGS. Long-term data is needed to assess efficacy and safety over time.

It is an exciting time to be a glaucoma surgeon. MIGS has filled a gap in glaucoma care, and with advances in techniques and devices, we have hope that our ability to care for patients with glaucoma will only improve in the future.

Clinics care points

- MIGS allows for surgical diversification in the care of patients with glaucoma.
- Angle-based surgery is a relatively newer surgical technique with distinct technical challenges. Given the differences among MIGS techniques, each can present a unique surgical challenge and learning curve.
- The wide array of MIGS devices and approaches can lead to confusion regarding appropriate surgical management of glaucoma.
- With appropriate research, preparation, and selection, MIGS can be a safe and effective approach to the surgical management of glaucoma, saving patients from more invasive surgeries, which are well known for short-term and long-term complications.

Disclosure
The authors have nothing to disclose.

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Vitreoretinal Disease

OUTLINE

Artificial Intelligence in Retina

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Artificial intelligence; Machine learning; Retina; Diabetic retinopathy; Age-related macular degeneration

Key points

- Artificial intelligence (AI) is the notion that a machine can mimic human cognitive function.
- Machine learning is a subset within AI that uses artificial neural networks to mimic human learning and adaptation.
- Deep learning is a subset of machine learning and refers to an increase in the number of artificial networks, also called “hidden layers,” used in the algorithm.
- The black box phenomenon is the concept that hidden layers are complex and convoluted, which may lead to a lack of medical explanation for how these algorithms arrive at their conclusions.
- AI algorithms are assessed using area under the receiver operator curve, sensitivity, and specificity.
- AI algorithms require large image databanks to train.
- Multiple deep learning algorithms have been developed to detect diabetic retinopathy, and many have shown sensitivities and specificities of greater than 90%, some perform the same as or better than retinal specialists.
- AI algorithms have been developed to detect and prognosticate age-related macular degeneration with similar performance to specialists.

Background and introduction

A report from the Health Resources and Service Administration in 2016 suggested that by 2025, across all surgical subspecialties, there will be an ophthalmologist shortage in all regions of the United States [1]. It is no wonder that creative solutions are being investigated to address this shortage. One such solution is the utilization of artificial intelligence (AI) to assist physicians in diagnosing, monitoring, and predicting the progression of certain diseases. Coronavirus disease 2019 and its requirement of social distancing have only furthered the development and usage of AI in ophthalmology.

One of the key tenets of modern medical education is pattern recognition. Recognizing the triad of epiphora, photophobia, and blepharospasm in an infant aides in making the diagnosis of congenital glaucoma. In the field of retina, recognizing that a hypertensive patient who has numerous dot blot hemorrhages confined to a single quadrant or hemisphere leads to the diagnosis of branch of hemispheric vein occlusion. Pattern recognition is critical in medicine to establishing a differential diagnosis. Recognizing patterns also is a cornerstone of computer science, so it is natural that attempts have been made to use computer algorithms to address problems encountered in the medical field.

Technology and medicine are becoming increasingly intertwined. Decades ago, there was no widespread usage of electronic medical records. Research and medical texts were only accessible in physical format. In contrast, entire medical reference guides like UpToDate and most, if not all, medical journals can be accessed anywhere. Modern medicine relies heavily on these technologies not only because of convenience but also due to the increasing burden of patient care. Utilization of risk calculators that aide in medical decision making has become pervasive in patient care.

In software engineering, writing code that predicts the probability of pulmonary embolism or calculating the likelihood of a temporary intravenous vena cava filter becoming permanent is trivial. These codes use static, well-established formulas to make their calculations. In contrast, AI is the concept that a computer or machine can mimic human cognitive function. These kinds of code are more complex and the variables contained within them may not be static. Machine learning, a subset of AI, uses artificial “neural networks” to learn and adapt to specific scenarios (Fig. 1). Deep learning is a subset of machine learning that adds even more

layers of complexity in the neural network, where deep refers to additional layers of “neurons” [2]. These complex algorithms can be used to mimic human pattern recognition and become a powerful tool for patient care.

Overview of artificial intelligence

With the growing number of publications on AI, machine learning, and deep learning in medicine, it is important to have some fundamental idea of how AI functions.

One popular example of AI is IBM's Deep Blue, a chess software developed in the 1990s with the intent of defeating Garry Kasparov, the chess world champion at the time. To better understand AI, we can postulate a thought experiment, creating a deep learning algorithm to recognize if a picture contains a face and to predict the person's age. Suppose the inputs are the individual pixels of the picture. These inputs are then passed into a "hidden layer." The purpose of this hidden layer is to assign weights to the various pixels. These weights can be assigned randomly initially, but as our AI learns which features are important, it will automatically be adjusted by our software. In deep learning, there may be multiple levels of "hidden layers" (see Fig. 1), and the function of these hidden layers is convoluted and may be difficult to interpret [3].

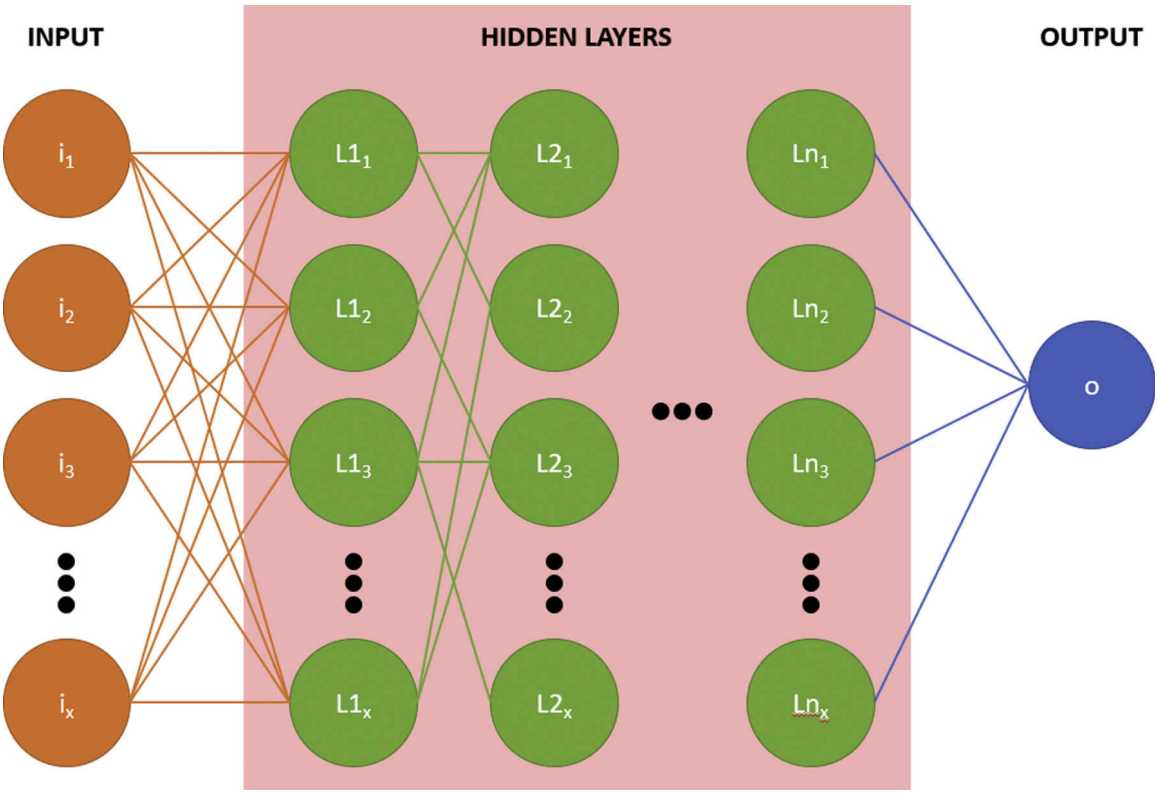

FIG. 1 Example of an artificial neural network that contains an input layer. The inputs are then passed to the "hidden layer," which are used to compute the output.
(Created by M. Trinh, MD.)

For the purpose of this example, let us assume that the hidden layers are able to recognize if the image has eyes, nose, mouth, or freckles. Then we can use the wrinkles around the eyes and forehead to estimate age. The next step would be to assign appropriate weights to these features. To train our AI, we will show it tens of thousands of pictures, some of which will be of faces and the associated age, others will be of non-faces. The goal of this dataset is to teach our algorithm when it was correct and when it was incorrect. It will then adjust its weights for each of the features and continue iterating through the training data set until it has guessed correctly on all images. This step is critical in distinguishing AI from a simple calculator. AI, specifically machine learning and deep learning algorithms, will change and adapt with each iteration, making it "smarter" every time, whereas a calculator is built on static variables that do not change unless the programmer modifies them manually. After optimizing its parameters, we can now use this algorithm on new pictures to see how well our machine performs.

For simplicity, we assumed the function of the hidden layers was to identify facial features such as having eyes, a mouth, and a nose. But in reality, the hidden layers of complex deep learning systems may not be easily understood or explained [4,5]. More importantly, deep learning algorithms use features abstracted from the raw inputs that are not hard-coded into the software. They are able to discern which features within the raw data are important to reaching the correct conclusion. These features may not always have a correlated anatomic significance. This process of automated feature abstraction is advantageous when coding for complex data, as it minimizes the reliance on hard-coded features and gives the algorithm more flexibility for feature detection.

Automated feature abstraction and weight adjustment function used by deep learning algorithms enable it to manipulate the inputs in complex ways. However, AI in general is primarily limited to its designed task at hand. For instance, if we used the deep learning algorithm we created to instead determine if the image is of a human or of an animal, our system would fail, as examples of this were not provided during training. Although we describe these systems as smart and adaptive, actually they are only proficient at very specific tasks.

Evaluating deep learning algorithms

To understand how well a specific algorithm functions, we must review how these algorithms are evaluated.

AI is evaluated using the same metrics as other diagnostic tools and calculators, such as the systemic inflammatory response syndrome (SIRS) criteria for sepsis [6]. These measures include evaluating the AI model's area under the receiver operator curve (AUC), plus using sensitivity, and specificity, same as if a human were doing the calculations. For example, the SIRS criteria uses temperature, heart rate, respiratory rate, and white blood cell count to determine if a patient has overwhelming systemic inflammation. SIRS is commonly used in the emergency department to determine if a patient is critically ill, usually from an infectious etiology. However, if a person were to have their heart rate and respiratory rate checked after vigorous activity, they would also meet SIRS criteria for inflammation but clearly the likelihood of this person being critically ill is very low. This is an example of a diagnostic tool that has high sensitivity but low specificity. If a diagnostic tool is highly sensitive, a negative test indicates a low chance of having the disease [7]. If a tool is highly specific, a positive test indicates high likelihood of having the disease [7]. Sensitivity and specificity are inversely related and are characteristics of the diagnostic tool. For instance, if we set the thresholds for parameters used by the SIRS criteria to be much higher, then we will have a much higher specificity for critically ill patients, but the sensitivity will be much lower.

Another metric used to evaluate diagnostic tools is the AUC. The AUC also is a characteristic of the diagnostic tool and is reported from 0 to 1. An AUC value of 1 means the device is capable of perfectly distinguishing between disease and no disease; there are no false positives or false negatives. An AUC of 0 means the device has actually reversed the disease and no disease outputs, meaning the device would misclassify all patients with disease as without disease and vice versa. An AUC at 0.5 means there is complete overlap between disease and no disease. This means the device will be unable to distinguish between disease versus no disease and has a 50% false positive and false negative rate [7]. The goal of any diagnostic tool is to have its AUC as close to 1 as possible. It is important to keep these metrics in mind as we delve into the discussion of AI in retina.

Diabetic retinopathy

It is projected that by 2045, more than 600 million people worldwide will have diabetes and approximately 40% to 45% of those will have diabetic retinopathy [8]. Approximately 75% of those with diabetic retinopathy live in underdeveloped countries with limited access to health care professionals [9]. In the United States, the prevalence of diabetic retinopathy among patients with diabetes is approximately 28% [10]. Because severe diabetic retinopathy can lead to blindness, close monitoring is required. Current guidelines from the American Academy of Ophthalmology recommend fundoscopic examination every 2 to 4 months [11]. The growing number of patients who require this frequency of screening for disease progression encompasses a large portion of the workload for ophthalmic care providers.

With a growing population, the utilization of AI to decrease physician workload is a very attractive approach to addressing both increasing physician workload and physician shortages. Multiple deep learning algorithms have been developed to address screening of diabetic disease.

Each of these algorithms functions differently, but their training approach is similar. Gulshan and colleagues [10] and Gargeya and Leng [9] used images from the EyePACS database (Eye-PACS LLC, Berkeley, CA), which consists of retinal photographs from a heterogeneous group of patients with varying stages of diabetic disease [9,10]. This dataset was graded by ophthalmologists; most were in practice, some were trainees. Ting and colleagues [12] used training data from the Singapore National Diabetic Retinopathy Screen Program (SIDRP) obtained between 2010 and 2013. This data set was graded by nonmedical professionals with years of training. For validation, Gulshan and colleagues [10] used a total of 10,000 images taken from both EyePACS and Messidor-2 datasets. Messidor-2 is a similar, but smaller, dataset to EyePACS. Ting and colleagues [12] used more than 100,000 images from the SIDRP from 2014 to 2015 for their validation analysis. Gargeya and Leng [9] used images from Messidor-2 and E-Ophtha for external validation. The same graders who were used for the training set(s) were used in the validation set(s). In all studies, any images used for validation did not overlap with images used for training.

The focus of the algorithm of Gulshan and colleagues [10] was to detect referrable diabetic retinopathy defined as moderate nonproliferative diabetic retinopathy or worse, and/or presence of macular edema. This algorithm had an AUC of 0.991 and 0.990 for the EyePACS and Messidor-2

datasets, respectively. At the point of highest sensitivity, for the EyePACS dataset, the algorithm had a sensitivity of 97.5% and specificity of 93.4%; for the Messidor-2 dataset, the sensitivity was 96.1% and specificity of 93.9%. At the point of highest specificity, for the EyePACS dataset, the algorithm had a sensitivity of 90.3% and specificity of 98.1%; for the Messidor-2 dataset, the sensitivity was 87.0% and specificity was 98.5%. These sensitivities and specificities were very comparable to the ophthalmologists who graded the training and validation sets. An important note: most of the investigators of this paper are affiliated with Google Inc (Mountain View, CA).

The primary outcome of the deep learning algorithm of Ting and colleagues [12] was if it performed better than the professional graders in detecting referable diabetic retinopathy and vision-threatening diabetic retinopathy. To determine the professional graders' sensitivity and specificity for detecting retinopathy, their results were compared with a retinal specialist. For referable diabetic retinopathy, the AUC achieved by this algorithm was 0.936. The algorithm's sensitivity was 90.5% and the graders' sensitivity was 91.2%, there was no statistical difference detected between the two. The algorithm's specificity was 91.6% and the graders' specificity was 99.3%, this difference was statistically significant. For vision-threatening diabetic retinopathy, algorithm versus grader sensitivity was 100% versus 88.5%, respectively, and for specificity it was 91.1% versus 99.6%, respectively. Both of these were statistically significant. This deep learning algorithm was more sensitive in picking up vision-threatening disease but had worse specificity compared with the professional graders.

Approaching the issue from a different perspective, Gargeya and Leng's [9] algorithm was designed to analyze and classify if a fundus photograph had evidence of any stage of diabetic disease. This algorithm achieved a 93% sensitivity and 87% specificity with an AUC of 0.94 when applied to the Messidor-2 dataset to detect any stage of diabetic retinopathy. When used for the E-Ophtha database (a small set of retinal photos from the French Research Agency), the algorithm achieved an AUC of 0.83, a sensitivity and specificity of 74% and 80%, respectively. However, when applying this algorithm to detect only mild diabetic retinopathy, the AUC dropped to 0.83, sensitivity and specificity decreased to 74% and 80%, respectively.

Existing algorithms directed at detecting diabetic disease have very promising results. These algorithms achieve a high level of sensitivity and

specificity, levels comparable to that of retina specialists. These results are very encouraging and, in the future, we may see these algorithms deployed in primary care clinics, not only to ease the burden on ophthalmic providers, but also to increase the screening of diabetic disease. This may be incorporated into an already existing photographic retinal screening program, to replace or enhance provider readings [13]. In addition, it may be used specifically by ophthalmologists, in either clinical or research settings.

Age-related macular degeneration

Classically, age-related macular degeneration (AMD) is categorized into a dry or wet form, the latter being associated with choroidal neovascularization [14]. AMD is a leading cause of vision loss in developed countries. In the United States, advanced AMD affects 1.75 to 3 million people [4,14]. With the growing aging population and anticipated increasing prevalence of AMD, it is no surprise that research into using AI for predicting the progression of AMD to assist with clinical decision making is gaining more traction.

Hwang and colleagues [15] developed an AI composed of 3 deep learning algorithms aimed at detecting and aiding in clinical decision making for AMD. This group collected a total of 35,900 optical coherence tomography (OCT) images and trained their AI on (287,200) 80% of these OCT images. The remaining 20% were used as an internal validation dataset. For verification, OCT images from 100 patients with AMD and 100 non-AMD patients (3872 total OCT images) was used. This AI system was able to discern between normal, dry AMD, inactive wet AMD, and active wet AMD with sensitivities and specificities of more than 90%. This rate was found to be comparable to retina specialists at Hwang and colleagues' institution.

Schmidt-Erfurth and colleagues [16] used a machine learning algorithm to develop a model that predicts anticipated 12-month best-corrected visual acuity. This group used biomarkers from the OCT images, such as presence of intraretinal fluid, subretinal fluid, and pigment epithelial detachment, in addition to known baseline, 1-, 2-, and 3-month visual acuity. The training data set used contained approximately 760 OCT images and the verification set contained 2456 OCT images. When using only the OCT images for prediction, the algorithm achieved an R^2 value of 0.21. This algorithm identified that the presence of intraretinal fluid in the central 3-mm area as being the most important prognostic factor. A low R^2 value indicates the model has poor correlation between prediction and truth. When baseline, 1-, 2-, and 3-month visual acuity were all taken into account, the model achieved an R^2 value of 0.71 and was able to more accurately predict 12-month best-corrected visual acuity. The factor more important in accurately predicting 12-month best-corrected visual acuity was the visual acuity at 3 months. The findings from Schmidt-Erfurth and colleagues [16] are particularly interesting, as they demonstrated that the

physical changes evident on OCT findings may not the be the best prognostic indicator at our disposal.

Burlina and colleagues [4] developed an algorithm using fundus photos to detect referrable AMD, defined as intermediate AMD or worse. Their reported algorithm had an AUC between 0.94 and 0.96 with an accuracy of greater than 90%. The sensitivity and specificity of this device was similar compared with a physician who graded the same set of images.

The success of these machine learning algorithms for the detection and prognostication of AMD suggests there may be a role for these devices in future ophthalmic care. With performances similar to physicians, these AI algorithms may be part of the solution for the anticipated ophthalmologist shortage. Similar to the case of diabetic retinopathy, if these algorithms are deployed in primary care offices, it could lead to improved screening and early diagnosis and treatment of AMD.

Future

Results of these disease detection and grading machine learning algorithms when applied to thousands of retina photographs and OCT images show very promising results. They have very high AUC, specificity, and sensitivity. These algorithms typically perform as well as, or better than, ophthalmologists. Despite these results, AI has yet to be fully adopted into the field of ophthalmology.

Although it is easy to conceive the idea for how we believe AI should function, after iterations of parameter optimization and feature abstraction, the actual innerworkings of the algorithm may be surprising. This leads to the concept of the "black box" in deep learning, that is, the functionality of the hidden neural networks between the input and output is largely unknown to the physician and patient. The features that a deep learning algorithm extracts and weighs heavily may not be an expected one. For instance, a deep learning algorithm by Keet and colleagues highlighted the optic disc and areas adjacent to retinal vessels as important in 3% of their detected retinopathy cases [5]. However, it is unclear the medical correlation to this abstracted feature or if this is an error in the abstraction. Another prime example of this phenomenon is a deep learning model developed by Google to predict cardiovascular risk using fundus photographs. This deep learning algorithm was able to accurately predict sex based on retinal vasculature, optic disc, and macula [17]. It is unclear how these features should be interpreted, whether they should be viewed as machine error or novel features that need further study. In addition, this "black box" phenomenon raises doubts on how reliant physicians should be on technologies in light of the lack of medical explanation for how these algorithms arrive at their, albeit accurate, conclusions. From a medicolegal standpoint, it also raises the question of whether liability lies with the physician or machine development company or both.

Although we only discussed diabetic retinopathy and AMD, and using AI to analyze fundus photography and OCT imaging, there have been forays into detecting retinal vein occlusions using OCT angiography and using retinal photography for retinopathy of prematurity (ROP) screening [18,19]. In addition, attempts have been made at using machine learning for detecting glaucoma [20]. Use of AI for ophthalmology is expanding rapidly. Although these algorithms are all being developed as standalone systems, perhaps one day they can be combined into an all-in-one unit. It

is likely that such an algorithm would require hundreds of thousands of photographs of disease versus no disease to train itself.

In the examples we discussed, most algorithms are trained on datasets nearing 100,000 images. There exist few large databases for training, which is one limitation of AI. In addition, these databases typically focus on specific disease such as diabetic retinopathy or AMD. To use an AI to screen for rare diseases may not be feasible given the magnitude of images needed to train. Furthermore, to train these algorithms, they still require a reference to train against. Meaning, an established "ground truth" must be known. Most studies choose to use a retina specialist who has manually graded several thousand images as the "ground truth." Obtaining a robust training dataset can be challenging in the field of AI.

Although not discussed in detail here, deep learning algorithms for detecting ROP have been developed. One of the earliest deep learning algorithms developed was capable of detecting the presence of a ridge in the periphery [18,21]. Other algorithms, which are able to distinguish retinopathy versus no retinopathy, were reported to have very high sensitivity and specificity [21], much like algorithms discussed in detail previously in this article. It is unclear if AI for the recognition of ROP will be deployed into clinical practice in the future, especially when considering the heavy medicolegal burden. However, we remain hopeful that one day this technology can at least be used to aide ophthalmologists in the detection of ROP.

The field of machine learning in medicine is still in its infancy but is undergoing incredible growth. There are still major hurdles and questions that need to be answered before there will be widespread adoption of AI technology for the detection of common retinal pathology. However, research into these technologies has yielded very promising results.

Summary

Deep learning algorithms have been growing in popularity in retina research. Retina lends itself to this by virtue of its reliance on objective photographs of the patient. The ability to consistently detect and grade diseases such as diabetic retinopathy and AMD is very attractive to addressing the anticipated physician shortage in the United States. Deep learning algorithms require large data sets to train, but their performance in detecting disease is often comparable to specialists performing the same task. Although we only detail the discussion of machine learning applied to diabetic retinopathy and AMD, forays have been made into pediatric ophthalmology and glaucoma as well. Despite these promising results, questions have been raised regarding the medicolegal implications of deploying this technology. In addition, deep learning algorithms use convoluted neural networks that often are difficult to interpret or may lack medical explanation, leading to the "black box" phenomena. Gaining a framework of how these algorithms are built is paramount because it is likely only a matter of time until deep learning algorithms become commonplace in the practice of medicine.

Clinics care points

- Deep learning algorithms designed to identify diabetic retinopathy or AMD have achieved sensitivities and specificities comparable to their retina specialist counterparts.
- Deep learning algorithms require large databanks for training.
- Deep learning algorithms are not yet in clinical practice, although promising early results suggests that in the future they may become routinely implemented.

Disclosure
The authors have no relevant financial disclosures.

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Retina in the Age of COVID-19

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Keywords

COVID-19; Pandemic; Social distancing; Personal protective equipment; Screening protocols; Urgent appointments; Disposable equipment

Key points

- The COVID-19 pandemic required improved protocols for patient safety and preventing exposure to potential vectors.
- In order to continue to provide care, patients had to be triaged, as restrictions required fewer patients to be seen in different stages of the pandemic.
- Disposable equipment, frequent surface cleaning, breath shields, and personal protective equipment were key to protect staff and patients.
- Screening patients in the office before entry according to symptoms prevented additional risk of exposure.
- Procedures and surgeries continued based on urgency, with appropriate steps taken for safety.

Background

The novel coronavirus SARS-CoV-2 (COVID-19) pandemic presented numerous challenges for ophthalmology practices with regard to safely operating and providing care to patients, especially those at risk of vision loss. These obstacles were significant especially for retina practices in which patients may be due for intravitreal injections or need urgent workup for vision loss. Similarly, many glaucoma patients have treatment plans with time constraints preventing extended delays in care. Numerous adaptations were implemented, including the use of personal protective equipment (PPE), rescheduling strategies, and precautionary measures to allow for safely performing procedures both in the office and operating room.

Introduction

Patients with sight-threatening disease faced the risk of vision loss because of their disease, which was then compounded by the risks posed by exposure to COVID-19 when seeking care. To curb the spread of illness, local, regional, and federal governments placed restrictions that also limited the ability of clinics to provide care for these patients. In order to adapt and safely protect patients from the risks of the virus while adhering to rapidly changing regulations, providers adopted many new practices. These included using improved infection control principles, triaging and screening patients to better settings, adjusting clinic patient flow to decrease exposure, and taking additional precautions with more efficient protocols for operating room cases. Although the recommended precautions and practices described later in this article changed the typical office flow and protocol for staff and physicians, they allowed crucial medical care to continue during an unprecedented crisis.

General cleaning and hygiene

All staff should be educated on COVID-19 precautions including appropriate use of PPE. Masks should be worn at all times by both staff and patients. Staff should clean hands often, including immediately after removing gloves and after contact with a patient by washing hands with soap and water for 20 seconds. If soap and water are not available and hands are not visibly dirty, an alcohol-based hand sanitizer may be used. A new pair of gloves should be worn for each patient encounter. Cleaning and disinfecting should be done before each patient being seen in an examination room and before the use of any imaging or testing [1]. The Centers for Disease Control and Prevention (CDC) recommends using bleach containing 5.25% to 8.25% sodium hypochlorite [1]. Alcohol solutions with at least 70% alcohol also may be used [1].

All slit lamps, imaging or testing equipment, and other patient contact surfaces including examination chairs should be cleaned and disinfected before each use. When cleaning any lenses, including those of imaging equipment, indirect lenses, or laser lenses, the manufacturer's manual should be consulted before cleaning to avoid damage to the lens surface or coating [2]. Alternatively, clear cling wrap can be used to surround the lenses, and then wiped down between patients and changed when soiled [3]. All slit lamps and imaging modalities should be equipped with commercial barriers or breath shields in order to maximize protection for the patient and physician [4,5]. Disposal covers or equipment should be used where appropriate, including tonometers, ultrasound probes, and applanator tips [2]. Care should be taken to avoid contaminating eye drop bottles during each encounter by avoiding direct contact with patients.

Personal protective equipment

Appropriate PPE is a necessity in order to provide care during a pandemic such as COVID-19. Although 95% of vitreoretinal fellows in one study believed that surgical masks were available, only 65% of those fellows believed they had an adequate supply of N-95 respirators available, and for 75% of those with respirators, a reuse policy was in place [6]. Extended use and reuse policies, although not recommended if avoidable, can be implemented when N-95 masks are in short supply [7]. Prior studies demonstrated that extended use of N-95 respirators can provide adequate protection for several hours before needing to be changed [8]. Appropriate measures must be taken to prevent the mask from becoming contaminated, such as wearing a surgical mask over the N-95 respirator and proper donning and doffing performed [9]. A face shield is also recommended to be used during close encounters with patients, which can even be used during indirect ophthalmoscopy examination [3]. Commercially manufactured breath shields also are recommended for slit lamp examinations [5]. Although both the patient and physician should be wearing masks, during the examination the patients' mask may slip, and because of the close proximity, a breath shield can protect from unexpected sneezing or coughing.

Pandemic restrictions

Under the guidance of local, state, and federal authorities, the COVID-19 required varying levels of restriction in order to safely protect the public and control disease outbreaks and hospital burden. When restrictions required lockdown of all nonessential businesses, stay-at-home orders, and other significant restrictions, disease activity was typically high or at risk of increasing, and these situations are described here as an “active pandemic.” As spread and incidence rates decrease, restrictions may slowly loosen and allow businesses to open in stages and social activities to resume gradually. As the course of the pandemic changes fluidly, so too do the restrictions on outpatient care providers fluctuate. Thus, rules and regulation for office visits of patients will differ between these disease activity levels, and the precautions under the most significant restrictions are described first.

Care in an active pandemic

Scheduling visits

Office visits should be limited to only urgent matters when under lockdown or regional stay-at-home orders. All nonurgent office appointments should be canceled or rescheduled into telehealth visits. Although there is a significant amount of pressure to use telehealth measures both during a pandemic and in the future, ophthalmology is poorly suited at present to use telehealth to any reasonable extent. Patients should be notified of the cancellations in a timely manner to avoid any unnecessary travel and exposure. All patients should be called on an individual basis to confirm knowledge of the closure and need to reschedule when it is safe, and the office is reopened. At this time, an over-the-phone symptom screening and chart review should be conducted by a physician to ensure that red flag symptoms are not overlooked. In addition, patients should be given appropriate instructions regarding signs and symptoms they need to be aware of that would necessitate a more urgent appointment or intervention. Finally, the appropriate information on how to contact the office in the event of any changes, questions, or concerns that the patients may have regarding their condition, appointments, or office functioning status should be communicated clearly.

Note that although the authors are limiting the discussion to retina practices, these guidelines can be extrapolated to other ophthalmic specialties, using their published guidelines.

Patients who are considered urgent or emergent and need to be seen during an active pandemic will need to be treated appropriately in order to ensure safety for the patient as well as the staff. Scheduling patients will need to be based on an appropriate risk assessment scale that takes into consideration patient characteristics, procedure factors, and disease factors. Patient characteristics consider the ability of a patient to attend the appointment and have appropriate follow-up. Procedural factors in a retina practice can be split up into procedures that can be performed in the office and

those that require an operating room. Operating room procedures include pars plana vitrectomy, scleral buckle, membrane peeling, enucleation, and brachytherapy for example. Office procedures include laser therapy, intravitreal injection, pneumatic retinopexy, and cryotherapy [10]. Disease factors play a major role in the stratification process for patients in a retina practice.

Patients can be divided into urgent, semiurgent, and delayed appointments [3,11]. Note that other factors (social, age, comorbidities, monocular status) must be taken into account, with each patient being considered individually.

Urgent visits include the following:

- Symptoms such as sudden painful or painless vision loss or metamorphopsia, new onset, flashes, and floaters
- New cases of retinoblastoma, other ocular tumors, or retinopathy of prematurity
- Conditions needing urgent surgery, including open globes, recent rhegmatogenous, tractional or combined retinal detachments, endophthalmitis, retained lens material with secondary glaucoma, and bilateral vitreous hemorrhage
- Any nonurgent condition in the functioning eye of a monocular patient
- Significant pain

Semiurgent appointments include the following:

- Patient receiving injections for macular degeneration, choroidal neovascularization, diabetic macular edema, retinal vein occlusion, or other retinal condition, especially if there is perceived vision loss
- Patients with ongoing laser therapy (pneumopexy)
- Patients operated on in the last 3 months who have silicone oil or gas
- A referred retina case by another ophthalmologist also may be considered semiurgent

Delayed appointments include the following:

- Patients receiving injections with stable clinical status
- Routine follow-up for macular degeneration, diabetic retinopathy, and retinal vein occlusions
- Stable postretinal detachment surgery
- Inherited retinal dystrophies
- Medication-induced retinal screening

Appointments scheduled during a pandemic require strict adherence to appropriate guidelines to ensure the safety of patients and staff. Staff and medical doctors alike must be cognizant of the fear that patients have coming into an office or hospital setting and must be able to reassure them as to the steps taken to assure their safety. Before the day of the visit, a travel history and symptom screen should be taken [6,12–14]. If the screening questions are negative, the patient may enter for the appointment according to the strict guidelines on distancing. Companions will be strongly discouraged in order to prevent spread of the virus. If a companion is necessary, only one companion may be allowed, undergoing the same testing and screening as the patient. The patient should be encouraged to wait in another location (home, car, outside, hospital, or medical center lobby) until there is room in the office to maintain social distancing. At that time the patient may be called in to the office for the appointment. At the door there should be another symptom screen and temperature test. All patients and companions would be required to wear a mask, and masks should be provided if the patient arrives without one. The patient should sit in a clearly marked, socially distanced location. When the office is ready for the patient to come in, they should be escorted to the appropriate room. If imaging is required, they should be brought to the appropriate imaging modalities at this time. It is important to maintain appropriate distancing, and no other patients should be in the halls or around the imaging locations. Some practices are using directionality (every hallway is one way) in order to decrease contact. After this is complete, they should be escorted to the room

where they will be examined by the physician. Patients should not leave the examination room from this point until they are finished. Although in some practices patients were shuffled from room to room for different aspects of the examination, such as vision testing, dilation, and examination, now, in order to limit the exposure of each patient and ease adherence to disinfecting protocols, the entire examination should take place in one room.

During the various parts of the examination, it is important that the nurse, technician, provider, and patient all wear the appropriate PPE for the given situation and that the surfaces are disinfected as described earlier. Use of the slit lamp only when medically necessary may be appropriate due to the close nature of the examination. If examination at the slit lamp would not change the management of the retinal disease, a 20D examination of the patient may be substituted. If required, a 78D or 60D lens examinations may be preferred to increase the working distance necessary for an examination at the slit lamp, decreasing exposure and helping prevent fogging of the lens from the patient's redirected exhalation from the mask. Although talking should be held to a minimum, appropriate discussion regarding patient care should be had at a comfortable distance where all the information can be understood clearly and safely. Masks should be worn through the entirety of the examination.

Precautions for procedures

When it is determined that a procedure is medically necessary, the appropriate safety protocols need to be followed to ensure safety of staff and patients. Although most of the procedure will be the same as any other procedure, there are certain aspects of the procedure that should be considered in light of COVID-19 and the necessary changes to practice.

Intravitreal injections

Because of their role in vision-threatening retinal disease and dosing interval, intravitreal injections have been one of the more common procedures done during an active pandemic. Appropriate anesthetic should be applied according to regular practice. Topical betadine should be applied in the usual manner. It is important to properly visualize the area of injection. If a practitioner finds that due to the face shield, he or she is unable to maintain proper visualization, the face shield should be removed before preparation for the injection. Alternatively, or if the practitioner needs glasses during the injection, it may be useful to tape the superior portion of the mask to the side of the face preventing exhaled breath from exiting the superior aspect of the mask and fogging the view. Similarly, the patient should have the superior portion of the mask taped as well. Although there has been much debate about the need for practitioners to wear masks during injections, during the COVID-19 era this a foregone necessity. Because patients must wear masks as well, there is a theoretic increased risk in infection due to their own redirected airflow superiorly from the mask. Given the concern, it, therefore, is recommended to tape the superior portion of the mask to the side of the face during the procedure to limit this exposure. Although masks will be worn, no talking during the injection is advised to avoid any possible increased risk of infection as well as movement from the patient. The rest of the procedure should be done in the usual manner.

Several international studies prioritized patients for intravitreal injections and split patients into 3 priorities [3,11,15]. Following is a summarization of these lists:

High priority—0 to 7 days from their original appointment or from referral.

- Monocular patients with macular disease
- Wet macular degeneration, choroidal neovascularization, and active proliferative diabetic retinopathy with recent vitreous hemorrhage and no prior laser
- New-onset central retinal vein occlusion
- Retinopathy of prematurity

- Any patient from moderate priority that was already deferred 10 to 15 days

Moderate priority—10 to 15 days from their original appointment or from referral.

- Other macular neovascularization patients such as those with proliferative diabetic retinopathy, retinal vein occlusion, and central serous chorioretinopathy with worsening vision
- Severe nonproliferative diabetic retinopathy, no prior laser with macular edema and worsening vision
- Any patient from low priority that was already deferred 30 to 40 days

Low priority—30 to 40 days from their original appointment or from referral.

- Diabetic macular edema, retinal vein occlusions, and choroidal neovascularization that are stable since their last injection

When deciding on modes of treatment, due to the nature of unknown follow-up time in the event of an active pandemic, it is recommended to attempt to use modalities that will require less frequent follow-up time when appropriate, for example, using photodynamic therapy for chronic central serous chorioretinopathy with macular neovascularization as well as using intravitreal corticosteroids or using treat and extend protocols with antivascular endothelial growth factor agents for eligible patients [16].

Precautions for laser procedures

Laser procedures pose a unique procedural problem that require prolonged time of exposure at a very close distance. Appropriate protocols should be maintained when such procedures are necessary to prevent vision loss. Both patient and physician should wear N-95

respirators if possible due to the close proximity. As stated before, breath shields and face shields should also be used during this procedure as long as it does not interfere with patient care and effectiveness of the procedure. When possible, indirect laser should be used to increase the patient to physician distance. If not possible, contact-lens laser therapy can be carried out with adjustments to decrease exposure and risk. Multispot therapy should be preferred to decrease procedural time. The risk and benefit of splitting the treatment to minimize exposure time should be weighed against the possible difficulty with follow-ups. If the patient and provider can remain in the masks or respirators for an extended period of time, applying more treatment in one session to prevent the need for follow-up in the near future would be preferred. If, however, the burden of the masks for an extended period of time would be too difficult, the appropriate treatment should be done in part and finished at a later date. If the office does not have other emergent procedures waiting, they can take a break and finish in the same session. Although disposable lenses are preferable, if not available, lenses must be cleaned, following manufactures guidelines, with soap and water, or dipped in to 0.5% hypochlorite solution. One international society has recommended for the use of cling wrap surrounding the lenses during laser treatment without apparent decrease in effectiveness [3].

Scheduling follow-up visits

Careful consideration and planning of follow-up visits is required. When clinically possible, patients should have extended time between intravitreal injections either by treat and extend measures or by changing to intravitreal corticosteroid injections. Televisits may be facilitated through the use of video to assess symptoms, in addition to obtaining objective data with applications on computers or smart phones where patients can perform tests for visual acuity, color vision, amsler grid, and possibly even fundus photos to assess for retinal pathology [17].

Patients with positive screening or testing for COVID-19

If a patient has a positive screening for any of the Covid-19 symptoms or a positive test the appropriate guidelines should be in place to prevent any possibility of spread of the virus [18]. First, consider the medical necessity of the appointment if it can wait until symptoms resolve and the patient is out of the window of spreading the disease [13]. If this is possible, rescheduling of the appointment should be done and close follow-up with the patient should be had to make sure the condition is not deteriorating and sooner management is required [13,18]. Appropriate communication to the patient and documentation of discussions including risks, benefits, and alternatives is important when dealing with possible visually threatening conditions.

When the patient who screens or tests positive must be seen or undergo a procedure, the decision has to be made whether or not the patient can be cared for safely in the office setting, rather than a nearby hospital or medical facility that can accommodate a patient with positive illness [6]. In order to safely treat a patient with possible COVID-19, ideally a negative pressure room will prevent further exposure to other staff or patients [6]. If a practice has the ability to do this, an examination or procedure can be done safely in such a room. If possible, any equipment necessary, including laser equipment, should temporarily be moved into this room for the procedure. If not possible, there needs to be appropriate referral or arrangement with a local facility that has the capability of managing patients with COVID-19.

When the patient is in the appropriate setting, the physician can begin the encounter. As much that can be taken care of over the phone without entering the room should be done to minimize time of exposure, including any additional pieces of information regarding the condition; explaining the risks, benefits, and alternatives of the procedure; and obtaining consent for the procedure. When this is complete and the physician is ready for the

examination, he or she should enter the room in full PPE. In addition to transmission from aerosolized or contacted respiratory droplets, 24% of patients with moderate-to-severe disease have been shown to test positive for the virus in samples of their tears, presenting another concerning vector for the treating ophthalmologist [19]. These risk factors necessitate the use of full PPE including gloves, N-95 respirator and face shield, as well as full body impermeable gown for the physician. The patient should be wearing an N-95, with minimal talking during the examination to prevent transmission. The examination should otherwise be a normal examination without compromising the care of the patient including appropriate visualization as needed.

Care after immediate pandemic restrictions are lifted

During this time, it is important to recognize that although the office will be opened, adhering to strict protocol is important to ensure appropriate patient care without risking increasing spread of the disease. Scheduling appointments will not result in the same volume as pre-COVID-19 numbers, but routine visits will be welcome at this point in addition to the urgent emergent cases that will continue from during the time when the pandemic is active.

Continued screening and scheduling precautions

Patients should be kept updated regularly on the functioning status of the clinic, which includes the office hours, contact modalities, and any scheduling changes. Providers should use modalities such as letters, voice messages, e-mails, and social media to ensure the availability of important information regarding their eye care is being populated appropriately and reaching everyone it needs to. Patients should be able to contact the providing office if they have questions in regard to scheduling, walk in procedures, testing requirements before office visits, as well as questions about symptoms they are having and the request for medical care over the phone and the ability to set up appointments if deemed necessary. Providing physicians should take extra care with patients who have retinal disease to be aware of signs and symptoms that may indicate grave prognosis such as flashing lights, numerous new floaters, and loss of partial or complete vision in one or both eyes. As part of a retina practice, patients should be properly educated on these signs and symptoms that may indicate the need for prompt medical treatment.

Every patient will be given a COVID-19 symptom questionnaire either by telephone or email 2 days before the office visit. Anyone with a positive screen should be offered to reschedule for a later time

period when the symptoms resolve. If this is an urgent or emergent situation as described earlier, the same protocols should be followed as described earlier, and COVID-19 testing should be done before entering the office. If the screen is negative, there is less risk, and the COVID-19 test may be omitted.

Day of appointment precautions

The patient should arrive at the office and, if necessary, with a maximum of one companion. Patients and companions should be screened regarding symptoms [20]. As per the CDC symptoms such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea may represent infection [20]. Although transmission through ocular surface and tears has been shown to be low, especially in patients who are asymptomatic, owing to the nature of the eye examination, including symptoms of conjunctivitis would be recommended to be included in the screening questionnaire [19,21].

If the screening test is negative, it should be documented as such in the medical record. If the screening test is positive the decision needs to be made whether this is an urgent or nonurgent visit as described earlier. In either case the primary care provider of the patient should be contacted in order for the patient to obtain the appropriate testing. If this is a nonurgent matter, the appointment should be rescheduled for a later date. Regular reminders are encouraged with nonurgent patients in order to prevent being lost to follow-up when the symptoms have resolved. If the decision is made that the patient has an urgent matter that needs to be dealt with, an appropriate protocol needs to be in place to facilitate appropriate care of these patient as documented earlier.

Because of the prevalence of false-negative tests, patients with documented negative testing are not excluded from screening [22].

Patients who have negative screening and temperature tests should be given the option to wait outside the office until there is a room ready and should not be allowed in the waiting room until the

waiting room can fit the patients properly socially distanced. When they are ready to be seen, similar guidelines will follow as if there was a pandemic. Patients should have any necessary imaging done before entering the examination room. Once they are in the examination room, ideally they should remain there for the duration of the examination and or procedure. Having patients move in and out of examination rooms for several parts of the examination increases exposure from patient to patient and should be avoided. PPE should be worn by staff at all times, which includes a mask such as surgical 3-ply or cloth mask, gloves when handling instruments or touching patients, and a face shield or glasses. The examination should be done in the usual manner, taking care to be efficient, without compromising patient care or unnecessarily increasing exposure. Using techniques such as 20D anterior examination and minimizing close contact at the slit lamp when able would still be appropriate in this setting. At the end of the visit, the patient and any companion should leave the office. Follow-up visits will be scheduled over the phone to avoid increased exposure time in the office.

Performing elective surgery

Preoperative testing may be performed for patients with no history of the disease. When there is regional presence of the disease, every patient needs to undergo screening and testing for the disease [23]. If negative, a patient can undergo the procedure as normal with appropriate precautions in place.

If a patient tests positive the procedure should be postponed as follows.

Elective surgeries requiring anesthesia for patients with symptoms or positive test: all positive patients with nonurgent elective procedures should be rescheduled for when they are out of the isolation and COVID-19 precaution phase [24]. CDC recommends a symptoms-based approach when discontinuing isolation precautions [25]. Patients with mild-moderate disease should fulfill all 3 criteria: at least 10 days since symptoms first appeared, at least

24 hours since last fever without the use of fever-reducing medications, and any symptoms (eg, cough, shortness of breath) have improved. Patients with severe disease or who are immunocompromised may follow these guidelines as well, with the exception that up to 20 days should be considered since symptom onset to make sure the virus has cleared. Repeat testing can be considered in the setting of suspicion for persistent infection with the knowledge that the patient can test positive for a prolonged period of time after the virus has cleared. Patients who were asymptomatic with a positive COVID-19 test need to be symptom free for 10 days from their positive test. Recommended wait times from disease until surgical procedures are as follows [24]:

- Four weeks for an asymptomatic patient or recovery from only mild, nonrespiratory symptoms
- Six weeks for a symptomatic patient (eg, cough, dyspnea) who did not require hospitalization
- Eight to ten weeks for a symptomatic patient who is diabetic, immunocompromised, or hospitalized
- Twelve weeks for a patient who was admitted to an intensive care unit due to COVID-19 infection. This is based on various studies showing the effect of Covid-19 and other respiratory illness on the postoperative recovery period [26–30]. There is no role for repeat testing in these patients at this time, unless new symptoms arise and/or 90 days have passed since the last test.

Operating room precautions

If there is a need for general anesthesia, only staff who are required to be present in the room for the intubation and extubation should be present and wearing N-95 respirators, face shield, and gown to prevent spread of infection through aerosolization.

For monitored anesthesia care with conscious sedation, if supplies permit, it is still recommended for the surgeon to wear an N-95 respirator and patient to wear a surgical mask, due to the prolonged

exposure and close proximity of the surgeon to the respiratory system of the patient [2]. Air conditioning can still be used during operating room cases. Although negative pressure systems are recommended, if this is not possible a positive pressure system can still be used. If an exhaust system is used, air should be expelled only by a high-efficiency particulate air filter. Five percent povidone iodine should be used in preparation before the case, as it is viricidal and disinfects in 15 seconds. In order to maintain sterility, mask, face shields, and shoe covers should all be donned before gowning in the operating room. Goggles may be preferred when using a microscope, and they can be decontaminated and reused. N-95 respirators can be reused the same day as long as they are not soiled during a case or touched in between cases. Other surgical instruments should not be reused from one case to the next without sterilization to prevent infection spread. Proper draping with water tight seal is important especially around lower eyelid to prevent upward redirected airflow into the sterile field.

Summary

COVID-19 required numerous changes as earlier in order to safely provide care to patients. This particular pandemic represented a steep learning curve that resulted in many “lessons learned” that should continue to be used. By minimizing risk of transmission through good infection control principles, patients and providers are able to safely continue operations. Frequent hand hygiene, disposable lens, office social distancing, and contact surface disinfection should continue to protect patients from other viral pathogens. Although masks may no longer be required at some point in the future, ophthalmology providers may choose to continue their use given the close proximity required for examination. Efficient operating room use and triaging of patients and procedures for clinic visits may have provided an improved flow to the practice, with less impact on nursing or other staff after the initial driving force of decreasing exposure necessitated by the COVID-19 pandemic has passed. These lessons and the experience gained, if carried forward and not disregarded, should help protect and allow safe measures to be implemented more quickly and efficiently to provide excellent, sight-saving care for those with vision-threatening disease when the next eventual crisis presents itself.

Clinics care points

- In the post-COVID-19 era, patient and health care worker safety is of utmost importance while maintaining appropriate clinical care.
- In addition to regular handwashing and use of PPE, all equipment and patient rooms should be wiped down and cleaned between patient exposures.
- Providing up-to-date information on guidelines for patients to schedule appointments and triaging visits to urgent, semiurgent, and delayed appointments can help manage patient flow through the office.
- In-office visits, when appropriate, should be done with proper screening and care taken in the office to minimize patient exposure.
- Reducing frequency of visits using methods of treatment, whether medical or surgical, that can extend follow-up time should be considered.
- Because society relieves restrictions, it is important to maintain safe practices and screening to minimize exposure.
- When permitted elective surgeries should be conducted with appropriate screening and safety precautions.
- Emergent procedures can be conducted with COVID-positive patients by following safe procedural protocol.

Disclosure
The authors have nothing to disclose.

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Diagnostic and Treatment Update on Sickle Cell Retinopathy

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Keywords

Sickle cell disease; Proliferative retinopathy; Imaging; Laser photocoagulation; Anti-VEGF; Management; Surgery

Key points

- Sickle cell disease has a wide variety of ocular manifestations, of which vaso-occlusive proliferative retinopathy is the main source of visual morbidity.
- Advances in retinal imaging have furthered our understanding of the structural and functional changes to the retinal vasculature.
- Although peripheral neovascular lesions may spontaneously regress, laser and cryotherapy treatments are effective modalities for decreasing visually significant complications in Stage III proliferative disease.
- Anti–vascular endothelial growth factor therapy may play a role in select situations, while future studies may further demonstrate its role and limitations in neovascular disease.
- Advances in the surgical management of proliferative retinopathy and its complications have led to improved outcomes and fewer complications.

Introduction

Characterized by sickled erythrocytes, sickle cell disease (SCD) is one of the most prevalent inherited blood disorders [1]. Aberrant hemoglobin-induced vascular stasis, ischemia, and occlusion can result in a spectrum of ocular manifestations affecting all parts of the eye. Sickle cell retinopathy is a potentially blinding ocular complication of this genetic hemoglobinopathy.

Pathophysiology

SCD is a group of autosomal recessive hemoglobinopathies characterized by abnormal hemoglobin proteins causing erythrocyte sickling, leading to intravascular hemolysis and impaired oxygen transport, with resultant tissue damage from ischemia and necrosis.

Inherited sickle cell hemoglobinopathies can create a spectrum of systemic and ocular presentations including sickle cell retinopathy as one of its myriad of manifestations. The genetic basis for SCD is due to mutations in hemoglobin, an iron-containing protein in red blood cells responsible for oxygen transport. Red blood cells, which contain hemoglobin, are produced in approximately 7 days with constant turnover and are in circulation for 100 to 120 days. Hemoglobin is made up of 2 alpha (α) polypeptide chains each paired with a beta (β), gamma (γ), or delta (δ) chain [2,3]. Hemoglobin F (HbF), is present at birth until approximately 6 weeks of life, is eventually replaced by hemoglobin A (HbA), with 2 α and 2 β chains, and is the predominant type in mature circulation [2,3].

SCD stems from abnormal hemoglobin due to a mutation in the β chain that causes the substitution of a single nucleotide and subsequent replacement of glutamic acid for valine [2]. The homozygous state, HbSS disease, also known as sickle cell anemia, is the most common form and results in the most severe systemic manifestations with the exception of vision loss. HbSC, resulting from a β chain substitution of glutamic acid for lysine, is known to cause a less severe form of systemic disease but is associated with the highest rate of vision loss and retinopathy [2]. The heterozygous HbAS, or sickle cell trait, rarely causes symptoms unless physiologic stresses such as dehydration, hypoxia, and acidosis are present leading to more sickling of the red blood cells. Protective factors such as the persistence of hemoglobin F and co-inheritance of α-thalassemia reduce disease severity. Other mutations such as HbS/βThal cause varying disease depending on the type of β thalassemia but are less common [2,3].

Epidemiology

Although present in Africa for thousands of years, the first description of abnormal sickled erythrocytes was described in a Grenadian dental student in 1910 [2]. Since then, our understanding of this disease and its complications has broadened to include knowledge of its pathophysiology and molecular basis, the benefit of neonatal screening, the use of penicillin to reduce mortality, and disease modification with hydroxycarbamide [2].

The burden of SCD is primarily in sub-Saharan Africa, where estimates suggest that nearly 230,000 children annually are born with SCD, representing 80% of worldwide cases, with an estimated total of 250,000 [1]. In North America and Europe, reports suggest a yearly incidence of 2600 and 1300, respectively [4]. Although the condition is more prevalent in those with African ancestry, SCD is also found in those of Mediterranean, Caribbean, Arabian, Indian, and Central and South American descent. In African American individuals, the disease is prevalent in approximately 1 in 500 births. Particularly in West Africa, the disease is a significant cause of mortality, especially in children 5 years of age and younger. In contrast to SCD, sickle cell trait is frequently asymptomatic, and is far more prevalent, noted in nearly 1 in 12 African American individuals. The high frequency of hemoglobin S in African and Mediterranean populations is thought to be due to the concomitant benefit of partial resistance to infection with plasmodium falciparum in malaria endemic regions [1,2].

Ocular manifestations

Ocular manifestations of SCD are varied, and can involve all parts of the eye, with manifestations in the orbit, adnexal structures, anterior segment, optic nerve, and posterior segment.

During a sickling-induced vaso-occlusive crisis, orbital infarctions and orbital apex syndrome can occur presenting with periorbital pain and edema, along with the possible presence of proptosis and ophthalmoplegia, with a significant risk of visual impairment [5,6]. Although rare, retrobulbar ischemic optic neuropathy has been ascribed to SCD [7].

In the anterior segment, some of the earliest findings include the "comma-shaped" conjunctival vessels described by Paton [8], that represent vessels distorted by packed red blood cells. Although ischemia of the anterior segment is rare, perhaps a limited form, sectoral iris atrophy or other pupillary irregularities, may occur secondary to iris infarcts [9]. With severe ischemic sickle cell retinopathy, iris rubeosis, and neovascular glaucoma can develop [1,10,11]. Hyphema, a condition with a typically benign course, is concerning in sickle cell patients. Sickled erythrocytes in the anterior chamber can lead to a mechanical blockage of the trabecular meshwork and result in profound intraocular pressure elevations. Permanent vision loss due to retinal artery occlusions may ensue without early and proper intervention. Acidotic conditions, such as those enhanced by systemic or topical carbonic anhydrase inhibitors, may further facilitate the process of erythrocyte sickling, with further rise in intraocular pressure and risk of vision loss. In addition, due to an already compromised vascular perfusion, even modest elevations in intraocular pressure with a hyphema in SCD is an emergent condition requiring aggressive treatment with possible early surgical intervention [12].

Sickling can cause numerous posterior segment complications and findings, including neovascularization, that can lead to vitreous hemorrhage [13]. Optic disc neovascularization has rarely been reported [14]. Macular findings may be present that include an enlarged foveal avascular zone [15] and paracentral acute middle maculopathy (PAMM) [16]. PAMM is a spectral-domain optical coherence tomography (SD-OCT) finding characterized by a hyperreflective band in the inner nuclear layer thought to be of vascular etiology. Linear breaks in the Bruch membrane, or angioid streaks, are a classic association, and are more common in the hemoglobin SS phenotype and with increasing age. In SCD, macula

involving choroidal neovascularization is less common, which explains the lower likelihood of visually significant complications compared with other causes of angioid streaks such as pseudoxanthoma elasticum [17].

Peripheral retinal findings are more common in SCD, with tortuosity of the retinal vasculature noted in the periphery, which is related to arteriovenous anastomoses [18]. Compared with other phenotypes, this finding is present more commonly in patients with hemoglobin SS [18]. As vessels terminate in the periphery, vascular occlusions may occur, with the appearance of silver wiring. Choroidal infarctions may occur as a result of occlusion of the posterior ciliary arteries [1]. The retinal clinical manifestations vary and are classified as nonproliferative sickle cell retinopathy (NPSR) and proliferative sickle cell retinopathy (PSR), depending on the presence or absence of vaso-proliferation.

Nonproliferative sickle cell retinal findings occur due to peripheral retinal vaso-occlusion and include salmon patches, black sunbursts, and iridescent spots. These peripheral vascular events cause superficial hemorrhages, initially reddish in appearance, beneath the internal limiting membrane (ILM) [19]. Over time, progressive hemolysis leads to the salmon-colored appearance known as a "salmon patch" [20]. On hemorrhage resolution, hemosiderin-laden macrophages appear as "iridescent spots" that may glisten or appear granular under the ILM (Fig. 1) [20]. Another nonproliferative retinopathy response involves the migration and proliferation of retinal pigment epithelium into the subretinal space in response to hemorrhage, creating a "black sunburst" or hyperpigmented appearance (Fig. 2) [20].

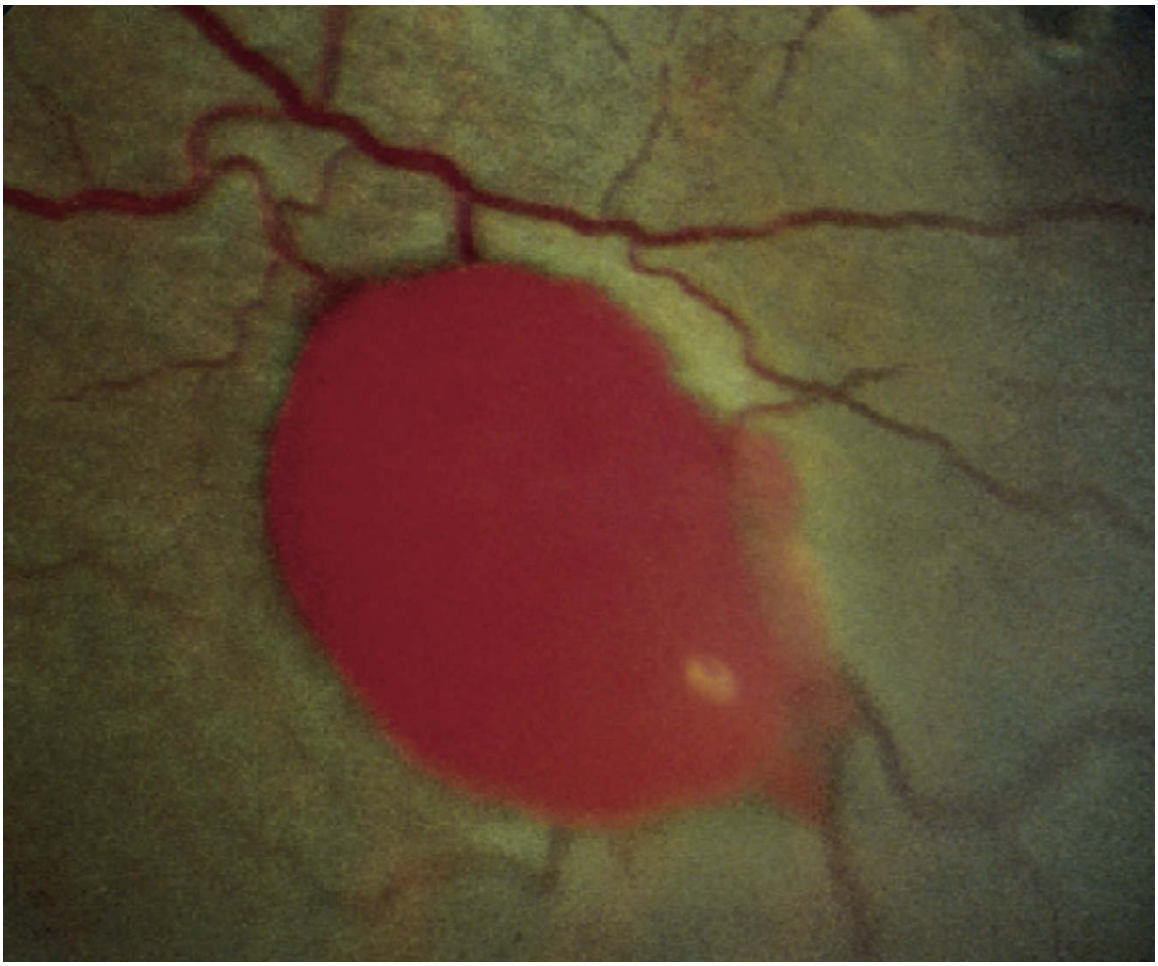

FIG. 1 Salmon patch in a patient with sickle cell retinopathy.
(*From*: Freund KB, Sarraf D, Mieler WF et al. Chapter 6: Retinal Vascular Manifestations of Systemic Disease. Freund KB, Sarraf D, Mieler WF et al. *The Retinal Atlas.* 2nd ed. Elsevier; 2016:596-596; with permission.)

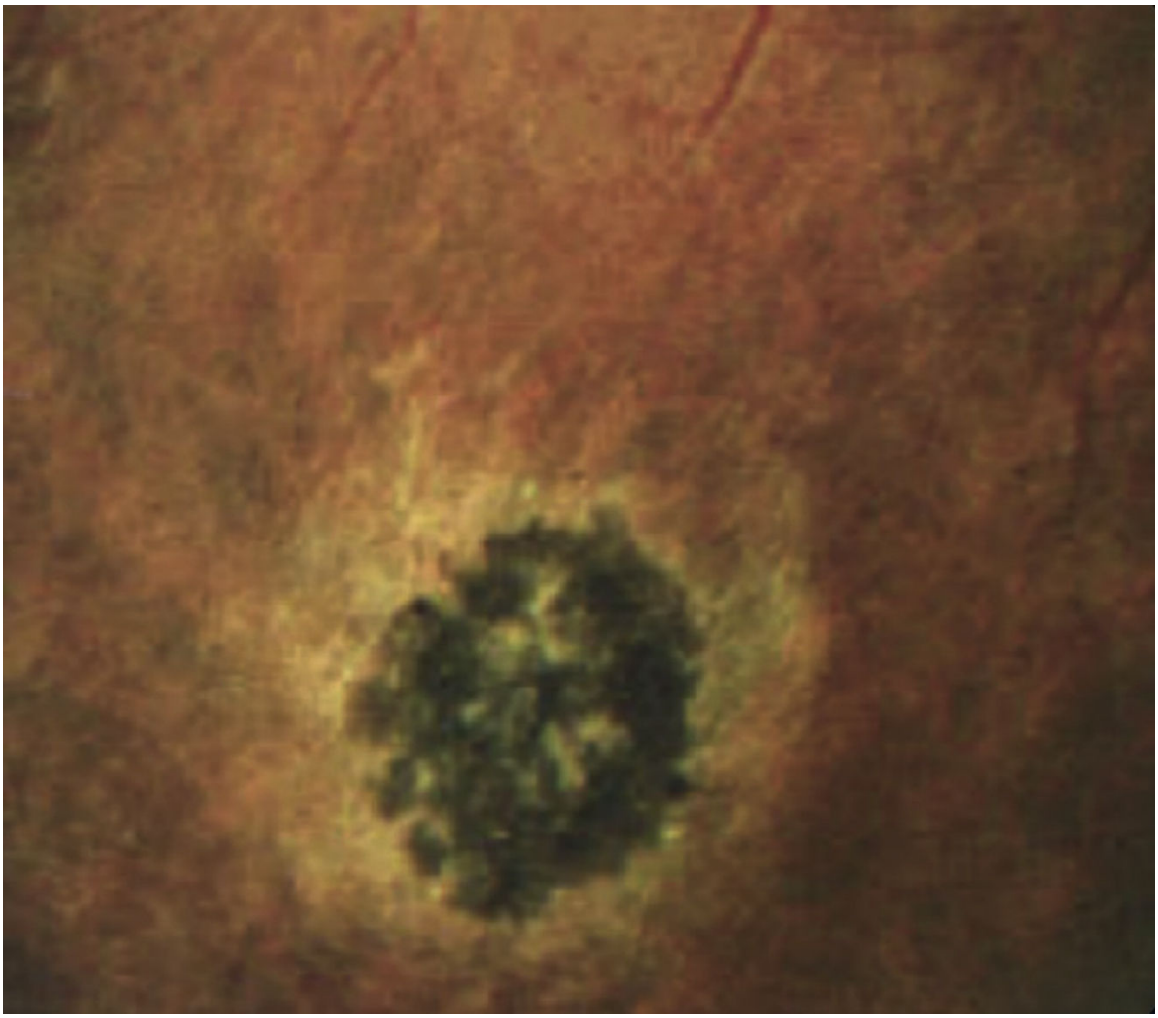

FIG. 2 Black sunburst lesion in a patient with sickle cell retinopathy. (*From* Freund KB, Sarraf D, Mieler WF et al. Chapter 6: Retinal Vascular Manifestations of Systemic Disease. In: Freund KB, Sarraf D, Mieler WF et al. *The Retinal Atlas.* 2nd ed. Elsevier; 2016:596-596; with permission.)

PSR findings, characterized by vaso-proliferation, are marked by extraretinal neovascularization or "sea fan" formation due to peripheral arterial occlusions (Fig. 3). These sea fans of neovascularization occur at the border of the vascular and avascular retina, usually in the temporal periphery. This may result in vitreous hemorrhage, tractional retinoschisis, and retinal detachments [21]. Unlike other vaso-occlusive retinopathies in which vision loss can be due to ischemia, these proliferative complications in SCD are the main source of vision loss.

Classification system

Proliferative stages of sickle cell retinopathy were defined by Goldberg in 1971 [22], whose classification is still most widely used. In proliferative disease, peripheral arteriolar occlusions lead to sea fan formation, followed by growth factor release and formation of neovascular fronds. Five stages of PSR were described by Goldberg [22], characterized by increasing levels of severity. In stage I, peripheral vascular occlusions are present. These tend to occur in the temporal retina, which can be explained by longer arteriovenous transit times with increased odds of occlusion at vascular bifurcation sites as well as decreased retinal perfusion [21]. Stage II is present when vascular remodeling occurs. Remodeling and dilation of preexisting capillaries may resemble hairpin loops and occur at the border of perfused and nonperfused retina. Retinal vascular nonperfusion without evidence of dye leakage is noted on fluorescein angiography, confirming that these changes are not neovascular in nature. The presence of sea fans, representing neovascularization, defines stage III [22]. Differences exist as to which quadrants are more commonly affected, with proliferation noted most frequently in the superotemporal quadrant, and then inferotemporal, superonasal, and inferonasal with decreasing frequency. Sea fans may auto-infarct, progressing to a fibrotic appearance associated with nonperfusion or leakage of fluorescein dye [21]. When sea fans do not auto-infarct, they may progress, leading to stage IV characterized by vitreous hemorrhage. Vitreous hemorrhage is caused by vitreous traction on neovascular fronds. Hemorrhage can be localized and asymptomatic or result in vision loss if dispersed. Vitreous hemorrhage is found more commonly in SC compared with SS disease [17,21,22]. When chronic, vitreous hemorrhage may be associated with fibrosis and traction leading to retinal detachment. Stage V represents the most severe form of sickle cell retinopathy, marked by the presence of tractional or rhegmatogenous detachments [22]. Combined rhegmatogenous and tractional retinal detachments can occur when vitreous membranes and localized atrophy lead to traction and subsequent retinal breaks. Unlike proliferative diabetic retinopathy, these tractional retinal detachments tend to involve the peripheral retina rather than the posterior pole, making them sometimes asymptomatic in their early stages.

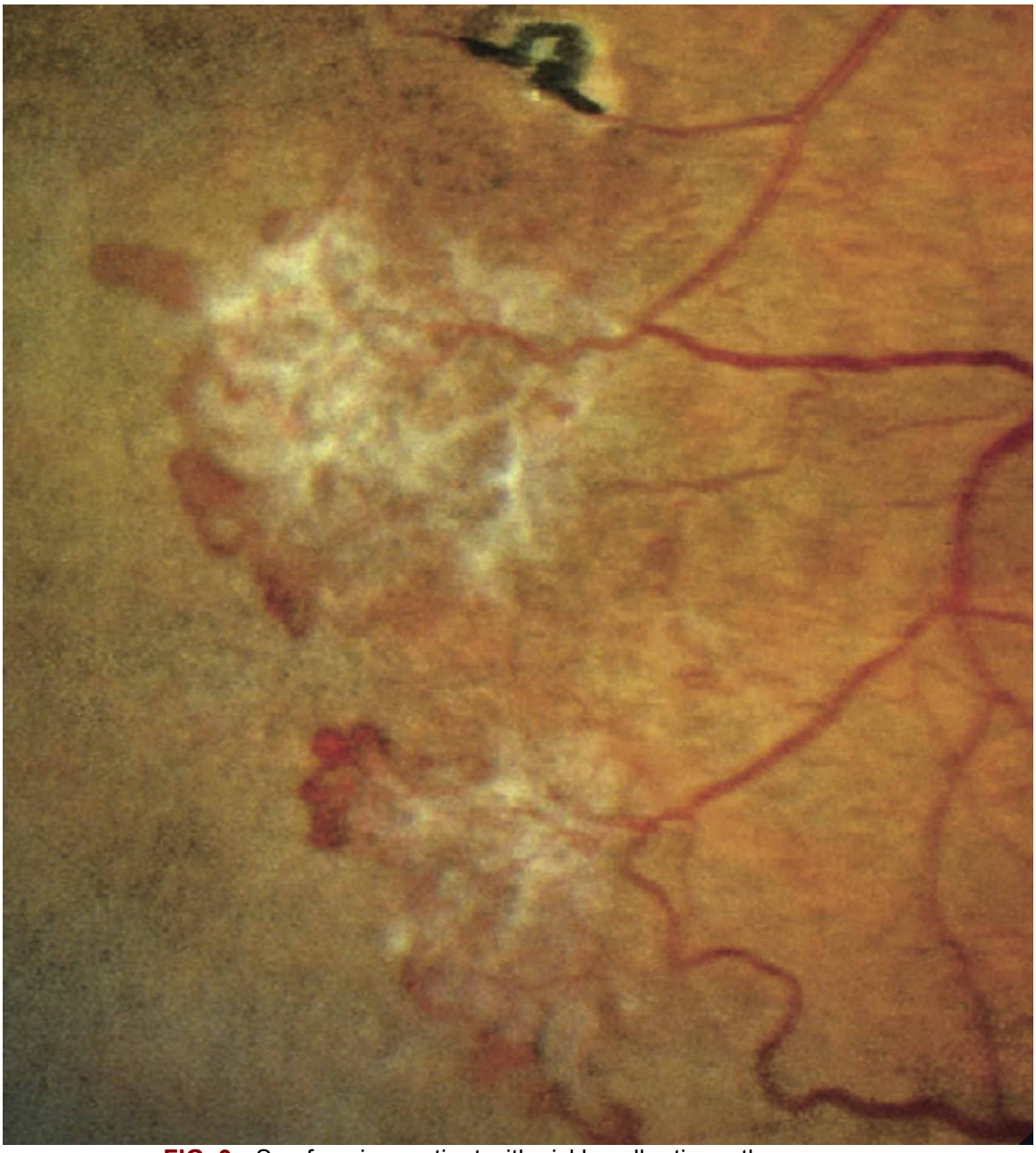

FIG. 3 Sea fans in a patient with sickle cell retinopathy.
(*From* Freund KB, Sarraf D, Mieler WF et al. Chapter 6: Retinal Vascular Manifestations of Systemic Disease. In: Freund KB, Sarraf D, Mieler WF et al. *The Retinal Atlas.* 2nd ed. Elsevier; 2016:596-596; with permission.)

Diagnosis

The use of multimodal imaging in diagnosing and staging sickle cell retinopathy is critical to optimize outcomes. The differential diagnosis of retinal vaso-occlusive disorders complicated by ischemia and neovascularization is extensive and includes vein occlusions, diabetic retinopathy, ocular ischemic syndrome, Eale disease, familial exudative vitreo-retinopathy, and other causes of an occlusive vasculitis, as well as SCD [23]. Early on in the course of the disease, patients may be entirely asymptomatic, highlighting the importance of thorough examination.

Optical coherence tomography

Although primarily located in the peripheral retina, findings secondary to sickle cell retinopathy have been found in the macular and peri-papillary region using SD-OCT. One of the descriptions of OCT findings were by Witkin [24] in which a patient with known sickle cell retinopathy was found to have temporal macula inner retinal thinning following a bilateral branch retinal artery occlusion. Histo-pathologic studies of vaso-occlusive diseases including sickle cell have correlated well with these findings and have demonstrated selective atrophy of the inner retinal layers (Muller cells, ganglion cell, and inner nuclear layers) [25]. The etiology of selective inner retinal loss may lie in the caliber of the vessels, as the inner retinal vessels are end arterioles and capillaries that are smaller in size compared with choroidal vessels that supply the outer retinal layers [24]. In addition, the temporal ischemia seen most commonly occurs in the watershed areas along the temporal horizontal raphe [26].

Other findings suggest the outer retina and choroid may not be entirely spared from ischemic insult, but any quantitative changes may not be clinically significant. This was demonstrated in a review of OCT findings in 21 asymptomatic patients with SCD who were noted to have central macular outer retinal thickness 10 μm thinner than controls [27]. In addition, choroidal thickness has been noted to be significantly thinner in patients with SCD than age-matched healthy controls suggesting outer retinal damage that remains subclinical [28].

These anatomic changes noted on OCT can be functional in nature, albeit subtle. Patients with SCD with focal macular thinning have been noted to have significantly decreased retinal sensitivities compared with controls in microperimetry testing [26].

Inner retinal thinning on SD-OCT (Fig. 4) is associated with increasing severity of disease and more prevalent in PSR [29]. It is the vaso-occlusive process that leads to inner retinal thinning and chronic ischemia with the subsequent production of vascular endothelial growth factor (VEGF) and neovascularization. Macular splaying (widening of the macular contour), peripapillary retinal nerve fiber layer thinning, and PAMM have been reported in several retrospective reviews of sickle cell patients' OCTs [27,30].

Optical coherence tomography angiography

As a relatively new technology, OCT angiography (OCTA) is a noninvasive method to evaluate the retinal vasculature at different levels quantitatively and qualitatively using interferometry similar to OCT. The inner retina vascular supply originating from the central retinal artery can be divided into the superficial capillary plexus (SCP) and the deep capillary plexus (DCP). OCTA has been found to detect early macular changes in the SCP and DCP before thinning of the retinal layers they supply [31].

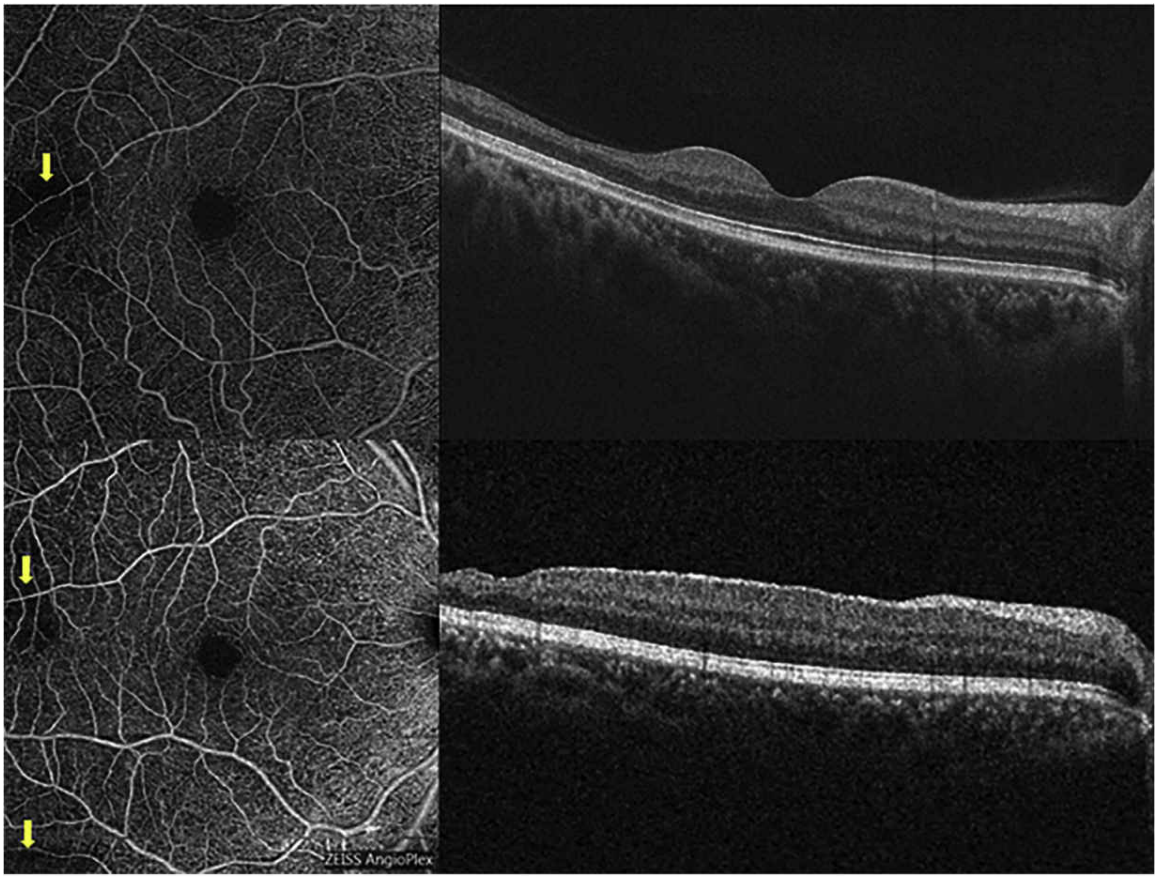

FIG. 4 OCT-A (*left*, *top* and *bottom*) and corresponding OCT (*right*, *top* and *bottom*) images of 2 patients with SCD. Yellow arrows correspond to flow voids in OCT-A images. The OCT images demonstrate temporal inner retinal thinning.
(*From* Pahl DA, Green NS, Bhatia M, et al. Optical coherence tomography angiography and ultra-widefield fluorescein angiography for early detection of adolescent sickle retinopathy. *Am J Ophthalmol*. 2017;183:91-98; with permission.)

Qualitative findings on OCTA in patients with SCD who may be assessed in a standard clinical setting include areas of nonperfusion in the SCP and DCP, irregularity and increase in the foveal avascular zone, increase in vessel tortuosity, and increase in vessel diameter. Quantitative changes that can be measured include decrease in the vascular density, increase in vascular diameter, increase in the nonflow areas, and increase in vessel tortuosity. Using these metrics, in a systematic review of 12 articles, 20% of patients younger than 18 were found to have macular microangiopathy on OCTA and 100% of patients older than 18 had signs of microangiopathy [31].

Quantitative analysis of vessel density has shown that the DCP is more affected than the SCP in sickle cell retinopathy (Fig. 5). Although not fully

understood, it may relate to the terminal anastomotic origin of the DCP making it more susceptible to ischemic events. Mean vessel density (MVD) was lower in the macular temporal area correlating to the area that is thinnest. PSR was also associated with decreased MVD compared with nonproliferative disease in all areas except the DCP of the fovea [32–35].

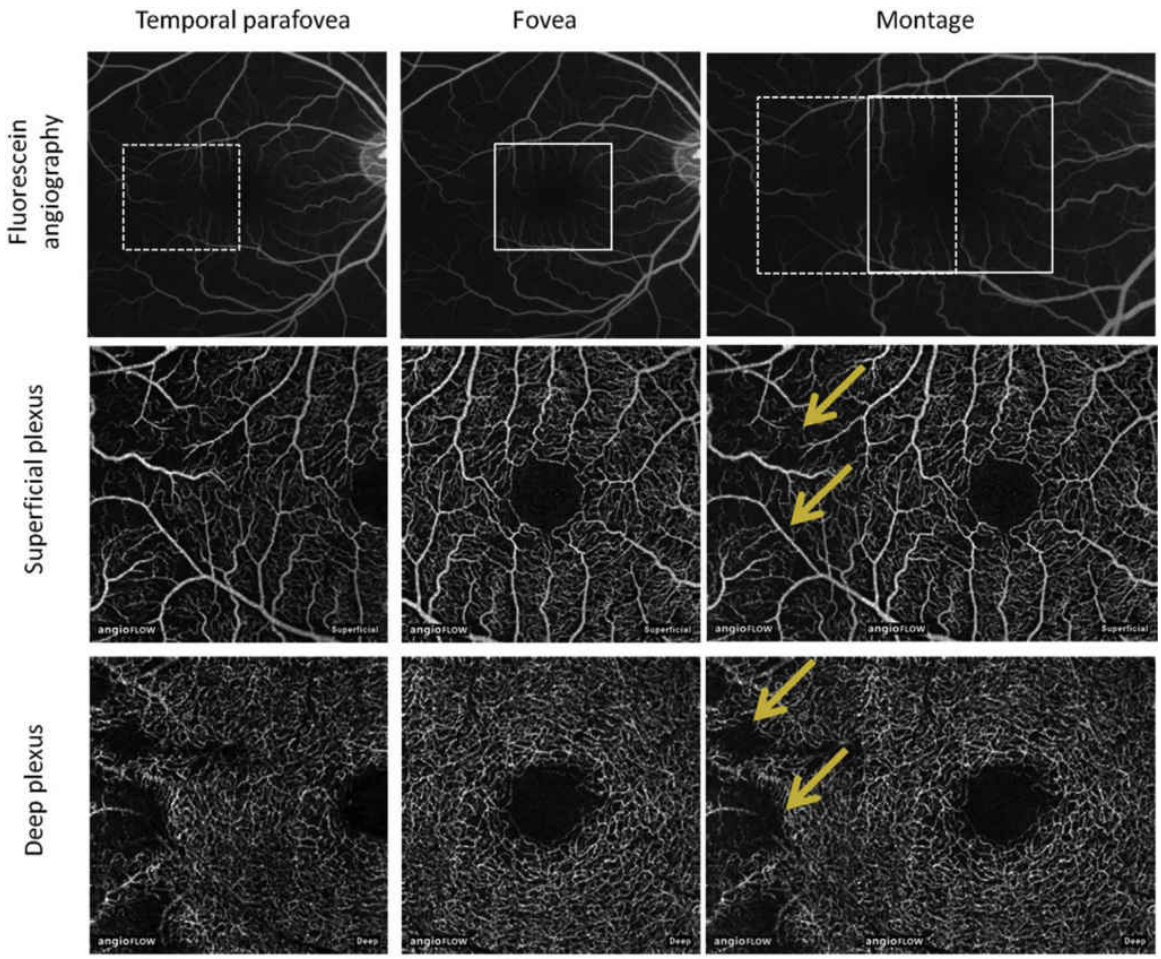

FIG. 5 Images from a patient with sickle cell hemoglobin SCD. First column: OCT-A scans temporal to the fovea demonstrating en face views of the SCP and DCP (*dotted box*, *top left*). Second column: OCT-A scans centered on fovea (*solid box*, *top middle column*). Third column: Montage of first 2 columns. The yellow arrows point to areas of flow void in the SCP and DCP. (*From* Han IC, Tadarati M, Pacheco KD, Scott AW. Evaluation of macular vascular abnormalities identified by optical coherence tomography angiography in sickle cell disease. *Am J Ophthalmol*. 2017;177:90-99; with permission.)

Sickle cell maculopathy has been found to be more prevalent than previously reported with the adjunct use of more sensitive imaging

modalities such as OCTA [32]. As its adoption continues to spread, so will the quantitative methods of assessing and following vascular abnormalities that may ultimately lead to meaningful clinical decisions in early treatment and prevention of sickle cell retinopathy complications.

Ultra-wide fluorescein angiography

Fluorescein angiography (FA) has been the gold standard in evaluating and following sickle cell retinopathy. Traditional cameras have the ability to take a photograph up to a 60-degree view in one exposure. The use of a composite image using the 7-standard fields has been used in an effort to assess more peripheral pathology with obvious limitations. The advent of ultra-wide imaging and FA (UWFA) allows for a 200-degree view of the retina extending to the posterior edge of the ora serrata in a single frame. With most sickle cell retinopathy occurring in the periphery, the ability to obtain a widefield image increases the sensitivity of retinopathy detection [36–38]. The efficiency of UWFA also allows the photographer to take high-quality images of the periphery with less patient cooperation required making it more appropriate in the pediatric population. Future longitudinal studies using UWFA in conjunction with OCT and OCTA may help elucidate which patients will progress to PSR, allowing for earlier detection and treatment.

Management

Screening

Neonatal screening involves hemoglobin electrophoresis or chromatography, which are not costly and widely available techniques worldwide [2]. Antenatal screening is available in some countries to women who are at higher risk of having an infant with SCD [2].

In a longitudinal study involving 100,000 screenings at a hospital in Jamaica, 311 patients with SS and 167 patients with SCD were recruited for observation for development of sickle cell retinopathy beginning at 5 years of age. After a period of about 20 years, 43% of patients with SCD developed PSR compared with 14% of patients with SS [38].

Recommendations have been made to start ocular screening at the age of 10 and continue at 1-year to 2-year intervals for normal dilated fundus examinations and FA with any abnormal examinations [39]. There is a strong consensus for this screening but little evidence to support this recommendation [40]. Consensus for treatment also comes into question, as 36% of proliferative lesions may spontaneously regress, although most physicians will treat once proliferative disease is present [38]. Risk factors for progression to PSR include age, history of PSR in the other eye, and vessels at the junction of the perfused and nonperfused areas with a capillary bud appearance that bifurcate [41].

Laser

Given the various complications associated with sickle cell retinopathy, including vitreous hemorrhage and retinal detachment, therapies including transpupillary or transscleral diode photocoagulation, cryotherapy, and diathermy have been used to treat patients effectively [42–48]. The primary indication for laser therapy is the development of stage III disease so as to prevent vitreous hemorrhage and retinal detachment. The conclusion of a Cochrane systematic review from 2015 determined that scatter laser photocoagulation and feeder vessel coagulation are both effective in preventing vision loss and vitreous hemorrhage [42]. Both forms of laser treatment were associated with an increased partial regression of PSR but no increase in complete regression compared with controls who also demonstrated spontaneous regression without treatment [42]. Feeder vessel treatment was associated with a

greater decrease in the rate of vitreous hemorrhage but was associated with a higher complication rate of choroidal neovascularization with xenon arc treatment and a higher rate of retinal detachment with argon laser [49]. The higher rate of complications associated with feeder vessel treatment has led to scatter laser photocoagulation being the preferred method of treatment [43,49,50]. Interestingly, results from autopsy of sickle cell retinopathy eyes have shown expression of VEGF and hypoxia-inducible Factor 1 (HIF-1α) posterior to the nonperfused retina. This supports a broad application of laser application up to 1 to 2 mm posteriorly to the area of neovascularization, as even the adjacent perfused retina may be producing factors that drive neovascularization [51].

When the view to the retina is obscured by media opacities (vitreous hemorrhage or cataract), or from poor mydriasis and posterior synechiae, other modalities for treatment exist. Cryotherapy has been shown to regress and attenuate sea fans with persistent effect without hemorrhage for 3 years after treatment [46]. Alternatively, transscleral diode laser could be performed if for any reason transpupillary laser photocoagulation is not possible. Laser treatment results in less dispersion of retinal pigment epithelial cells and less breakdown of the blood-retina barrier and, therefore, is safer to use whenever possible [50]. Although laser treatment is fairly benign, it is not without its risk, as patients can develop retinal breaks and detachments [52].

Anti–vascular endothelial growth factor

The ratio of a variety of angiogenic and anti-angiogenic factors such as angiopoietinlike 4, VEGF, HIF-1α, pigment epithelium-derived factor (PEDF), and soluble intercellular adhesion molecule 1(sICAM-1) have been shown to play a role in determining progression of PSR [51,53–56]. Although first-line treatment involves scatter laser to the ischemic areas of retina, anti-VEGF agents have been found to be helpful as an adjunctive treatment, particularly when the view is obscured by media opacities such as vitreous hemorrhage. Similar to treatment of diabetic retinopathy, anti-VEGF agents such as bevacizumab and ranibizumab have been demonstrated to rapidly improve vitreous hemorrhage and induce regression of neovascularization in eyes with PSR [57–59].

The first documented case of anti-VEGF use in PSR dates back to 2006 with successful regression of neovascularization [57]. The promising role of anti-VEGF agents in the treatment of PSR was also described by Shaik

[60] in the case of a 32-year-old woman with vision loss from vitreous hemorrhage and PSR. Intravitreal bevacizumab resolved the hemorrhage after 1 month with involution of the sea fan complex that persisted without need for laser treatment at the 6-month visit. In a case series reported by Cai and colleagues [61] involving 5 patients with stages III and IV PSR treated with intravitreal bevacizumab, 2 patients developed recurrent vitreous hemorrhages at 4 and 13 months, indicating some persistent suppression of the neovascularization drive. Bevacizumab also has been shown to be useful preoperatively to reduce bleeding in patients with stage V PSR [62]. Careful follow-up is necessary, as patients are prone to spontaneous hyphema, and a secondary hyphema has been reported after intravitreal bevacizumab [63]. Many questions remain regarding the use of anti-VEGF agents and their role in treatment of PSR. Optimal frequency of injections, safety, which agent is more efficacious, and efficacy compared with scatter photocoagulation are some of the few that remain to be answered. Further investigations with large-scale randomized controlled trials are warranted.

Surgical treatment

Surgery is indicated in the setting of bilateral vitreous hemorrhage, nonclearing visually significant vitreous hemorrhage, vitreous hemorrhage in a monocular patient, and tractional retinal detachment. Stress has been shown to induce vaso-occlusive and ischemic processes and the ensuing visual threatening complications in patients with SCD. As a result, it is necessary to identify and correct any preoperative risk factors to mitigate ischemic complications.

For a long period, scleral buckling with cryotherapy was the first line of surgical treatment for retinal detachment [64]. Before the widespread use of vitrectomy, scleral buckling was reported to have caused anterior segment ischemia (ASI) in up to 71% of cases with preoperative exchange transfusion recommended to avoid such complications [65]. Scleral buckles are thought to cause compression of the anterior choroid, ciliary body, and ciliary processes resulting in ASI. In a review of 11 patients by Pulido and colleagues [66], measures taken to reduce ASI, such as adequate hydration, supplemental oxygen, avoidance of sympathomimetics, high and wide encircling elements, and carbonic anhydrase inhibitors, as well as minimization of extraocular muscle

manipulation, and minimal use of cryopexy, all but eliminated this risk with no reported cases.

Advanced pars plana vitrectomy techniques now have managed to make this complication a rarity. Widefield viewing systems, smaller incisions, shorter operating times, and valved cannulas allowing for better intraocular pressure management have contributed to lower rates of adverse events. In a series of 108 eyes undergoing surgery for PSR-related complications over a 16-year period, not one had ASI related to SCD [64].

Various techniques to improve outcomes have been described in the literature. In 2009, Williamson and colleagues [67] evaluated the surgical results of patients with SCD undergoing 20-gauge vitrectomy. In 7 of the 18 patients, iatrogenic breaks were created during delamination of the sea fan complexes. This technique has since been abandoned in favor of a segmentation technique that can be used to remove vitreal attachments to the sea fans when necessary [67]. Utilization of smaller-gauge vitrectomy may also improve surgical outcomes. In the largest cohort reported of 71 patients undergoing vitrectomy for sickle cell–related complications by Chen and colleagues [64,68,69], there was a trend toward 23-gauge vitrectomy to be more beneficial for visual and anatomic success with lower rates of complications.

Summary

SCD is a lifelong condition that may lead to significant ocular morbidity. Advancements in imaging including OCT, OCTA, and UWFA have been instrumental in earlier detection and improved monitoring of progression of disease. This has allowed for earlier initiation of treatment and better outcomes. Results of anti-VEGF use in the few reported cases are promising, but more data are required to determine efficacy and the role it will play in future management. For those patients with stage IV and stage V PSR, modern techniques in scleral-buckling and smaller-gauge vitrectomy have led to better outcomes. Surgical treatment of PSR has come a long way, but ultimately controlling the underlying disease in conjunction with a hematologist is of extreme importance. Taking the appropriate perioperative measures will reduce the risk of perioperative complications and ensure the best possible outcome for the patient.

Clinics care points

- Consensus for screening is to begin at age 10 with dilated fundus examinations at 1-year to 2-year intervals with subsequent testing for abnormal examinations.
- Multimodal imaging, including UWFA, OCT, and OCTA are key in evaluating the extent of disease and progression over time.
- Spontaneous regression of neovascularization can occur, but most physicians will treat with pan-retinal photocoagulation regardless.
- Anti-VEGF therapy has had promising results in several cases, but further studies are needed to further demonstrate its role and limitations in proliferative disease.

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Glaucoma

OUTLINE

Glaucoma Surgery

Which Surgery to Pick for Your Patient?

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Keywords

Trabeculectomy; Nonpenetrating glaucoma surgery; Tube shunt/glaucoma drainage device; Minimally invasive glaucoma surgery; Subconjunctival implants; Schlemm canal procedures; Suprachoroidal implants; Failed glaucoma surgery; MIGS

Key points

- There are 3 main approaches to glaucoma surgery: subconjunctival, Schlemm canal–based, and suprachoroidal/ciliary body.
- Subconjunctival glaucoma surgery is ideal for patients with advanced disease, low target pressures, and prior failed surgery.
- Although transscleral cyclophotocoagulation has classically been reserved for patients with refractory glaucoma, micropulse technology might become an indispensable tool used earlier during the disease process, sparing the higher frequency of serious complications of the older technology.
- Although Schlemm canal–based procedures are usually considered in mild to moderate glaucoma cases with controlled or slightly above-target intraocular pressure and are often combined with cataract surgery, suprachoroidal shunts are still struggling to find their role and currently undergoing further trials to validate their efficacy and safety.
- Preliminary evidence implies a possible role for some of the newer microinvasive glaucoma surgery in treating patients with prior failed incisional surgery.

Introduction

The field of glaucoma has been going through an era of renaissance during the last 2 decades, with a quickly expanding armamentarium of new innovative surgical options adding to the classic filtration surgery.

Trabeculectomy is generally considered the gold-standard treatment for glaucoma patients and is still considered one of the most effective procedures, although one that is associated with serious possible complications, making many surgeons reconsider its role in the treatment paradigm. Nonpenetrating glaucoma surgery (NPGS) and enhanced versions, such as canaloplasty, also were developed, aiming to increase the safety profile, sometimes at the expense of less efficacy.

Tube shunts have classically been implemented both after failed glaucoma surgeries and in patients with complex secondary glaucoma cases, which carry a higher risk of failure with trabeculectomy.

Cyclodestructive procedures have been mainly reserved for refractory glaucoma cases with a very low visual potential. The introduction of micropulse laser technology has reshaped the way many surgeons think of these types of procedures, making them more attractive to perform at an earlier stage of the disease and in patients with good visual potential.

The term microinvasive glaucoma surgery (MIGS) was coined in 2012 to describe an ab interno procedure, with minimal trauma, efficacy, high safety profile, and rapid recovery [1]. As the safety of these newer glaucoma procedures is thought to be usually superior to classic filtration surgery, usually at the expense of efficacy, the term interventional glaucoma has been suggested to infer surgical intervention to be done earlier in the disease process.

Many new procedures have been introduced since then, while still grouped under the umbrella of MIGS, although many of them differ in their efficacy and safety profile, and some may be done by an ab externo approach, such as the XEN gel stent or Preserflo microshunt.

It might be prudent, however, to classify glaucoma-surgical options according to the target site of treatment, namely subconjunctival, Schlemm canal, and the ciliary body/supraciliary space, and not merely as classic versus modern technologies, with the former approach capable of giving a better indication to the degree of efficacy, helping to make surgical decisions, and helping postoperative management.

In view of this increasing number of surgical instruments in our toolbox, the choice of which tool to choose for which patient might become increasingly more challenging for the glaucoma surgeon, keeping in mind many other

important factors, including the level and type of disease, surgeon experience, availability of the different devices, and reimbursement issues.

Significance

Many factors come to mind when deciding on which procedure to choose:

- Age and life expectancy
- General health status, type of work, comorbid eye disease, and so forth
- Type of glaucoma
- Angle status (narrow, closed, open)
- Lens status (phakic, cataract, pseudophakia, aphakia)
- Level of glaucoma damage
- Preoperative IOP
- Target IOP
- Refractive status (myopia, presbyopia)
- Past ocular surgeries and ocular comorbidities
- Resource availability
- Reimbursement issues

Often several surgical options might be found appropriate, or different procedures might be chosen by different surgeons considering the surgeon's experience and comfort with any given procedure.

Fig. 1 summarizes the different surgical options available for the glaucoma surgeon.

Subconjunctival surgery

Fig. 2 summarizes the main indications for the choice of subconjunctival glaucoma surgery.

This route usually is opted for when the patient has uncontrolled disease under maximal tolerated medical therapy, and after possible trial of selective laser trabeculoplasty (SLT) if indicated. Surgeries under this group usually are capable of bringing the intraocular pressure (IOP) into the low-teen values, rendering them a good option to choose in more advanced disease requiring low target pressures, and in patients with very high preoperative IOP.

When not to opt for subconjunctival surgery?

Patients with scarred and cicatricial conjunctiva and those with significant ocular surface disease and chronic blepharitis may not be ideal candidates for this route, as healing is often suboptimal, with higher risk of bleb leaks and failure, blebitis, and tube or microstent erosion. Blebs are generally to be avoided if contact lens wear is necessary postoperatively.

Nonpenetrating glaucoma surgery

This group includes several techniques, among which the most commonly used techniques today include deep sclerectomy (DS), viscocanalostomy, and canaloplasty.

DS aims to promote filtration primarily to the subconjunctival space through a thin trabeculo-Descemet membrane (TDM), providing some resistance to outflow. It involves the dissection of a superficial scleral flaplike trabeculectomy, followed by a deeper flap dissection extending anteriorly into clear cornea, on the way to unroofing the outer wall of Schlemm canal, and anteriorly leaving a thin membrane of trabeculo-Descemet thought to be responsible for filtration. The inner wall of Schlemm canal also can be removed with special forceps, possibly augmenting filtration. DS usually is augmented by the use of antifibrotics, such as mitomycin-C (MMC), to enhance the efficacy in the long term.

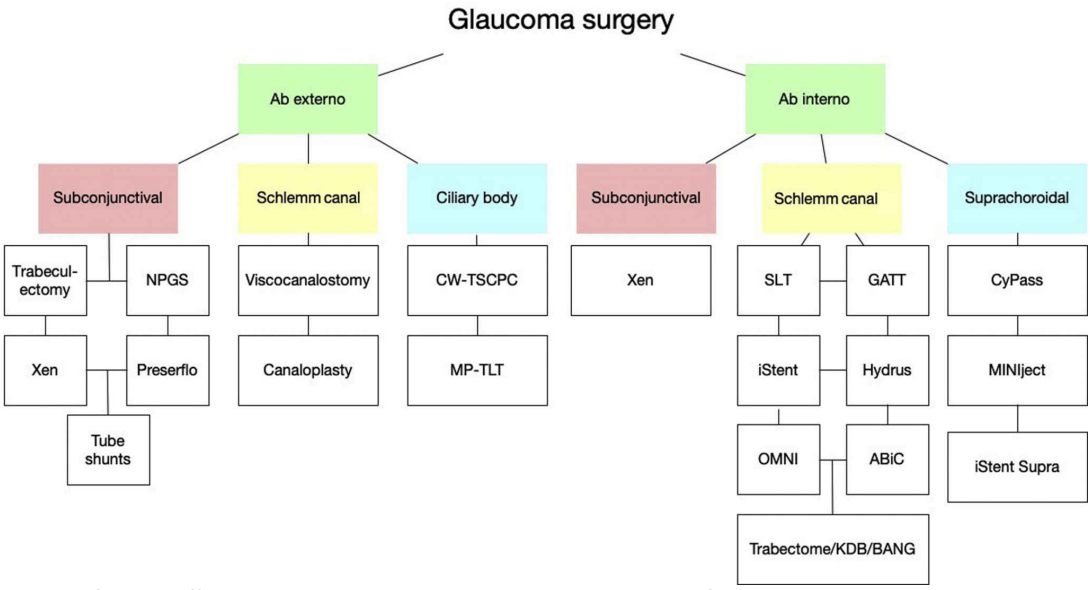

FIG. 1 Different approaches to glaucoma surgery. ABiC, ab interno canaloplasty; BANG, bent ab interno needle goniectomy; CW-TSCPC, continuous-wave transscleral cyclophotocoagulation; KDB, Kahook dual blade; OMNI, viscocanaloplasty and ab interno trabeculotomy.

CO_2 laser has been used for ablation of the deep scleral flap and unroofing the Schlemm canal in a procedure called CLASS–CO_2 laser assisted sclerectomy surgery. This surgery minimizes the risk of perforation as compared with manual deep flap dissection.

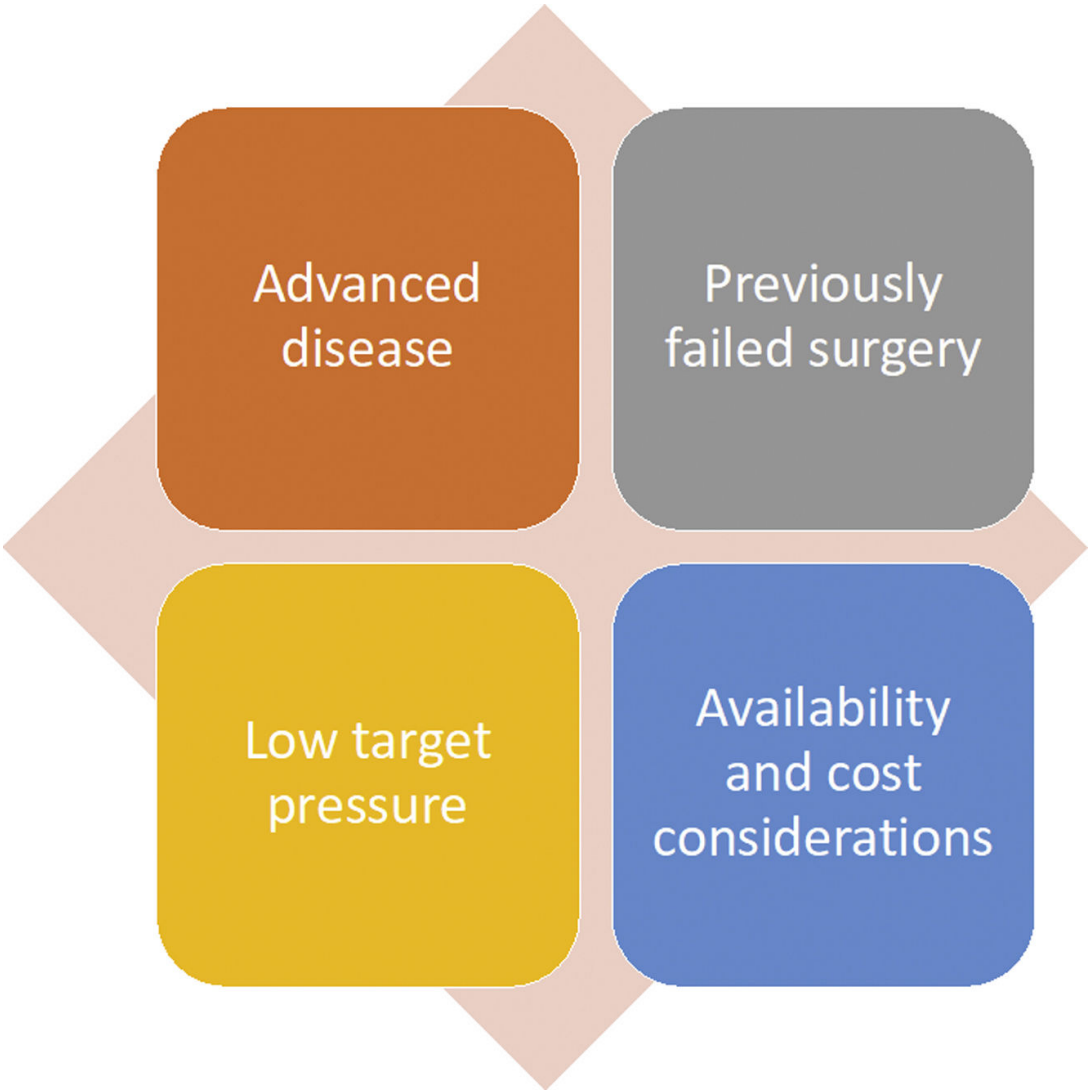

FIG. 2 Main indications for the subconjunctival glaucoma approach.

The implantation of a collagen, hyaluronic acid, or Hema implant, under the superficial scleral flap, might be used to keep the patency of the deep intrascleral lake after DS.

Complications with DS usually are less severe than with trabeculectomy with more rapid visual rehabilitation and less chance of hypotony.

Possible complications include the following:

- Microperforations and macroperforations intraoperatively with possible iris incarceration. In the latter case, there is need to convert to a classic trabeculectomy procedure.
- Insufficient deep flap dissection causing high pressures postoperatively.
- Postoperative hyphema, which usually absorbs within a few days without complications.

Laser goniopuncture with Q-switched 532-nm YAG Laser usually is needed in more than half of the cases in order to increase filtration through the TDM window postoperatively, as this structure is prone to scarring in the long run, or in the case of insufficient deep dissection.

Contraindications:

- Neovascular glaucoma (NVG)
- Iridocorneal endothelial (ICE) syndrome
- Chronic angle-closure glaucoma (relative)
- Posttraumatic angle recession with extensive damage to the trabecular meshwork (TM)

Literature on the comparison between NPGS and trabeculectomy has shown contradictory results, because of the different techniques used and different surgeon experience when comparing the 2 techniques.

A meta-analysis comparing NPGS versus trabeculectomy concluded that DS augmented with MMC was as effective as trabeculectomy with MMC with less postoperative complications. The addition of a subscleral implant was not advisable, as it gave no advantage while raising the complexity and the cost [2].

In the authors' experience, DS is especially beneficial in cases of very high preoperative IOP or patients with high myopia who are at a higher risk of postoperative hypotony after trabeculectomy [3].

Viscocanalostomy and canaloplasty are thought to promote filtration through the natural outflow pathway, namely the Schlemm canal. It usually is performed similar to DS, with the main difference being the instillation of cohesive viscoelastic material (Healon GV) into the cut edges of the canal. Canaloplasty is a variation of viscocanalostomy by the addition of Schlemm canal dilation 360 using a microcatheter (iTrack 250) and placement of a permanent suture in the stretched canal (Fig. 3).

These procedures are indicated in patients with primary open-angle glaucoma (POAG) and most of the secondary open-angle glaucomas (OAGs). They are especially beneficial in the authors' experience in young patients requiring target pressures in the mid- to high-teens, and mechanistically also may increase trabecular and circumferential aqueous outflow.

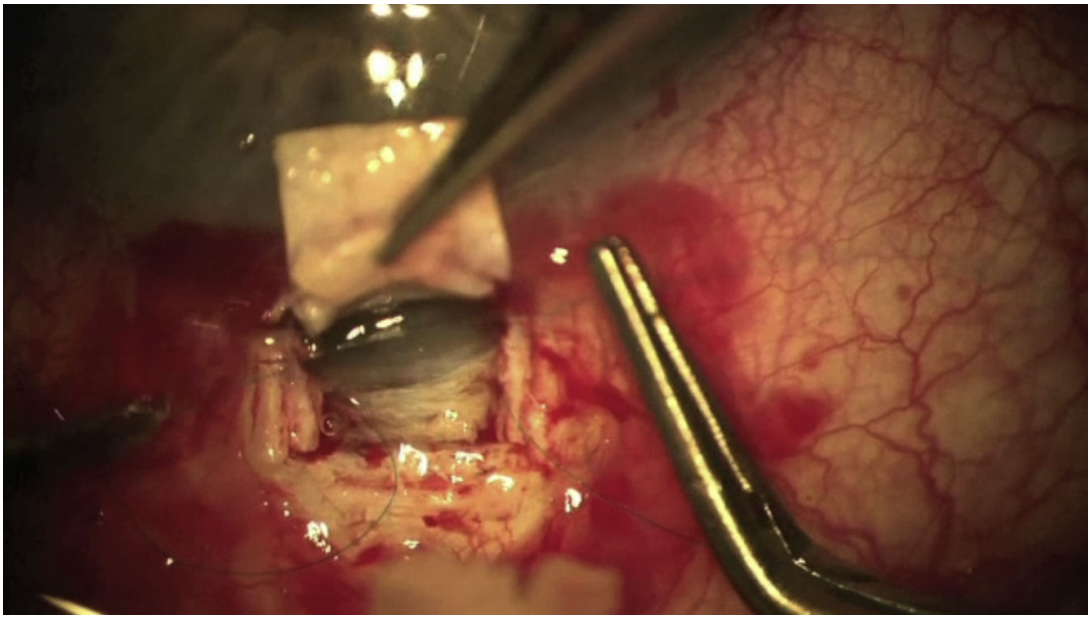

FIG. 3 Two ends of a looped Prolene 10-0 suture are being tied after passing 360° though the Schlemm canal, guided by the iTrack 250 microcatheter, stretching the canal in a canaloplasty procedure.

Trabeculectomy

Trabeculectomy has been considered the gold-standard glaucoma surgery for years, since its introduction by Cairns [4]. It involves the creation of a scleral flap under which access to the anterior chamber is created to promote creating a subconjunctival bleb. An antimetabolite, such as MMC or 5-Fluorouracil (5-FU), usually is used to prevent excessive scarring and hereby reduces the risk of failure, at the expense of more postoperative complications, such as hypotony and endophthalmitis.

It is mainly indicated when very low target pressures (single digit) are required, as it possibly has the best chances of achieving this target.

Care should be taken when operating on highly myopic young patients, as these are more prone to develop hypotony postoperatively.

Relative contraindications

- Aphakic glaucoma
- Active ocular inflammation
- Thin sclera

XEN Gel Implant (Allergan Inc, Irvine, CA, USA)

The XEN implant is a hydrophilic tube composed of a porcine gelatin and cross-linked with glutaraldehyde. It has an external diameter of 150 μm and an internal lumen of 45 μm, which is claimed to provide approximately 6 to 8 mm Hg internal pressure resistance, according to the Hagen-Poiseuille law, and protection against postoperative hypotony [5].

It can be implanted in an ab interno or ab externo approach, shunting aqueous to the subconjunctival space. The ab externo approach sometimes is preferred when done as a standalone procedure, aiming to create more superior blebs by avoiding the common nasal blebs sometimes created with the ab interno approach with possible bleb dysesthesia afterward.

The Xen Glaucoma Treatment System was approved in the United States for the management of refractory glaucoma where previous surgical treatment has failed, or in patients with POAG, pseudo-exfoliative (PXE), or pigmentary glaucoma that is unresponsive to maximum tolerated medical therapy. It also has been described for use in juvenile OAG and uveitis patients [6].

Results from the APEX study have shown success in around two-thirds of the patients at 2 years after standalone or combined phacoemulsification with Xen implantation in POAG [7].

Another retrospective study comparing standalone Xen implantation versus trabeculectomy has shown comparable risk of failure and safety profile at 1 year with more needling procedures needed in the first [8].

The main advantages of the XEN Gel Implant over other filtering procedures include its less-invasive surgical procedure, favorable safety profile, more rapid visual recovery, and short surgical duration, rendering this implant especially appropriate for patients who are unable to tolerate long surgical procedures or when access to operating room time is more limited.

Preserflo Microshunt (Santen Pharmaceutical Co Ltd, Osaka, Japan)

The MicroShunt is an 8.5-mm-long microincisional filtration surgery device with a 350-μm outer diameter and 70-μm lumen. It is composed of poly(styrene-*block*-isobutylene-*block*-styrene), or SIBS, which is a highly biocompatible, bioinert material. It is implanted via an ab externo approach, allowing hemostasis control, precise placement, and verification of flow. Aqueous humor flows from the anterior chamber to a posterior bleb formed under the Tenon capsule. Several studies have shown promising results for this procedure in reducing IOP and medication burden, although this device is still investigational and not yet approved by the Food and Drug Administration (FDA) [9,10].

Tube shunts

The use of tube shunts in glaucoma surgery has been largely increasing in the past 2 decades [11]. Indications for use have been increasing among glaucoma surgeons [12].

Tube shunts involve the insertion of a silicone tube into the anterior chamber, ciliary sulcus, or the pars plana in vitrectomized eyes, connected to an external plate fixated 8 to 10 mm from the limbus, creating a reservoir modulated by the creation of a fibrous capsule several weeks after the procedure, preventing long-term hypotony.

Tube shunts are divided into valved, such as Ahmed (New World Medical, Rancho Cucamonga, CA, USA), and nonvalved implants, including Baerveldt (Johnson & Johnson, New Brunswick, NJ, USA), Molteno (Katena Products, Parsippany, NJ, USA), and Ahmed ClearPath (New World Medical).

Tube shunts are usually indicated in several following scenarios:

1 Patients with previous ocular surgeries, including failed glaucoma surgery. The Tube versus Trabeculectomy study (TVT) was a multicenter randomized controlled trial (RCT) that compared the safety and efficacy of these 2 procedures in eyes with previous ocular surgeries. The trabeculectomy group had a higher rate of failure at 5 years, with higher rates of early postoperative complications.
2 High risk for trabeculectomy failure, such as in NVG, chronic or recurrent uveitis, ICE syndrome, and pediatric glaucoma.
3 Patients with scarred conjunctiva owing to ocular cicatricial pemphigoid, Stevens Johnson syndrome, and so forth.

Pooled data analysis from the Ahmed Baerveldt Comparison study and the Ahmed versus Baerveldt study comparing the valved Ahmed FP7 to the nonvalved Baerveldt 350-mm^2 has shown that the latter was more effective and less likely to fail at 5-year follow-up, at the expense of higher rates of postoperative hypotony [13].

As the nonvalved implants need to be restricted to flow during the first 4 to 6 weeks after surgery to prevent hypotony, this makes the valved implants a more attractive choice when a need exists for immediate reduction of extremely high IOPs, such as the case in NVG, whereas the nonvalved implants may be a better choice when lower target pressures are required in the long term.

Possible complications associated with tube shunts include endothelial cell loss and persistent corneal edema, diplopia, tube erosion, and persistent hypotony.

When examining tube shunts as an initial glaucoma procedure, the Primary TVT study has shown similar failure and complications rates at 3 years for trabeculectomy and Baerveldt-350 mm^2, with lower IOP and medication use in the trabeculectomy arm. As the options for secondary operation after a failed tube are usually more limited, tube shunts may be less suitable to choose as a primary procedure in low-risk glaucoma patients.

Cyclodestructive procedures

Transscleral diode cyclophotocoagulation (TSCPC) classically has been used in refractory glaucoma patients with a guarded visual prognosis. It employs the use of an external diode handpiece to ablate the ciliary body's secretory cells, therefore reducing the IOP. As these cells have regenerative potential, sometimes several treatments must be used to get the desired effect. Two main modes of external laser delivery are currently in practice: continuous wave (CW-TSCPC) and micropulse transscleral laser treatment (MP-TLT).

With CW-TSCPC, usually 18 to 24 spots are treated at around 1.2 mm from the limbus, sparing the 3 and 9 o'clock, where the ciliary nerves lie. Serious complications, such as VA loss of more than 2 Snellen lines, intractable inflammation, persistent hypotony, and phthisis, may ensue, making it an option mainly for refractory glaucoma after other options have failed.

The MP-TLT is a relatively new technology delivering treatment in duty cycles with periods of rest, thereby reducing collateral tissue necrosis and giving a better safety profile.

In a randomized exploratory study comparing the 2 modes in refractory glaucoma, both reduced the IOP similarly by 45%, with no significant difference in re-treatment rates or number of IOP-lowering medications. The ocular complication rate was higher in continuous wave–treated eyes, although a higher prevalence of NVG cases was noted in this group.

Finally, an ab interno approach to cyclodestruction can be done using the endoscopic cyclophotocoagulation (ECP) probe, which is usually done in combination with a cataract surgery, for mild to moderate glaucoma patients requiring additional IOP control or medication reduction. The only RCT described on ECP was published lately comparing phaco-ECP to phaco only in primary angle-closure glaucoma (PACG) patients, showing a mild additional reduction of IOP and medication use at 24 months in the treatment arm [14].

Schlemm canal–based procedures

Selective laser trabeculoplasty

SLT is a 532-nm Q-switched frequency-doubled neodymium-YAG laser aiming to increase trabecular outflow through several possible mechanisms. It is known to decrease the pressure by around 25% to 30% as a primary treatment, and to a variable extent in different other scenarios [15]. It usually is performed 360° under gonioscopic view, in one or multiple sessions.

Main indications

1 Ocular hypertension
2 POAG and normal-tension glaucoma
3 PXE glaucoma
4 Pigmentary glaucoma
5 Primary angle closure (PAC)/PACG with patent iridectomy and visible angle at least 180°
6 Steroid-induced glaucoma

This type of treatment usually is well tolerated, with very rare serious complications. One should beware in cases of pigmentary glaucoma owing to a higher rate of IOP spikes [16].

It can be presented at any stage of the disease with possible supplementary additive effect on IOP control. It can be done on phakic and pseudophakic patients, although some evidence has suggested some attenuated response in the early posttreatment period in pseudophakic patients [17].

Contraindications:

1 Uncontrolled uveitic glaucoma
2 NVG
3 Poor visualization of the TM

Schlemm canal–based microinvasive glaucoma surgery

Fig. 4 shows some examples of various MIGS procedures classified by their target route of treatment.

In humans, 75% of the resistance to aqueous humor outflow is thought to occur at the level of the TM, where most of this resistance is supposed to stem from the juxtacanalicular meshwork [18,19]. Mounting evidence has shown that the resistance to outflow is more complex and consists of 3 different levels

contributing to the total resistance: loss of permeability of the TM, collapse of the Schlemm canal, and downstream distal resistance [20]. Therefore, any procedure targeting any of these levels aims to augment the physiologic outflow through the conventional pathway that usually is impaired in patients with glaucoma. Although these procedures are known to have a higher safety profile than classic filtration surgery, their IOP-lowering efficacy usually is restricted to the episcleral venous pressure (EVP) at best, and their long-term results are far from being known.

These types of procedures as MIGS in general are usually approved by the FDA for implantation in conjunction with cataract surgery in patients with mild to moderate glaucoma, although in other countries, they might be used as stand-alone procedures, even in severe disease [21].

Procedures falling under this category can be subdivided into subcategories according to their mechanism of action:

1 Removal of the TM and inner wall of Schlemm canal
2 Disruption of the TM and inner wall of Schlemm canal
3 Implantation of a microstent to bypass the TM

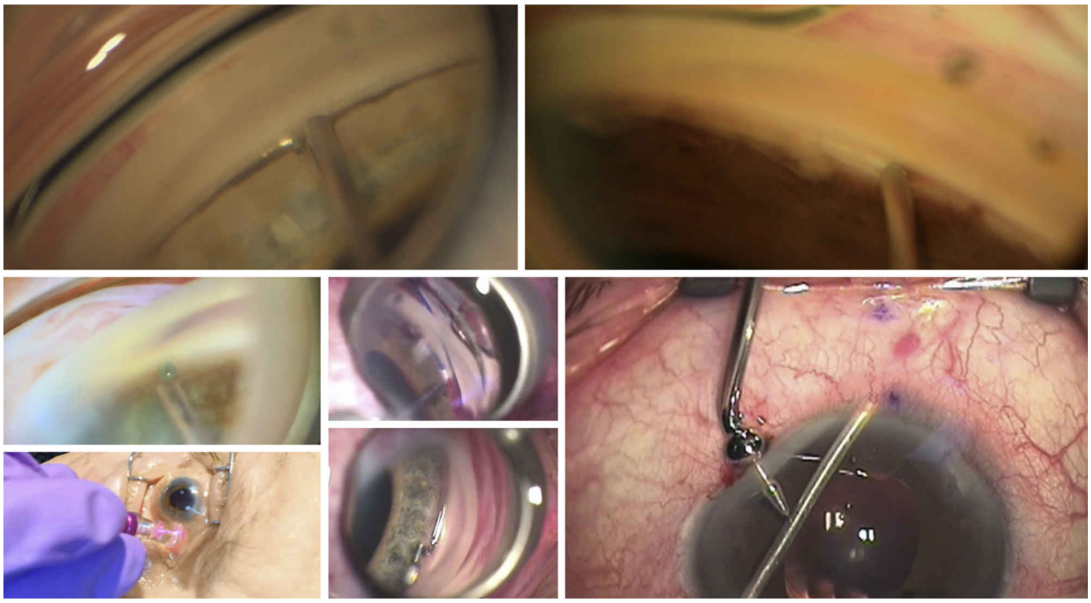

FIG. 4 Minimally invasive glaucoma surgery targeting different routes of filtration. (*upper left to lower right*) iStent G1, BANG, iStent inject, ab interno trabeculotomy using a Prolene 5-0 suture, micropulse CPC, hydrus, and ab interno Xen implantation. CPC, cyclophotocoagulation.

4 Dilation of Schlemm canal via an internal approach

Table 1 summarizes the main techniques used in either of the aforementioned subcategories, with relevant data on their safety and efficacy from select relevant studies.

Patients who are usually found suitable for these types of procedure include the following:

1 Patients well controlled or slightly above target under medical treatment presenting for cataract surgery
2 Patients with OAG mainly owing to trabecular dysfunction, including patients with PXE and pigment-dispersion glaucoma, and select cases of angle-closure glaucoma
3 Patients willing to reduce burden of medical treatment owing to cost, comfort, or tolerance issues
4 Patients with uncontrolled pressures found inapt to undergo subconjunctival surgery

Patients less suitable to undergo of these procedures include the following:

1 Patients with high EVP, such as Sturge-Weber syndrome
2 Patients who perform Valsalva maneuver very often, such as heavy weight-lifters, because of the increased risk of recurrent hyphemas mainly after excisional procedures
3 Patients with active ocular inflammation
4 Phakic patients with angle closure as a standalone procedure
5 Patients requiring low target IOPs
6 Multiple drug allergies precluding possible additional glaucoma medications postoperatively

Because of the paucity of large RCTs reporting on the efficacy and safety of different procedures and long-term effects, including clinical parameters other than IOP, it is difficult to draw firm conclusions on the efficacy of different MIGS procedures. In a recent large review of MIGS procedures summarizing the accumulating evidence on the efficacy and safety of MIGS procedures, certain conclusions possibly can be made [22]:

1 Phaco-MIGS procedures in general achieved higher mean reduction of IOP and postoperative medications relative to control.
2 iStent as a standalone procedure is more effective than medication alone and reduces postoperative medication use.
3 Implanting a second iStent adds to the IOP reduction, while implanting a third has a less pronounced additive effect.

4 Hydrus standalone procedure performs better when compared with iStent or ABiC.
5 Data regarding other Schlemm canal–based surgeries were less conclusive, and some did not meet the quality criteria set by the researchers.

Complications associated with these types of procedures mostly include different degrees of hyphema (generally less severe with the TM-bypass procedures), inflammation, stent obstructions, peripheral anterior synechiae (PAS) formation, and less commonly, vision loss.

Table 1 Minimally invasive glaucoma surgery, techniques, and efficacy

Removal of the trabecular meshwork and inner wall of Schlemm canal (ab interno trabeculectomy)			
Device	**Manufacturer**	**Design and technique**	**Efficacy**
Trabectome	NeoMedix, Tustin, CA, USA	Single-use electrocautery handpiece with irrigation and aspiration unit, for removal of 60°–120° of the trabecular meshwork	Inconclusive results regarding efficacy Seventy-eight percent of patients achieve IOP between 6 and 15 mm Hg and at least 20% IOP reduction without medications when combined with phaco at 2 y according to 1 report [22]
Kahook Dual Blade	New World Medical, Rancho Cucamonga, CA, USA	Single-use disposable blade with a sharp tip, which is used to pierce the trabecular meshwork, a ramp which stretches the trabecular meshwork, and dual parallel blades, which create paired parallel incisions in the trabecular meshwork	Phaco combined Kahook Dual Blade might be at least as effective as phaco-iStent for reducing IOP and medication burden [23,24]
Bent AbInterno Needle Goniectomy		Trabeculotomy using the bent tip of a 25-gauge needle	No long-term data available

Disruption of the trabecular meshwork and inner wall of Schlemm canal (ab interno trabeculotomy)			
Device	**Manufacturer**	**Design and technique**	
Gonioscopy-assisted transluminal goniotomy (GATT)	Ellex iScience, Fremont, CA, USA	Trabeculotomy 180°–360° using a 250-μm iTrack microcatheter with a fiberoptic tip advanced through the canal Trabeculotomy 360° using a Prolene 5-0 suture	Efficacy reported in primary, secondary, and juvenile open-angle glaucoma and prior incisional glaucoma surgery [25,26] Younger age may be predictive of success [27]

Disruption of the trabecular meshwork and inner wall of Schlemm canal (ab interno trabeculotomy)			
Device	**Manufacturer**	**Design and technique**	
Trab360/OMNI	Sight Sciences, Menlo Park, CA, USA	Single-use handpiece with a microcatheter advancing from the tip allowing 2 opposite 180 trabeculotomies	

Implantation of a microstent to bypass the trabecular meshwork			
Device	**Manufacturer**	**Design and technique**	
iStent G1	Glaukos Corporation, San Clemente, CA, USA	Snorkel-shaped heparin-coated, nonferromagnetic titanium stent Central inlet: 120 μm	At 48 mo follow-up, a 14.2% between-group difference in favor of the combined iStent-phaco group vs phaco-only group was statistically significant for mean IOP reduction, compared with the phaco-only group, with a significant reduction in number of medications in both arms [28]
iStent inject-W	Glaukos Corporation, San Clemente, CA, USA	Bullet-shaped heparin-coated, nonferromagnetic titanium stent Inject: 0.36 width × 0.23 height Central inlet: 80 μm Inject: W: 0.36 mm width × 0.36 height Central inlet: 80 μm	At 24 mo, 75.8% of phaco-iStent inject eyes vs 61.9% of control phaco only eyes experienced ≥20% reduction from baseline in unmedicated IOP, while 83% of treatment arm achieving target unmedicated [29]

Table Continued

Implantation of a microstent to bypass the trabecular meshwork		
Device	**Manufacturer**	**Design and technique**

Implantation of a microstent to bypass the trabecular meshwork			
Device	**Manufacturer**	**Design and technique**	
Hydrus	Ivantis Inc, Irvine, CA, USA	Biocompatible nitinol 8-mm-long trabecular bypass device with 3 openings Increases trabecular outflow and scaffolds the Schlemm canal	At 24 mo, 77% of open-angle glaucoma patients achieved 20% or more decrease in unmedicated IOP after phaco-Hydrus compared with 57.8% in the phaco-alone group, with 1.4/1 medication reduction, respectively [30]

Dilation of Schlemm canal via an internal approach			
Device	**Manufacturer**	**Design and technique**	
Ab Interno Canaloplasty		iTrack microcatheter inserted through a small goniotomy and passed 360° with viscodilation on retraction	When compared with Hydrus, both implants allowed significant IOP reductions, with comparable rate of clinical success and safety profile [31]
VISCO360/OMNI	Sight Sciences, Menlo Park, CA, USA	OMNI system combines the TRAB360 with the VISCO360	

Suprachoroidal

Suprachoroidal MIGS usually are implanted ab interno under clear corneal incision, into the suprachoroidal space, and can be combined with cataract surgery. The only device that was FDA approved for use is the CyPass Micro-Stent (Alcon Laboratories Inc, Fort Worth, TX, USA), which was voluntarily withdrawn in 2018 because of issues concerning endothelial cell loss at 5-year follow-up data.

CyPass (Alcon, Fort Worth, TX, USA)

This implant is 6.35 mm long with an outer diameter of 430 μm, an inner diameter of 300 μm, and with 76-μm fenestrations along the length of the device. It is implanted under clear corneal incision, using a guidewire advancing it to the scleral spur under gonioscopic view, where it is passed after blunt dissection with the guidewire into the supraciliary space. Three retention rings at the proximal end of the implant help to keep the implant in place.

The implant was mainly indicated in patients with mild to moderate POAG in conjunction with cataract surgery.

Two-year data from the COMPASS trial revealed compelling efficacy with 7.4-mm Hg mean IOP reduction from unmedicated preoperative IOP, with 85% of patients off glaucoma medications. Seventy-seven percent of the phaco-CyPass treatment arm and 60% of the phacoemulsification control arm achieved an unmedicated IOP reduction of ≥20% at 2 years [32].

Possible complications of the procedure include hypotony, IOP spikes, hyphema, device occlusion, device malposition, and VA loss.

Later unpublished data from the COMPASS-XT study have shown a significant ECL loss in the phaco-CyPass group at 5-year follow-up, with ECL loss correlated to the length of the tube in the anterior chamber [33].

MINIject (iSTAR Medical, Isnes, Belgium)

The *MINIject* (iSTAR Medical, Isnes, Belgium) is a biocompatible porous silicone implant built for optimal tissue integration aiming to reduce fibrosis.

iStent Supra (Glaukos, San Clemente, CA, USA)

The *iStent Supra* (Glaukos, San Clemente, CA, USA) is a 4-mm implant made from polyethersulfone and titanium, with a 165-μm heparin-coated lumen, planned for ab interno implantation.

Both devices use the suprachoroidal outflow pathway and are still awaiting FDA approval.

Special considerations

Patients with very advanced disease

The risk of long-term vision loss after classic filtration surgery, such as trabeculectomy, has been estimated to be up to 7% in some studies. Risk factors include preoperative split fixation and postoperative choroidal effusions with eventual resolution [34]. As the risk for postoperative choroidal effusions is present even with the less-invasive subconjunctival procedures, the use of Schlemm canal–based procedures, even at the expense of less IOP reduction, might be a safer choice, in patients with very diffuse visual field loss and residual central islands of vision.

Patients with very high intraocular pressure

Some patient populations are considered high risk for the development of choroidal effusions and suprachoroidal hemorrhage, 2 potentially devastating complications after filtration surgery. These patients include those with systemic hypertension and tachycardia, using anticoagulant or antiplatelet therapy, having very high preoperative IOP, or high EVP. Preventing hypotony in this particular population is of special importance, in order to reduce the risk of development of these 2 serious complications. Choosing procedures with lower risk of hypotony and choroidal detachment should be of high priority in these patients [35].

Fig. 5 summarizes some preferred options for treatment in this subset of patients.

Patients with angle-closure glaucoma

Most of the previously described surgical options are indicated in patients with OAG, whereas some of the procedures might not be an option for patients with angle closure.

Patients with angle closure are usually classified into the 3 following groups [36]:

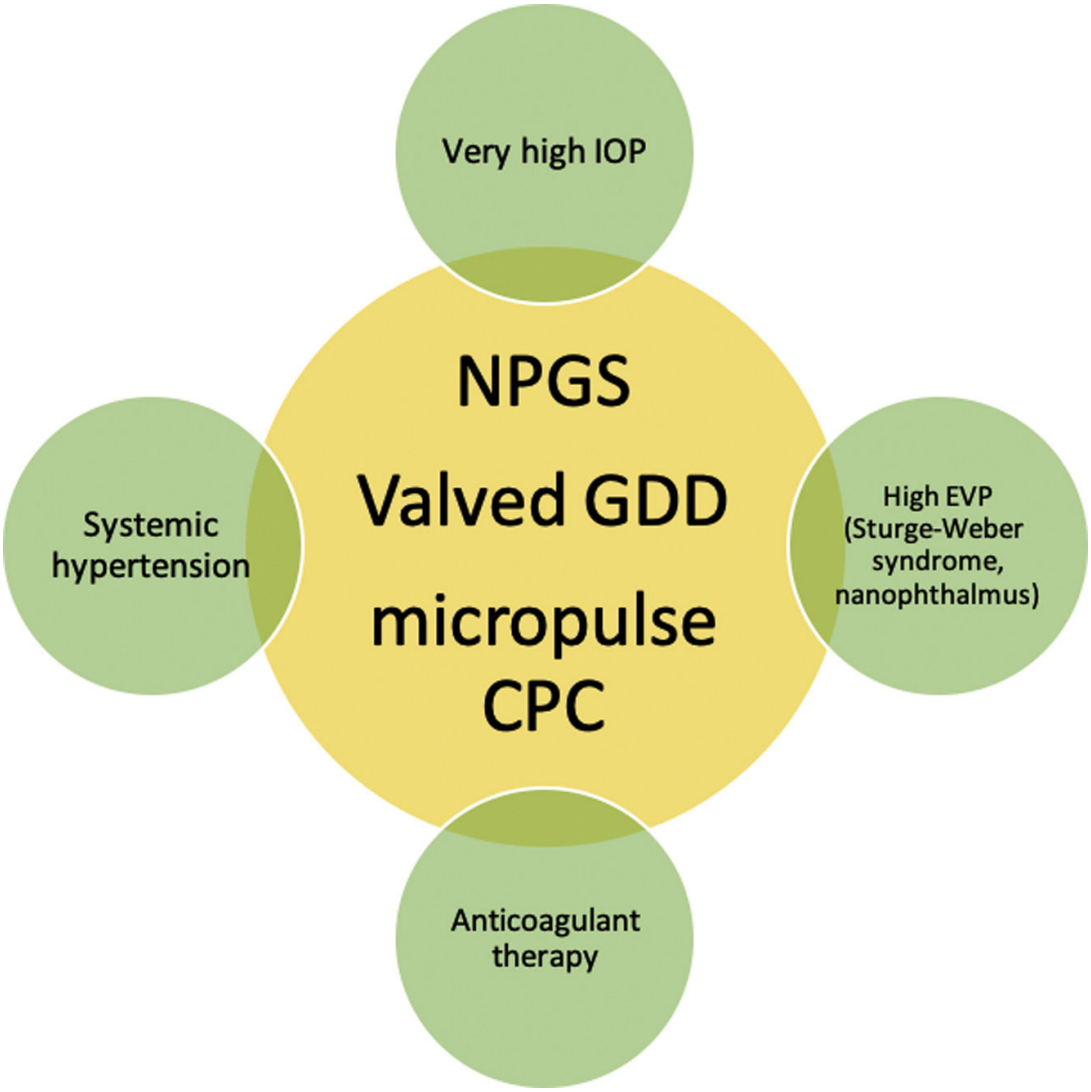

FIG. 5 Recommended procedures in patients with risk for choroidal detachment.

- Primary angle-closure suspect (PACS)
- PAC
- PACG

Laser peripheral iridectomy (LPI) classically has been the treatment of choice in patients with PACS, mainly for the prevention of acute angle closure (AAC) glaucoma crisis and progression to PAC.

It is mostly a benign procedure, although with possible short-term and long-term side effects, such as iritis, pressure spikes, cataract formation, and dysphotopsias.

The Zhongshan Angle Closure Prevention (ZAP) trial was the first RCT examining the effect of LPI on PACS progression compared with observation

[37].The study concluded that LPI had a limited, although significant, prophylactic effect on progression of PACS to PAC, advising against the widespread use of LPI in this setting. Notably, the restriction of the population study to Chinese population and other methodology issues might preclude the generalization of the study results to all the patients with PACS.

The decision to treat should be made on an individual basis. Factors supporting treatment with LPI include the following:

- Patients with symptoms characteristic of intermittent or impending episode of AAC
- Patients with low compliance to treatment and follow-up
- Patients with AAC in the fellow eye
- Patients with family history of angle-closure glaucoma
- Patients with retinal disease necessitating frequent fundus examinations

Primary angle closure

Phacoemulsification is especially useful in PAC and PACG patients associated with cataract, as it not only helps improve vision by removing the cataract but also helps to significantly reduce IOP and improve angle parameters.

The EAGLE trial included patients with PAC or mild to moderate PACG patients aged 50 years and older, with pressures greater than 30 mm Hg but no cataracts, who were randomized to clear lens extraction or LPI. Patients who underwent clear lens extraction had lower pressures, had more open angles, and needed less glaucoma medications and later surgical interventions than the laser group. In addition, the cost-effectiveness of treatment and the patients' quality of life were slightly better in the phaco group [38].

In general, older patients with PAC and PACG, especially if they have cataractous lens changes and or presbyopia, are now being offered earlier lens extraction as an option to treat their condition, although discussion with the patient is warranted if they do not have the same inclusion criteria as those in the Eagle study.

Primary angle-closure glaucoma

In this subtype of patients, glaucomatous damage is already evident, associated with PAS formation and or high IOP. As noted before, phacoemulsification alone might be sufficient to decrease the IOP to target and is known by itself to improve the angle parameters, anterior chamber depth, and PAS extent.

Goniosynechiolysis (GSL) is another tool that might be combined with the phacoemulsification procedure, especially when a significant amount of anterior synechiae is still present during intraoperative gonioscopy after the cataract is removed [39]. Combining GSL to phacoemulsification seems to be superior to phacoemulsification alone and comparable to trabeculectomy or phacotrabeculectomy in terms of IOP reduction in chronic angle-closure patients [40].

GSL can be done during phacoemulsification surgery using cohesive viscoelastic alone, cyclodialysis spatula, or microinstruments to pull the peripheral iris in the anterior-posterior axis. Possible complications include postoperative inflammation, hyphemas, iridodialysis/cyclodialysis formation, and possible corneal damage.

Angle-based MIGS also might play a role in patients with PACG. A more recent article compared phacoemulsification with injection of 2 iStents (G1 or inject) to phacoemulsification alone, in patients with PACG. The former intervention yielded significantly greater reductions in IOP and medication use and was more protective against early postoperative IOP spikes [41].

Patients with neovascular glaucoma

The aim of the treatment in this case is usually multifaceted. Proper treatment for the cause of ischemia-producing angiogenic factors, usually with panretinal photocoagulation and anti-VEGF injections, should be provided alongside treatment for controlling IOP.

This diagnosis is usually a harbinger of a poor prognosis, and the glaucoma may be refractory to treatment.

For control of their glaucoma, medical treatment might be enough. In more advanced cases, intervention usually in the form of tube shunts or cyclodestructive procedures should be done.

Often patients with good visual acuity have a valved glaucoma drainage device (GDD; eg, Ahmed) implanted because of the immediate reduction of IOP and lower chance of hypotony and risk of choroidal effusion given the high preoperative pressures.

Patients with low visual potential more often are treated with cyclodestructive procedures, usually with TSCPC. MP-CPC also might be a viable option in both scenarios. A recent study has shown promising results for high-energy MP-CPC with adjunctive use of intravitreal ranibizumab with a good durable effect until 24 months without serious complications.

Fig. 6 proposes a simplified approach for the choice of the right glaucoma procedure. As mentioned earlier, many other factors should be balanced into the equation, and various surgical options might fit into the same clinical

scenario at the discretion of the glaucoma surgeon according to his/her experience.

Reoperation after failed glaucoma surgery

Glaucoma is a chronic disease associated with successes and failures. It is like a rollercoaster with many ups and downs, where each sudden turn is associated with increased emotional load for both the surgeon and the patient.

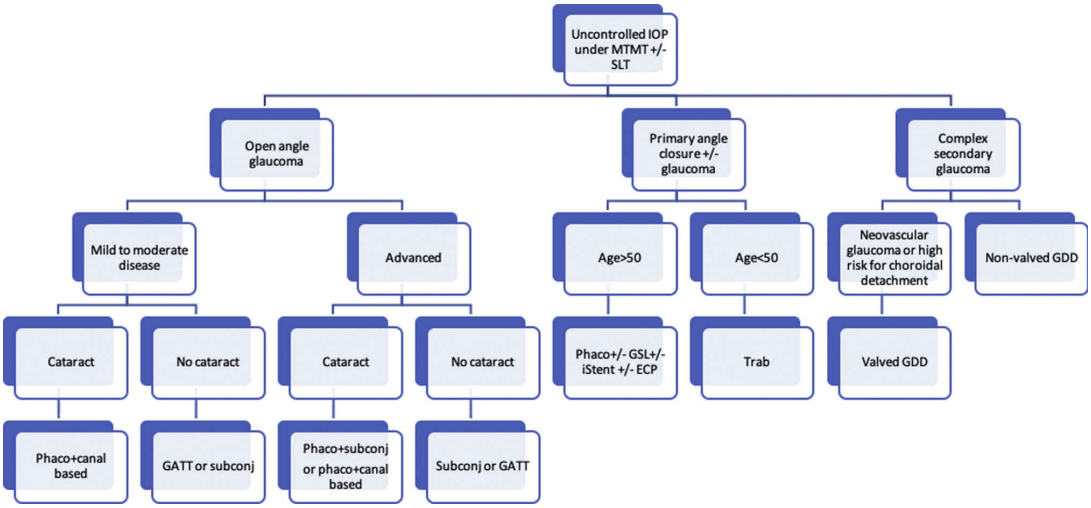

FIG. 6 Flowchart for the choice of primary surgery in the glaucoma patient. MTMT, maximally tolerated medical treatment; Trabeculectomy.

The biggest dilemma each glaucoma surgeon faces is what to do when the primary glaucoma surgery fails, especially when even maximally tolerated medical therapy cannot bring the pressure down into the target pressures zone.

In deciding on successive glaucoma surgeries, the same factors described earlier should be kept in mind with adjustments made as required. In addition, one should strongly consider switching to another route of filtration, as choosing the same route might bring about the same factors causing failure in the first place.

The following are 3 different scenarios any experienced glaucoma surgeon will encounter:

1 Failed conjunctival surgery:

- If the first surgery is salvageable, it might be wise to save the resting conjunctiva for later options and try to perform needling or revision of the bleb with injection of antifibrotics to increase the chances of success. Reports about revision of trabeculectomy surgery have yielded good long-term results [42].

- If the first operation is not salvageable, as in the case of high risk for postoperative leak because of an ischemic bleb or very scarred conjunctiva, then one should think about performing another type of conjunctival surgery if the condition of the conjunctiva allows, and in any case, performing a tube surgery should be strongly advised, as the chances of success might be higher with this type of surgery, as reported in earlier studies.
- Angle surgery also might be an option to be considered. Gonioscopy-assisted transluminal trabeculotomy (GATT) was shown to be safe and successful in treating 60% to 70% of open-angle patients with prior incisional glaucoma surgery, including trabeculectomy and tube shunts in 1 retrospective study [26].

2 Failed angle surgery:

Early failure of a Schlemm canal–based surgery might indicate a diseased distal outflow rendering a second-angle surgery less plausible. In the case of a later failure, another angle-based operation might be not feasible, as in the case of removal of large portions of the TM in GATT surgery.

Similarly, after trabectome surgery in which only part of the TM is excised, treating the rest of available TM with SLT, has shown a very limited duration of significant IOP-lowering effects with low success rates [43]. A histopathologic study comparing changes after iStent, which spans a very limited area of the TM, when compared with specimens from normal and glaucoma human TM tissues showed histopathologic changes adjacent to the location of implants consistent with inflammation and scarring [44], a fact that might preclude a second-angle surgery spanning the nasal angle. In this case, one might opt directly for the subconjunctival route or ciliary body procedures, as they have a higher chance of success.

3 Failed tube surgery:

In this case, there are several options to consider:

- If the tube is thought to be functioning, but to a limited extent, one might try flushing the tube with saline or viscoelastic using a 30-cc syringe via an ab interno or externo approach
- Revision of the bleb over the tube with excision of the capsule restricting flow
- Replacement of valved implant to a nonvalved implant
- Insertion of a second tube in an opposite quadrant
- Performing CPC laser. One study comparing this technique to insertion of a second tube has shown a superior long-term

efficacy for CPC with more VA conservation at 12 months, but with more secondary interventions needed [45]. The American Glaucoma Society (AGS) is sponsoring a trial to compare a second Baerveldt shunt to diode cyclophotocoagulation (the ASSISTs trial [AGS Second aqueous Shunt Implant vs TransScleral Treatment Study]).

- Performing Schlemm canal procedures. One study reported a success rate of 84% at 12 months after trabectome surgery for a failed tube surgery [46]. Similar success rates have been described as mentioned earlier with the GATT procedure after incisional surgery.
- Limited reports have described the use of a retrobulbar shunt device connecting the anterior chamber into the retrobulbar space, although it is not yet commercially available and is undergoing further studies [47].

As data on the failed tube management are mainly from reported retrospective case series, it is difficult to draw conclusions on the efficacy of each surgical intervention, and the decision for intervention should be done on an individual basis (Box 1).

Current relevance and future avenues

The surgical treatment of glaucoma has seen a huge revision in the past 2 decades, with the addition of incremental tools in the surgical repertoire. The choice of which surgery to do after medications or laser trabeculoplasty can be less straightforward than it has been once, because of the more abundant options to choose from, sometimes with overlapping indications to use.

Subconjunctival surgery with trabeculectomy as the classic representative, tube shunts as the classic opponent, and other less penetrating candidates on the way, have proven to be the most efficacious route of IOP reduction, usually with a higher complication rate and opted for when more significant intervention is needed. This route of intervention has seen the increase of modern representatives, such as the Xen implant and Preserflo microshunt, which are undergoing major evaluation to elucidate their exact role and share in the overall picture, with very promising preliminary results. Furthermore, new devices have been designed lately that aim to add more controlled postoperative course, possibly preventing hypotony after nonvalved tube shunts. The EyeWatch (Rheon Medical, Lausanne, Switzerland) is one such device, composed of a deformable silicone tube, which drains aqueous humor to a nonvalved implant, such as Baerveldt. Resistance to flow can be adjusted using a magnetic pen laid and rotated externally over the implant, which contains a magnetic disk that controls the compressibility of the draining tube and hereby the resistance to outflow.

Box 1 Re-treatment options after failed primary surgery

Failed subconjunctival
- Bleb revision
- GDD
- Schlemm canal–based
- Ciliary body/suprachoroidal

Failed angle
- Subconjunctival
- Ciliary body/ suprachoroidal

Failed GDD
- Tube revision
- Implant replacement
- Second GDD
- Ciliary body/suprachoroidal
- Schlemm canal–based

- Retrobulbar shunt

The introduction of Schlemm canal–based MIGS into the glaucoma surgeon's life has made a huge update to the capabilities of intervening at an earlier stage with a well-predictable high safety profile, even at the expense of reduced efficacy. The physiologic outflow pathway that is usually the endpoint for damage in most glaucoma diagnoses seems like a very natural factor to target, with many procedures aiming to bypass or eliminate this impediment to natural outflow, usually in combination with phacoemulsification surgery. Although many of these procedures may be either modest in effect and duration or awaiting more evidence-based data to support their role, the ability to introduce them at an earlier stage with the possibility to buy time on the long journey with our glaucoma patients may be beneficial. Delaying more significant surgery with several failed "safer" procedures, however, may result in higher cost and progression of the disease with irreversible visual field loss.

The ability to predict which patient might respond best to these types of procedures should be the focus in the years to come. Aqueous angiography is one of these lately described invasive methods of visualizing the distal outflow pathways, which might prove indispensable in predicting treatment response to different Schlemm canal–based procedures. Future advances might lead to the development of less invasive methods of visualizing the distal outflow structures.

The suprachoroidal pathway for glaucoma treatment is another route of target that has been examined over the years. The Gold shunt was 1 promising example of such device, but unfortunately has been plagued by high rates of failure because of fibrosis. CyPass was another device pulled off the market because of safety issues concerning the corneal endothelium, which has elevated the need for more long-term safety-focused research on different MIGS procedures. Other new devices described above, some of which were designed to address the issues of reduced fibrosis, need to be examined in the coming years to show their potential efficacy and safety.

Among these 3 routes of interventions, less-invasive laser treatment options exist that target the different outflow pathways and should be considered along the treatment spectrum whenever indicated. SLT has been used more often as a primary treatment, even replacing medications, in suitable glaucoma patients, in the shadows of the LiGHT study published recently. It comes with a very high safety profile, short-term efficacy, which might buy time in many different scenarios [48]. Newer SLT platforms exist, such as the Direct Selective Laser Trabeculoplasty (BELKIN Laser Ltd, Yavne, Israel), which provide automated noncontact SLT treatment delivered transsclerally, providing shorter treatment

courses with preliminary comparable results to the conventional delivery method [49].

The introduction of MP-TLT has possibly changed the notion of keeping cyclodestructive interventions until later in the disease process, when all other options have been exhausted, and might integrate nicely in different scenarios along the spectrum, although it awaits firmer data from RCTs to pinpoint its exact role. Still, care should still be taken when using this procedure early on, as it might prove to affect the success of later surgical intervention, because of its proinflammatory potential [50]. Time will tell if it is going to replace the older G-probe TSCPC treatment, which has been traditionally saved for refractory neovascular or chronic glaucoma patients with low visual potential, giving results ranging from inefficacy and need for repeated treatments, and rarely, phthisis bulbi.

Cataract surgery has been offered more commonly to patients with PAC or PACG. Apart from the EAGLE study, several studies have shown the superiority of early cataract surgery to LPI in preventing IOP increase after AAC and improving angle parameters in these patients [51]. Together with the ZAP trial, which has shown LPI to be not cost-effective and recommended against its routine use for in PACS patients, it would be interesting to see the changing trends of LPI use by glaucoma practitioners over the next years.

Patients with failed glaucoma surgeries pose a rising burden on the system, challenging the glaucoma surgeon faced with the diminishing options. The classic Trab-Tube-CPC pathway has been challenged recently with the rising new treatment options, with limited data on the utility of different options in re-treatment. Again, it might be wise to consider less-invasive methods along the way even at the expense of reduced or short-term efficacy, as the journey is long, and opting for more invasive traditional surgery, such as tube shunts, might considerably limit options in the case of failure. As mentioned before, the ASSIST study is a running study aiming to better understand our mode of action in the case of a failing tube.

That said, many new devices are on the way, some of them using different routes to reduce the IOP. One such device, the Beacon Aqueous Microshunt (MicroOptx, Maple Grove, Minneapolis, MN, USA), shunts the aqueous humor directly to the ocular surface, implanted through an ab externo approach, theoretically providing an advantage to glaucoma patients suffering also from dry eye syndrome, although possibly raising the issue of long-term infections. This device is still undergoing preliminary trials to examine its safety and efficacy. Other devices combine elements of both classic filtration surgery and MIGS. One such device, the minimally invasive microsclerectomy (Sanoculis, Kiryat Ono, Israel) device, uses an ab interno approach to perform a sclerocorneal drainage channel resembling that of trabeculectomy. Last,

renewed interest has been shown lately in the ExTra Laser System (ExTra ELT; MLase AG, Germering, Germany), which received a CE mark in 2014. This treatment uses a 308-nm xeon chloride excimer laser to create openings through the TM and inner Schlemm canal. It was shown to be effective in patients with POAG refractory to medical treatment and has shown good results comparable to those of SLT, with the advantage of being combined with phacoemulsification [52].

Summary

The question of which glaucoma procedure best fits which patient has been complicated recently by the enlarging advances of new glaucoma devices and techniques, which have on one hand enriched our possibilities for intervention, but on the other hand have produced the need for much more quality research to examine their efficacy. Although in the past, the choice to surgically intervene would mean opting for either a classic filtration surgery, such as trabeculectomy, or a tube shunt when refractory to medical treatment, nowadays intervening at an early level is recommended by many to control other factors, such as medication burden, compliance, and quality of life.

The decision of which treatment to choose should be dictated in part by the type of the disease, level of the disease, preoperative and target pressures, ocular status, different patient parameters, and surgeon preference.

It is reasonable to classify glaucoma interventions according to the route of targeted treatment into the following: subconjunctival, Schlemm canal–based, and suprachoroidal procedures, as this might give a better indication of the level of efficacy achieved by each approach.

The choice of the subconjunctival route should be made when in need of a lower target pressure, in advanced disease, or when past angle-based surgery has failed to provide the required target. Although trabeculectomy can be chosen when in the need of a single-digit target pressure, other interventions, such as the Xen, and the Preserflo implants might provide similar or slightly reduced efficacy in exchange for a faster surgery, better safety profile, and faster recovery, yet awaiting results from head-to-head RCTs. DS might give good results comparable to those of trabeculectomy, with a safer postoperative course. Tube shunts, on the other hand, should be reserved mainly for patients with failed subconjunctival surgery, conjunctival scarring, and secondary complex glaucoma cases precluding the option for other procedures in the category.

Cyclodestructive procedures are usually indicated in patients with low visual potential refractory to medical or surgical treatment, but the addition of micropulse laser treatment to the arsenal has raised the possibility of earlier treatment owing to the higher safety profile compared with continuous-wave TSCPC. Endocyclophotocoagulation is another ab interno approach to cilioablation that awaits further validation in future studies.

Schlemm canal–based procedures are more suitable for patients with mild to moderate glaucoma and concomitant cataract, in need of more control of their IOP or medications. It might also be considered in patients who have failed prior incisional surgery, unwilling or at risk of serious complications undergoing additional surgery.

The suprachoroidal space is yet to be studied more to provide answers to fibrosis issues, and some promising devices are on the way, while others have failed because of safety or efficacy issues.

Patients with PAC or PACG might benefit from early cataract surgery, as it might be a more permanent solution to their IOP and improve significantly their angle parameters. Additional interventions, such as GSL, should be considered strongly, especially when a significant amount of residual PAS is remaining at the end of the cataract surgery. The addition of an MIGS procedure when visualization of the angle is rendered feasible, might have an added benefit in these cases.

Patients with NVG are usually more refractory to treatment and entail the choice of a tube shunt, preferably with a valved mechanism or ligated tube in a nonvalved shunt to provide an immediate reduction of IOP with less risk of hypotony and choroidal effusion in view of the very high IOPs usually present. Cyclodestructive procedures are to be strongly considered when the visual potential is very low, although micropulse laser treatment also should be considered in patients with good visual acuity.

In conclusion, the increasingly enlarging treatment arsenal for glaucoma has fortified our capabilities of defying this chronic disease and makes us wait for more data on their use and anticipate with eagerness further innovations and scientific breakthroughs in the field.

Clinics care points

- In patients requiring low target pressure postoperatively, one should opt for subconjunctival surgery.
- Avoid doing Schlemm canal–based procedures, especially excisional procedures, in patients who perform Valsalva or those with high episcleral venous pressure.
- One must make all efforts to prevent hypotony in patients undergoing subconjunctival surgery, especially in older patients with very high preoperative pressures and advanced disease.

Disclosure
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Ocular Blood Flow as It Relates to Race and Disease on Glaucoma

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Keywords

Glaucoma; Ocular blood flow; Race; African descent; Modeling; Disparity; Artificial intelligence; Demographics

Key points

- In certain individuals, glaucoma involves, in part, an impaired blood supply to the retina and/or optic nerve head, contributing to glaucomatous damage.
- The vascular contribution to glaucoma pathogenesis and progression has been shown to play a more significant role in persons of African descent compared with European descent.
- Current research highlights the importance of considering demographics, including race, and the inclusion of vascular risk factors in the management of glaucoma.
- Artificial intelligence and mathematical modeling may provide the framework for a comprehensive glaucoma model inclusive of race, vascular biomarkers, and clinical outcomes to reduce disease disparities.

Introduction

Glaucoma, a progressive multifactorial optic neuropathy characterized by retinal ganglion cell and retinal nerve fiber layer (RNFL) degeneration, is the world's leading cause of irreversible blindness, accountable for approximately 12% of global cases [1]. Although the pathophysiology of glaucoma is still not fully understood, primary open-angle glaucoma (OAG) has been historically attributed to elevated intraocular pressure (IOP). Currently, reduction of elevated IOP is considered the only approved modifiable risk factor (RF) to arrest the onset and progression of glaucoma. However, many patients develop and experience glaucoma progression without elevated IOP, whereas some patients with elevated IOP never experience glaucomatous vision loss. As a result, other RFs have been proposed, including vascular contributions to the glaucomatous disease process [2–4]. It has been demonstrated over many decades that OAG in certain individuals is, at least in part, the result of an impaired blood supply to the retina and/or optic nerve head (ONH; (Figs. 1 and 2). Over time, a strong association between ocular blood flow biomarkers and glaucoma has been established; however, it often is unclear whether vascular abnormalities are the primary insult of the disease or rather secondary to the disease process itself [2,4]. Rather than a singular RF, it is likely a combination of physiologic events, including elevated IOP, poor vascular health, lifestyle, and genetics and demographics, that combine to determine the overall risk for the onset and progression of glaucoma in a given individual.

Although glaucoma is a disease that universally affects all humans, significant OAG disease disparities exist within certain population groups, especially in persons of African descent (AD) [5,6]. Compared with their European descent (ED) counterparts, in persons of AD, OAG presents earlier, is more severe, and has a stronger ocular vascular component; in turn, AD populations also are known to have higher rates of systemic vascular disease [5–8]. As a result, researchers [2] have sought to understand not only to what extent hemodynamic mechanisms are involved in OAG but also how in part they might be responsible for the observed racial disparities seen in glaucoma.

Herein, the authors review the relationship between ocular blood flow and race and explore their potential involvement in the onset and progression of glaucoma. By summarizing key population-based and prospective studies, potential connections can be made between vascular

health, glaucoma, and racial disparities of the disease. In addition, mathematical modeling and artificial intelligence applications that consider patient demographics and vascular biomarkers alongside clinical RFs may provide the framework to achieve individualized precision medicine and improved outcomes for vulnerable populations.

Significance

Glaucoma is the single largest cause of irreversible blindness worldwide and is responsible for significant racial disparities and impact, especially in persons of AD [5,6]. Disease management is currently limited to IOP-modifying medications and surgical interventions, yet many treated patients continue to experience disease progression, whereas considerable proportions of glaucoma are represented by normal-tension glaucoma (NTG) [1]. Ocular vascular abnormalities involving biomarkers of perfusion, metabolism, and blood flow, along with optic disc hemorrhages, migraine, and nocturnal hyper/hypotension, also have been associated with OAG [2–4]. The extent to which IOP-induced mechanical damage versus vascular insult occurs in glaucoma, either separate or in combination, may be dependent on a person's overall vascular health, genetics, and ocular resiliency.

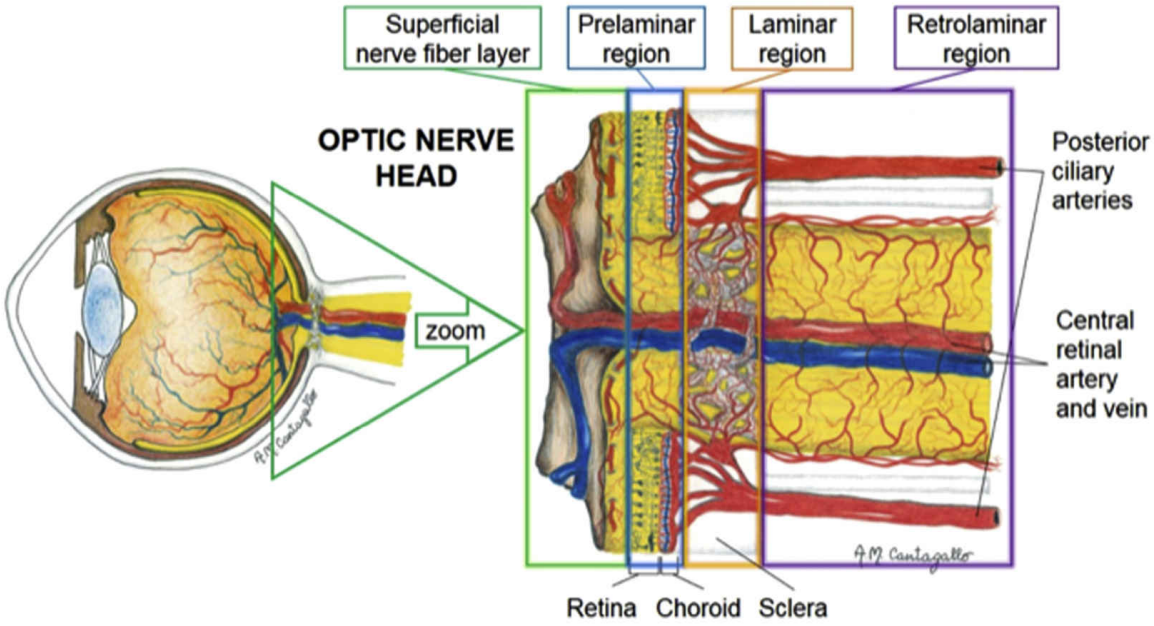

FIG. 1 Anatomy and vascular supply of the ONH. The ONH includes the superficial nerve fiber layer, the prelaminar region, the laminar region, and the retrolaminar region.
(*From* Prada D, Harris A, Guidoboni G, Siesky B, Huang AM, Arciero J. Autoregulation and neurovascular coupling in the optic nerve head. Survey of Ophthalmology 2016 Mar 1;61(2):164 to 86; with permission.)

Racial disparities in glaucoma

Population-based studies have demonstrated significant racial differences in glaucoma onset and progression, suggesting genetics/demographics and especially race may be a particularly important RF to consider. Specifically, OAG disproportionately affects persons of AD when compared with those of ED, with approximately 6 times as many cases reported in AD populations [9]. In addition, AD populations have been shown to have earlier disease onset, more rapid glaucomatous progression, worse disease severity, and greater visual function and higher IOP compared with ED populations [5,6]. Glaucoma patients of AD have been shown to have increased visual field variability compared with patients of ED, possibly delaying detection of progression and effective treatment [10].

Across other populations groups, those of Asian descent and Latin American descent (LAD) have average prevalence rates of OAG that are greater than ED but less than AD, whereas the prevalence in Middle Eastern (ME) populations is estimated to be similar to that of Asian populations with relatively limited data available [11–15].

Mechanisms behind racial disparities in glaucoma

Although the underlying mechanisms explaining racial differences in OAG are not entirely clear, a variety of hypotheses have been suggested, including differences in aqueous humor dynamics, anatomic variation, such as differences in corneal thickness and optic disc area, oxidative stress, lamina cribrosa and scleral morphology, and vascular mechanisms [5,6,16]. Importantly, populations of AD tend to have a higher prevalence of systemic vascular conditions, including cardiovascular disease, diabetes mellitus, and associated RF, such as sedentary lifestyle and smoking, with resulting organ damage that generally is more severe and occurs earlier than in other populations [8]. Given the known differences in rates of systemic vascular disease in AD populations, the vascular cause of glaucoma may be particularly relevant when considering mechanisms behind racial disparities of glaucoma in persons of AD [6,17].

Ocular perfusion pressure

A key vascular biomarker associated with differential glaucoma outcomes in different racial populations is ocular perfusion pressure (OPP). OPP is an estimate of the pressure difference between arterial (estimated by mean arterial pressure [MAP]) and venous circulation (estimated by blood pressure [BP]-IOP) with various calculations for mean, systolic, and diastolic OPP measurements [2]. Many population-based studies have demonstrated a consistent relationship between estimates of OPP and glaucoma prevalence [2,4]. Specifically, in 2000, the Egna-Neumarkt study demonstrated that lower levels of diastolic OPP (DOPP = diastolic BP − IOP) were associated with an increased prevalence of OAG in an ED population (DOPP < 68 mm Hg, odds ratio [OR]: 1; 68 to 78 mm Hg, OR: 0.33, 95% confidence interval [CI]: 0.14–0.58; P<.001) [18]. Similarly, the Barbados Eye Study demonstrated that the prevalence of OAG was associated with low DOPP in an AD population (DOPP < 52.3 mm Hg, OR: 3.29; CI: 2.06–5.28; P<.05) [19]. These results were confirmed by the Baltimore Eye Study, which found that both ED and AD patients with DOPP less than 30 mm Hg had a race-adjusted risk of OAG higher than patients with DOPP ≥50 mm Hg (OR: 6.22, CI: 2.15–17.94) [20]. Within LAD populations, the Proyecto Ver Study associated low OPP with OAG (X^2 = 28.8; P = .001, test for trend; age-adjusted OR: 0.96, CI: 0.94–0.99), whereas the Los Angeles Latino Eye Study associated low systolic OPP (SOPP = systolic BP − IOP) (OR: 2.5), DOPP (OR: 1.9), and mean OPP (MOPP = MAP − IOP) (OR: 3.6) with higher prevalence of OAG [12,21].

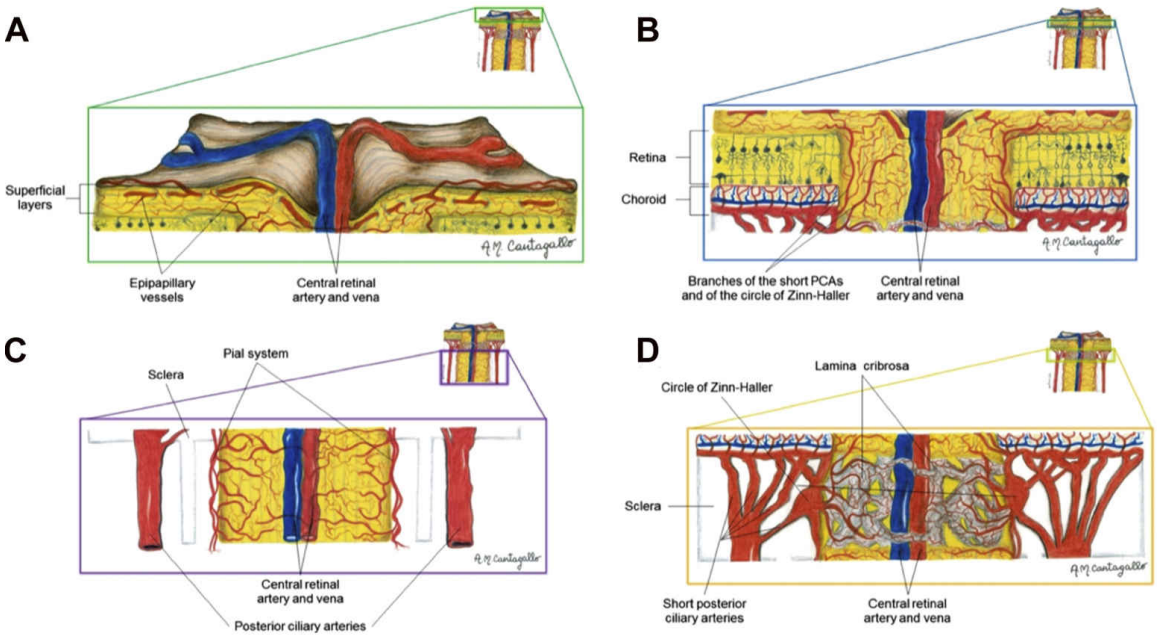

FIG. 2 Detailed views of the ONH regions. (*A*) Superficial nerve fiber layer (SNFL). The SNFL receives oxygenated blood primarily from retinal arterioles. These small vessels, called epipapillary vessels, originate in the peripapillary SNFL and run toward the center of the ONH. (*B*) Prelaminar region. The prelaminar region is mainly supplied by direct branches of the short PCAs and by branches of the circle of Zinn-Haller. The circle of Zinn-Haller, if present, is a complete or incomplete ring of arterioles within the perineural sclera formed by the confluence of branches of the short PCAs. (*C*) Laminar region. Blood flow to the laminar region is provided by centripetal branches of the short PCAs. The centripetal branches arise either directly from the short PCAs or from the circle of Zinn-Haller. The lamina cribrosa is shown as a 3D network. (*D*) Retrolaminar region. The retrolaminar region is supplied by the CRA and the pial system. The pial system is an anastomosing network of capillaries located immediately within the pia mater.
(*From* Prada D, Harris A, Guidoboni G, Siesky B, Huang AM, Arciero J. Autoregulation and neurovascular coupling in the optic nerve head. Survey of Ophthalmology 2016 Mar 1;61(2):164-86.; with permission.)

In Asian populations, the Singapore Malay Eye Study found glaucoma risk was higher for patients with low MOPP (OR: 1.73, CI: 1.05–3.15), whereas the Handan Eye Study showed that OAG patients had consistently lower SOPP, DOPP, and MOPP (P<.05) [22,23]. In addition, the Barbados Eye Study suggested that lower SOPP, DOPP, and MOPP were associated with increased glaucoma incidence in an AD population (relative risk [RR]: 0.66, CI: 0.54–0.80 per 10 mm Hg higher). Conversely, the Rotterdam Study found a nonstatistically significant association with incidence in an ED population (hazard ratio [HR]: 0.995 per mm Hg

increase in MOPP; CI: 0.971–1.019) when adjusted for IOP [24,25]. Referencing the wealth of population-based data, in 2009, the World Glaucoma Association identified low OPP as an independent RF for OAG [4].

In addition to data on OAG prevalence and incidence, OPP has been identified as a possible biomarker for glaucoma progression. In 2007, the Early Manifest Glaucoma Trial identified low SOPP as a baseline predictor of structural glaucoma progression (≤160 mm Hg; HR: 1.42, CI: 1.04–1.94) [26]. Similarly, McGlynn and colleagues [27] identified MOPP as associated with structural progression measured by both RNFL thickness (OR: 0.3 per 10 mm Hg, CI: 0.08–0.8; $P<.02$) and by progressive parapapillary atrophy (OR: 0.4 per 10 mm Hg, CI: 0.2–0.9; $P<.02$) using flicker chronoscopy. A recent systemic review and meta-analysis suggested diurnal variability or fluctuation in OPP, as opposed to a single timepoint of OPP, may be more relevant to OAG progression especially in NTG patients [28].

Directly measured ocular blood flow biomarkers

Numerous directly assessed hemodynamic biomarkers from a wide variety of imaging modalities have been identified as being associated with OAG [2,4]. Imaging techniques used to quantify ocular vascular biomarkers include ultrasound Doppler imaging techniques, scanning laser Doppler modalities such as Heidelberg retinal flowmetry (HRF), laser speckle flowgraphy, optical coherence tomography angiography (OCTA), and retinal photographic oximetry. It is important to note that there is no gold-standard imaging modality capable of assessing all relevant ocular vascular beds in glaucoma. In addition, hemodynamic biomarkers assessed by each different imaging technique have inherent limitations, require expertise, and generally are not interchangeable [2,29].

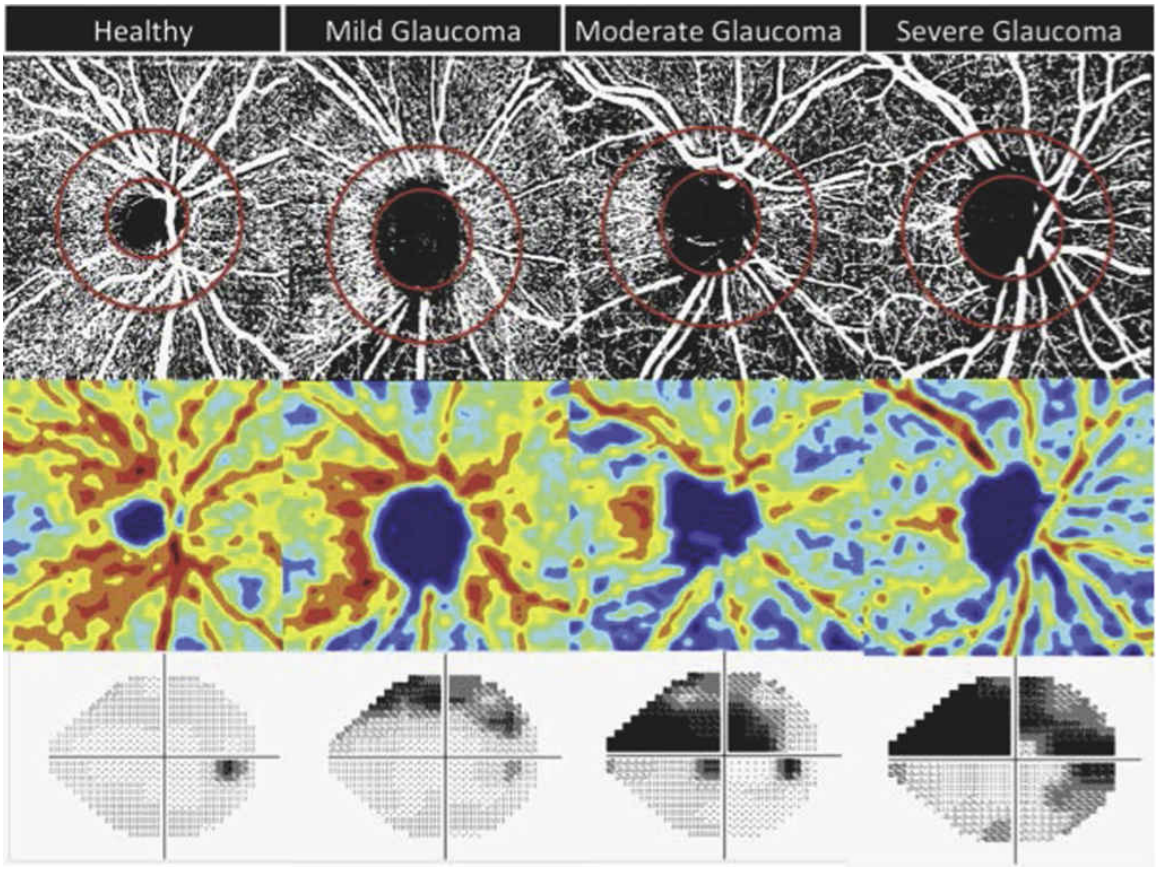

FIG. 3 OCTA images with corresponding visual fields. Correlation between vessel densities measured with OCT-A and visual field results, in both healthy controls and patients with glaucoma. Patients with glaucoma of several degrees have progressive peripapillary vessel deficits that correspond to greater relative visual field loss. This demonstrates a relationship between structural changes and functional changes. (*From* Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Relationship between optical coherence tomography angiography vessel density and severity of visual field loss in glaucoma. Ophthalmology 2016 Dec;123(12):2498-2508; with permission.)

Many studies have routinely shown an association between retrobulbar blood flow and glaucomatous disease [2–4]. For example, Galassi and colleagues [30] conducted a longitudinal study on the association between retrobulbar blood flow and functional progression demonstrating a 6-fold increased risk of perimetric disease progression in patients with an elevated ophthalmic artery (OA) resistance. Similarly, Martínez and Sánchez [31] identified higher baseline OA and short posterior ciliary artery (PCA) resistance were predictive of functional disease progression. Calvo and colleagues [32] also found that patients who progressed structurally had a lower OA end-diastolic blood flow velocity and higher

OA resistance. More recently, in 2017, Moore and colleagues [33] identified that lower baseline OA blood flow velocities and OA resistance were associated with both structural and functional glaucoma progression after 4 years.

In 2015, Siesky and colleagues [7] identified that OAG patients of AD had significantly lower retrobulbar blood flow biomarkers in the OA, central retinal artery (CRA), and short PCAs. Specifically, they found lower OA peak systolic (PSV) (P = .0001) and end-diastolic (EDV) (P = .0008) velocities, lower CRA PSV (P = .01), and lower temporal PCA PSV (P = .0037) and nasal PCA PSV (P<.0001) in OAG patients of AD. It is important to note that these lower blood flow velocities in AD OAG patients were independent of IOP and visual field differences, which were similar in AD and comparative ED cohorts [7]. In 2016, Siesky and colleagues [34] confirmed these findings in a prospective study over 4 years demonstrating PCA EDV and vascular resistance were more strongly correlated to glaucomatous changes in the ONH structure in AD patients when compared with ED patients. Importantly, Kaskan and colleagues [35] further identified lower retrobulbar blood flow biomarkers in nonglaucomatous AD eyes finding lower EDV in nasal PCAs (P = .01) and higher vascular resistance in the temporal PCA (P = .01) and CRA (P = .04). Together, these data suggest persons of AD may both be at an elevated risk for OAG development and have a higher risk of vascular involvement in the glaucomatous disease process.

OCTA modalities attempt to bridge the gap (in a single imaging device) of assessing proven clinical outcomes, such as RNFL, macular, and ONH structure, with vascular biomarkers in critical ocular tissues. Using laser light to generate high-resolution images, OCTA can quantify papillary and peripapillary vessel density (VD) and the ONH flow area at a specific point in time, allowing scientists to map the superficial vasculature. Initial studies using OCTA demonstrated that decreased VD was associated with glaucoma when compared with healthy eyes, whereas correlations between structural parameters, such as RNFL thickness, ONH parameters, and ganglion cell complex thickness, have been correlated with decreases in VD [2,36]. Fig. 3 shows OCTA imaging of vascular biomarkers from both glaucomatous and healthy eyes.

In 2019, the African American Eye Disease Study found healthy AD eyes had lower peripapillary perfusion that was influenced by thin RNFL and longer axial lengths [37]. It is important to note a recent finding by Moghimi and colleagues [38], who found peripapillary capillary density

parameters had good diagnostic accuracy for detecting glaucoma in patients of ED patients, but significantly worse diagnostic accuracy in patients of AD. Physiologic variability in age, sex, and systemic vascular health conditions, such as diabetes, also have been shown to influence OCTA vascular biomarkers in AD populations [39]. A recent small pilot study of 28 AD and 56 ED eyes found no significant differences in OCTA assessed peripapillary and macular microcirculation; however, both biomarkers were significantly correlated with disease severity in AD and ED [40].

Retinal capillary beds assessed with other imaging technologies, such as HRF, have shown reduced retinal capillary activity and vascular density in OAG patients of AD compared with ED. In 2014, Kanakamedala and colleagues [41] found that AD OAG patients had strong negative correlations between change in superior mean retinal capillary blood flow and cup/disc ratio (CDR) ($r = -0.78$; $P = .020$) and cup area ($r = -0.75$; $P = .0283$), and strong positive correlations with change in rim area ($r = 0.74$; $P = .0328$), with similar associations between inferior mean retinal blood flow and CDR (−0.88, $P = .0156$) and linear CDR ($r = -0.86$; $P = .0265$) over 3 years. When compared with ED OAG patients, the same correlations were weak and lacked statistical significance. Similarly, Siesky and colleagues [34] used customized HRF applications, finding a significantly larger increase in the avascular area of the inferior retina in patients of AD compared with ED that strongly correlated with reductions in macular thickness and that was independent of IOP.

Retinal oximetry is a photographic imaging technique that estimates blood oxygen saturation levels in retinal blood vessels. Generally, retinal oximetry has been used to note that glaucoma patients have higher oxygen saturation in retinal veins compared with healthy patients, whereas they have a lower arteriovenous saturation difference [2]. In consideration of race, Siesky and colleagues [42] found AD OAG patients had a significantly decreased arteriovenous difference (Fig. 4A, B) compared with OAG patients of ED (24.4% ± 9.3% vs 36.4% ± 14.1%; $P = .03$), with no significant difference in the mean oxygen saturation of retinal arteries ($P = .25$) nor veins ($P = .33$). This may be due to the lower vascular density described [34] in AD OAG patients, reduced capillary function in AD patients, and/or reduced functional oxygen utilization [2,42]. It is important to note, however, that differing levels of retinal pigment represent an unknown limitation when analyzing retinal oximetry across different population groups [2].

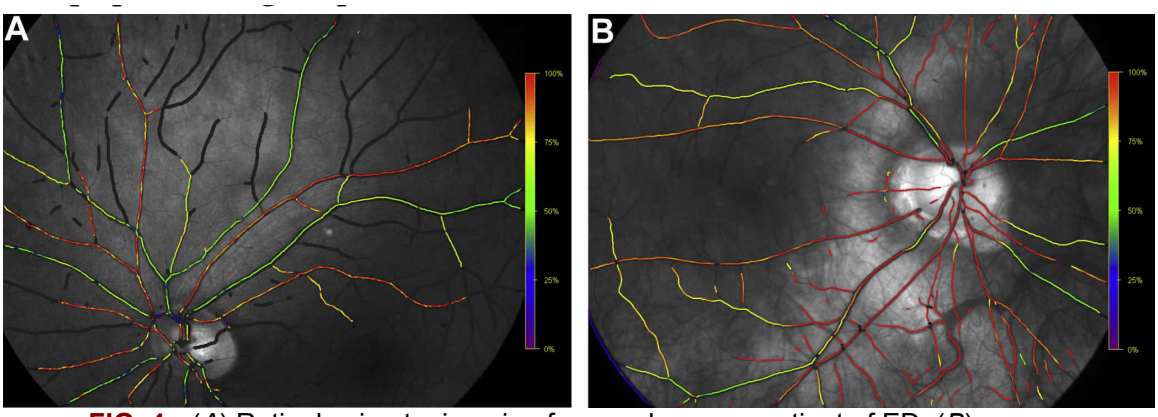

FIG. 4 (*A*) Retinal oximetry imaging from a glaucoma patient of ED. (*B*) Retinal oximetry imaging from a glaucoma patient of AD showing reduced arterial/venous difference in oxygen content of vessels.

Although some pilot data are available on ocular blood flow differences in OAG patients of AD and ED, little is known about other racial population clusters. In Asian populations, some studies have shown that systemic hypertension is associated with NTG, whereas others have shown evidence of vascular changes associated with glaucoma and independent of IOP [43,44]. Many studies suggest a higher level of vascular involvement in NTG, a condition frequent in Asian populations [2,4]. Studies of LAD populations have shown the association between glaucoma and low DOPP, but studies directly examining the vascular contributions to disease are severely lacking [12–14]. Currently, almost no information is available on ME glaucoma populations and its relationship to vascular health.

Current relevance and future avenues to consider or to investigate

Understanding the vascular contributions to glaucoma, as well as the interplay of race and individual susceptibilities, is a key factor to improving glaucoma management and patient outcomes. Alongside IOP, vascular involvement in the disease process has been well documented for many decades with recent pilot data suggesting a more significant contribution in persons of AD compared with ED. Other racial groups, including persons of Asian descent, LAD, and ME descent, lack available comparative data in the literature, rendering the understanding of mechanisms, including possible vascular causes, behind their disease disparity rates difficult to uncover [11–15]. This stresses the urgent need

for data from large, population-based studies that are carefully designed to include and analyze OAG patients of different races.

Multidisciplinary research using mathematical modeling and artificial intelligence may help bridge the gap in available data to better understand racial, vascular, and demographic impact on glaucoma outcomes. This is an especially important approach to understand ocular hemodynamics and metabolism, as currently no gold standard exists for determining ocular vascular health with many ocular tissue beds relevant to glaucoma. Mathematical modeling techniques thus allow for a virtual laboratory where hypotheses surrounding retinal perfusion and tissue oxygenation changes can be built and tested in a controlled environment [2]. The benefits of mathematical approaches are especially relevant for modeling vascular contributions to glaucoma as well-understood hemodynamic laws, and principles can be built testing specific hypotheses that are unable to be directly visualized with imaging instrumentation.

Historically, mathematical modeling has been used to test everything from Newton's laws to Poiseuille's laws of hemodynamic flow. More recently, mathematical models have been developed to test the hypothesis of glaucomatous damage that is unable to be observed in real time. For instance, modeling has been used to investigate ocular biomechanics with regard to tissue strain and stress from IOP and cerebrospinal fluid pressure (CSFp), with more theoretic studies regarding circulation and oxygenation currently in development [2,45,46]. These mathematical models allow for hypotheses to consider the individual contributions of BP, IOP, vascular regulation, CSFp, and a variety of hemodynamic biomarkers at once as opposed to multiple different clinical measurements assessed by standard statistical analysis. For example, in 2014, Guidoboni and colleagues [45] created the first mathematical model to account for retinal vascular blood flow, blood flow autoregulation, BP, and IOP by using an electric circuit analogy, as seen in Fig. 5. By modeling retinal vascular blood flow as an electric current, with resistors and capacitors to model vascular resistance and compliance, a model was developed that was able to clinically predict variance in hemodynamic outcomes in trabeculectomy patients [47]. As for the vascular theory of glaucoma, the model posits that as IOP shifts, a patient's plateau of vascular regulation similarly shifts, leading to possible blood flow reductions secondary to venous collapse in lower BP individuals, making these individuals more susceptible to ischemia [45].

Clinically, this suggests that in patients with low BP, an IOP greater than 21 mm Hg would lead to venous collapse at lower IOP values than patients with higher BP, findings that are reflective of known correlations with glaucoma and diurnal hypotension [2]. Interestingly, these findings were further corroborated when applied to data from the Singapore Epidemiology of Eye Diseases study, a population-based analysis of nearly 10,000 people from a multiethnic Asian population. When data from this study were applied to the mathematical model, individuals with high IOP (≥21 mm Hg) and low systolic BP (<124 mm Hg) had a 1.69 times higher risk of glaucoma [48]. Perhaps the most relevant clinical takeaway from the Guidoboni and colleagues [45] model, however, is that a given IOP in an individual may not communicate higher risk for glaucoma alone; rather, IOP represents a complex clinical picture that is dependent on more comprehensive data. As modeling and artificial intelligence networks advance and become more inclusive of all RFs, race and demographic inputs will likely improve specificity of disease management and reduce the economic and quality-of-life impacts seen in glaucoma disparity, especially in persons of AD.

A comprehensive approach to understanding risk in OAG requires careful weighting of clinical markers, such as IOP and ONH structure, as well as consideration of demographics, including age, gender, and race, alongside vascular health and ocular hemodynamic biomarkers. A significant challenge exists in understanding the impact of a single variable, such as IOP or OPP, for a given individual. Individual variance in ocular structure and vascular networks lends complexity to a given biomarker's impact on the glaucoma disease process. Given the incredibly fine nature of the retinal and ONH microvascular network, modeling has used poroelasticity and structural viscoelasticity to describe the vasculature in ways previously unseen [2]. Clinically relevant outcomes of these models suggest that aging or other disease may lead to reductions in structural viscoelasticity, and, therefore, prevent ocular tissues from maintaining perfusion when affected by sudden changes in IOP. In fact, this suggests that physiologic sudden changes in IOP, such as from blinking or rubbing eyes, may in fact have pathologic consequences and induce glaucomatous change in the ONH [2]. Other mathematical models have built on these findings, as well as explored the interplay between hemodynamics and oxygen transport in order to explore the impact of hypoxia on ocular tissues [2].

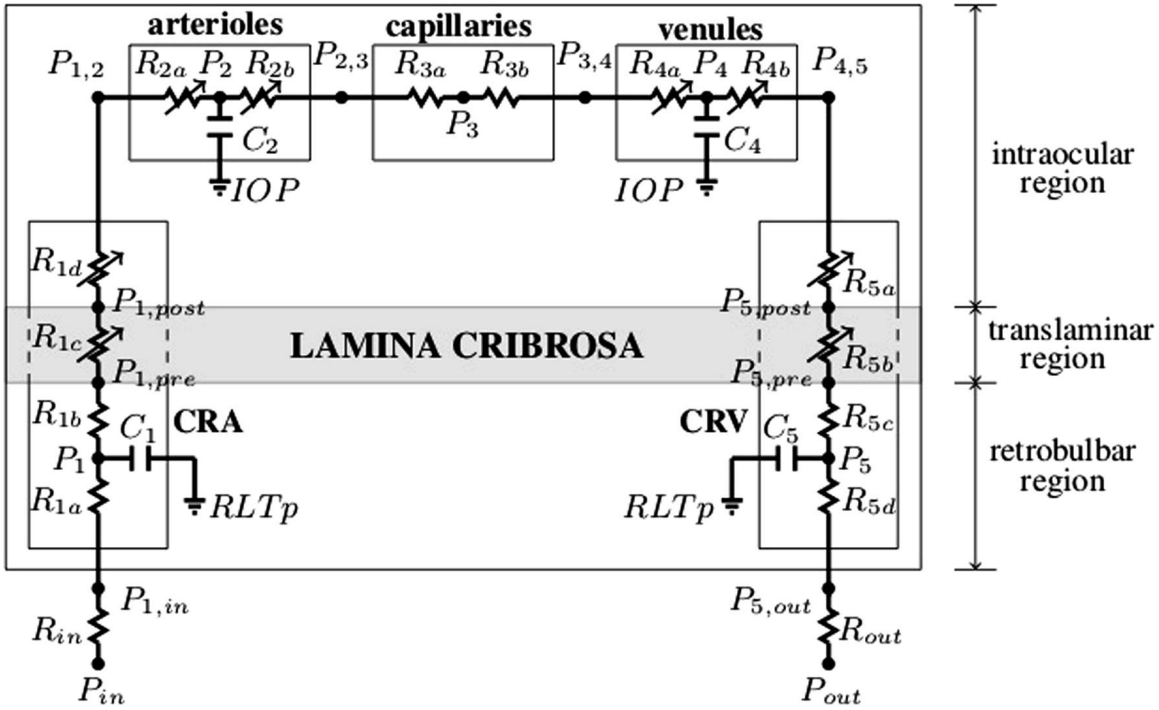

FIG. 5 Network model for the retinal vasculature. The vasculature is divided into 5 main compartments: the CRA, arterioles, capillaries, venules, and the central retinal vein (CRV). Each compartment includes resistances (*R*) and capacitances (*C*). The intraocular segments are exposed to the IOP; the retrobulbar segments are exposed to the retrolaminar tissue pressure (RLTp), and the translaminar segments are exposed to an external pressure that depends on the internal state of stress within the lamina cribrosa (*gray shaded area*). Diameters of venules and intraocular and translaminar segments of the CRA and CRV are assumed to vary passively with IOP, whereas arterioles are assumed to be vasoactive.
(*From* Guidoboni G, Harris A, Cassani S, et al. Intraocular pressure, blood pressure, and retinal blood flow autoregulation: a mathematical model to clarify their relationship and clinical relevance [published correction appears in Invest Ophthalmol Vis Sci. 2015 Oct;56(11):6247]. Invest Ophthalmol Vis Sci. 2014;55(7):4105-4118; with permission.)

Mathematical models based on the principles of physics and physiology have the potential of being translatable across studies in different populations, thereby yielding an opportunity to provide a mechanistic understanding of differences in glaucoma pathogenesis and progression in different races. The future of these approaches may allow individualized demographic characteristics, such as age, gender, race, and other confounding disease states, such as diabetes, to be incorporated into a comprehensive model to provide evidence-based individualized glaucoma management plans [49]. The future inclusion of clinical and vascular data from specific ethnic cohorts into established models of glaucoma damage

may help identify the underlying mechanisms for racial disparities in glaucoma that currently remain enigmatic. For example, according to Guidoboni and colleagues [45], racial differences have been detected in a variety of ocular tissues, including the geometric properties of the cornea. Given the influence these tissues have on IOP and optic nerve tissues, it is possible that the complex interplay between biomechanics and ocular tissues could explain racial disparities in glaucoma. As for hemodynamics, the individual variations of ocular tissues seen in populations of different races may lead some to be more prone to vascular insult, and mathematical modeling will allow for a better understanding of the mechanisms of these hemodynamic variations [17]. Currently, many more factors are observed to vary among individuals of different races than those that can be accounted for in principle-based mathematical modeling; yet principles of physics and physiology are translatable across races and yield hope to identify differences in RFs and disease mechanisms. In recent years, artificial intelligence techniques show great promise to bridge the gap between the rigor of principle-based modeling and the variety of real data [50].

Summary

Glaucoma is the worldwide leading cause of irreversible blindness, with significant disease disparities in the AD population. Current treatments remain limited to reduction of IOP, and modern therapies have failed to fully arrest the disease in many individuals. Vascular insult and hemodynamic contributions to the glaucomatous disease process are well established in certain patient groups, especially in persons of AD. A lack of available ocular hemodynamic data from certain population groups, including persons of LAD, ME descent, and Asian populations, limits the current understanding of racial differences in OAG pathologic condition. Glaucoma is likely a disease initiated by a multifactorial collection of RFs that include IOP, ocular structure, ocular circulatory health, and demographics, including age, gender, and race. These RFs may interact in synergistic ways that elevate risk yet are unseen and unaccounted for during normal clinical examinations.

Mathematical modeling and artificial intelligence applications may help better understand the unseen forces acting in glaucoma pathogenesis. Current modeling is limited by availability of data, especially directly assessed vascular biomarkers in differing racial groups. As these models expand and undergo rigorous testing, and more robust data can be incorporated, a comprehensive model of glaucoma may be finally realized. This will require, however, integration of individual patient characteristics with proven clinical outcomes, such as IOP and retinal and ONH structures, alongside biomarkers of vascular structure and oxygen transport efficiency.

At the base level of these complications and complexities, however, is the fact that glaucoma itself is a complex, heterogeneous disease. Glaucoma pathogenesis and progression are difficult to study, requiring longitudinal data collection that is complicated by aging processes, medication regimens, and other chronic disease. In addition, because populations of AD are most impacted by glaucoma, there may be a resource allocation challenge inherent to the studies required to fully understand glaucoma RFs. Other population clusters, such as persons of LAD and ME, remain significantly understudied in regard to ocular blood flow and glaucoma.

Despite these challenges, a wealth of research points to a bright future with improved understanding of glaucoma, particularly as it relates to vascular involvement in racial disparities. Currently, an urgent need exists

for large, carefully designed prospective trials to advance the understanding of vascular involvement in glaucoma, especially in vulnerable patient populations. Technological limitations in imaging modalities may be mitigated by modeling approaches that provide mechanistic understanding of vascular insult in combination with elevated IOP, or through IOP-independent pathways. Going forward, reducing racial disparities in glaucoma remains an important goal for clinicians and researchers alike. Designing future prospective studies in collaboration with mathematical modeling and artificial intelligence approaches may uncover previously unseen synergies of clinical RFs, vascular health, and patient demographics. Advancing knowledge of glaucoma RFs specific to high-risk population groups will ultimately culminate in reduced racial disparities through improved diagnosis and disease management.

Clinical care points

- Glaucoma is a multifactorial disease with high variation in risk factors and a cause that affects each person differently.
- Reductions in ocular blood flow and/or faulty vascular regulatory function are involved in the onset and progression of glaucoma in certain individuals.
- Persons of African descent are at elevated risk for glaucoma and have higher levels of vascular involvement in the disease process.
- Understanding of vascular contributions to the glaucomatous disease process is hindered by methodological limitations and a lack of sufficient longitudinal data.
- Mathematical modeling of risk factors inclusive of clinical, vascular, and demographic considerations may improve diagnosis and disease management.

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Neuro-ophthalmology

OUTLINE

Glaucoma as a Neurodegenerative Disease

A Clinician Perspective

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Keywords

Glaucoma; Neurodegenerative; Neuroprotection; Retinal ganglion cells; Neuro-ophthalmology

Key points

- Glaucoma is a neurodegenerative disease with changes in other parts of the central nervous system. Glaucoma should be viewed as a dichotomy, as a sole disease of the eye, not as a primary neurologic disease.
- Intraocular pressure, cerebrospinal fluid pressure, translaminar cribrosa pressure, as well as other ocular or systemic risk factors all play an intricate role in the disease development and progression.
- A neurologic perspective is crucial for clinicians to understand retinal ganglion cell insult, subsequent brain damage, and concomitant functional morbidity in the glaucoma patient. It may bring insights into future therapeutic innovations and open up opportunities for better patient care.

Introduction

Rather than being considered primarily an eye disease, glaucoma is increasingly being recognized as a neurodegenerative disease in recent years. This transition is further propagated by the increasing awareness of the existence of normal tension glaucoma (NTG) and the recognition of the presence of non-intraocular pressure (IOP) - dependent risk factors. Despite the paradigm shift in thinking, controversies persist as to whether glaucoma should be viewed as a neurologic disease.

Is glaucoma a neurodegenerative disease?

Neurodegenerative disease classically is characterized by selective loss of a specific neuron population with subsequent progressive functional decline. Classical examples include Parkinson disease (PD), Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD). Anatomically and developmentally, the optic nerve should not be considered a nerve but rather an extension of the brain with retinal ganglion cells (RGC) representing a specialized part of the central nervous system. Glaucoma is a progressive optic neuropathy resulting from a decrease in axonal transportation with subsequent loss of RGC, resulting in irreversible visual loss [1]. In this context, it is not difficult to understand why glaucoma is a neurodegenerative disease. Increasing evidence shows that glaucoma shares similar pathophysiological mechanisms as other neurodegenerative diseases. The question of interest is whether glaucoma begins as a brain disease and, second, whether glaucoma is related to other neurodegenerative diseases.

Sick eye comes with a sick brain

Like other axons, damage of the RGC will result in both anterograde and retrograde axonal degeneration of the injured tract proximally and distally through transsynaptic degenerative processes. In glaucoma, where RGC is the primary injured site, retrograde degeneration will lead to a loss in the cell bodies in the retina, whereas anterograde (or Wallerian) degeneration will result in degenerative changes of all the connected visual pathways [2]. Evidence exists that physiologic or functional abnormalities account for the reduction of retrograde transportation before structural loss and axonal dystrophy become apparent [3]. Instead of an ocular disease, it is important to perceive glaucoma as a disorder of visual neurons of the eye as well as the brain. This concept will help understand the progressive nature of the disease and the importance of comprehensive treatment strategies in the future to prevent visual loss in glaucoma [4].

Experimental models in primates have demonstrated loss of magnocellular and parvocellular lateral geniculate nucleus (LGN) neurons in glaucoma when compared with controls. Studies also were able to indicate that the loss of LGN neuronal area follows a linear pattern with increasing mean IOP or optic nerve fiber loss [5], and that a higher mean IOP reduced the period during which these changes occur [6]. Evidence shows that these visual pathway disturbances in glaucoma is a relatively early phenomenon, as decreased dentritic complexity of LGN neurons can occur with elevated IOP without detectable optic nerve fiber loss in primate glaucoma [7]. Elevated IOP with or without optic nerve fiber loss also reduced the expression of a major postsynaptic density protein in the koniocellular neurons [8], leading to the theory of impaired transsynaptic changes in LGN in early glaucoma.

Beyond the LGN, a postmortem case report has shown pathologic evidence of neural degeneration in multiple vision stations within the brain, including the visual cortex in the presence of advanced glaucoma with 50% visual field loss [9]. Neuroimaging studies are now able to measure LGN volume and objectively document LGN

atrophy in patients with glaucoma with the extent correlating to clinical stage [10]. Compared with normal controls, diffusion tensor imaging of the visual pathway using a 3-T MRI has further confirmed radiological evidence of neurodegeneration of the optic tracts and optic radiations [11] as well as occipital white matter [12] in primary open-angle glaucoma (POAG) patients. High-resolution structural MRI detected significant bilateral cortical thinning in the anterior half of the visual cortex around the calcarine sulci and in some smaller regions located in the left middle temporal gyrus, and fusiform gyrus of which the reduction of visual cortex thickness correlated positively with the retinal nerve fiber layer (RNFL) thickness [13]. With the advent of functional MRI (fMRI), function-specific neuronal activity of the visual afferent pathways can be assessed in glaucoma patients noninvasively in vivo. By using fMRI signals to assess cortical function, blood oxygen level–dependent signal in visual cortex was found to be altered for patients with POAG in a manner consistent with the loss of visual function [14].

Although one may consider the atrophy of the relaying visual pathway as part of the anterograde degeneration from RGC, there are intracranial changes for which transsynaptic degeneration cannot account. Three-dimensional MRI has revealed widespread abnormalities in the central nervous system beyond the visual cortex with significant reduction of bilateral gray-matter volume in lingual gyrus, calcarine gyrus, postcentral gyrus, right cuneus, right inferior occipital gyrus, left occipital gyrus, left paracentral lobule, and right supramarginal gyrus [15]. More recent imaging study using multimodal MRI has demonstrated anatomic and functional connectivity changes since early glaucoma in visual as well as nonvisual systems, such as working memory networks and subcortical networks, whereas atrophy is confined to severe stage [16]. These widespread disruptions of anatomic connectivity and altered functional connectivity beyond the visual system can be detected from the early stage of disease. A more recent cross-sectional observational study using multimodal MRI has demonstrated that, like inner retinal layer or RNFL thinning, reduced visual cortex activity occurred at a tipping point long before

visual field impairment in glaucoma patients. Primary visual cortex was found to be more severely affected than higher-order cortical region in glaucoma, whereas its activity loss has a stronger association with RNFL thinning than ganglion cell inner plexiform layer thinning. However, further longitudinal studies are required, as the decreased visual cortex activation could be secondary to reduced retinal visual input in established glaucoma patients.

Intracranial vascular changes were also identified in glaucoma patients. Case control studies using MRI have shown an increased number of white-matter hyperintense lesions (a reflection of covert vascular brain injury) in POAG patients [17] and diffuse cerebral small-vessel ischemic changes in NTG [18]. The potential ischemic pathophysiological basis in low-tension glaucoma is further supported by the findings of a greater extent of cerebral infarcts and corpus callosum atrophy in this group of patients [19]. NTG patients with ischemic changes in the brain MRI also were found to have more depressed inferior pericentral visual fields [20]. The authors' group has shown that the most common location of silent cerebral infarction (SCI) in NTG patients was at the basal ganglia, and SCI may be an independent risk factor for visual field progression in patients with NTG [21]. Besides brain volume, glaucoma patients were noted to have lower middle cerebral artery blood flow velocities and an absence of vasoreactivity to hyperoxia compared with controls [22]. This finding suggested that diminished central visual function may be 1 manifestation of widespread cerebrovascular insufficiency in certain POAG patients.

Common clinical characteristics between glaucoma and neurodegenerative disease

Besides intracranial changes in glaucoma patients, one can easily identify common clinical features shared between glaucoma and other neurodegenerative diseases, including insidious onset with preclinical stage, progressive nature, increased incidence with age, predisposing genetic susceptibility, and early functional deficit preceding loss of neuronal substrates. Despite the heterogeneous phenotypes, there is a predilection of specific target population cells in each of the different neurodegenerative diseases. AD affects hippocampal and cortical neurons; PD affects nigrostriatal dopaminergic neurons; ALS affects upper and lower motor neurons, while glaucoma affects RGC [23].

Epidemiologic studies have examined the hypothesis of the connection between glaucoma and other neurodegenerative diseases. The occurrence rate of glaucoma in AD patients was found to be higher than age-matched controls (23.8%–25.9% vs 5.2%–9.9%) in the absence of altered IOP levels [24–27]. Similarly, incidence of glaucoma was noted to be higher in PD patients (16%-23.7% vs 6.5%–6.6%) despite a normal or low IOP [25]. Besides abnormal glaucomatous visual fields, PD patients were found to have significantly reduced RNFL and macular ganglion cell volume [28]. Conversely, a retrospective population-based cohort of patients aged 60 or over reported that patients with POAG have a higher risk of developing AD but not PD [29]. These observations may suggest similarities between AD and POAG at a molecular or pathophysiological level. However, other nationwide cohorts did not find any increased risk of AD in POAG patients [30]. Later, a meta-analysis concluded that the association of AD and glaucoma is heterogenous, and further studies are warranted to clarify the association [31]. On the other hand, a weak association between glaucoma and dementia was being identified [32], whereas a

prospective study confirmed the finding and noted that POAG patients were 4 times more likely to develop dementia after adjusting for age, gender, education, family history, vascular comorbidities, and apolipoprotein E-e4 [33]. The actual mechanisms contributing to this association are not fully understood, but the adjustment analysis suggests that vascular risk factors are not the sole mechanism [32,33].

Overlapping pathophysiology between glaucoma and other neurodegenerative disease

Different neurodegenerative diseases share common pathogenic mechanisms leading to impaired axonal transportation, neuronal apoptosis, and eventual neuronal death. Emerging evidence suggests that glaucoma bears striking similarities in the pathophysiology, including neuroinflammation, oxidative stress, mitochondrial dysfunction, disrupted calcium homeostasis, alteration of autophagy machinery, protein misfolding, and glial activation.

Neuroinflammation

Neuroinflammation is one of the major contributors in the development of chronic neurodegenerative diseases like AD and PD. Similarly, mounting evidence suggests neuroinflammation is a key process in the pathogenesis of glaucoma. In the past, neuroinflammatory process was thought to be a result instead of a causative factor in neuronal death. Epidemiologic studies indicate that prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) can prevent or delay the development of AD [34] and PD [35]. However, randomized controlled trials and meta-analysis failed to demonstrate the efficacy of NSAIDs in the treatment of AD [36]. Ongoing research has led to the identification of the pivotal molecule in the inflammatory process of AD, such as glycogen synthase kinase-3 or nuclear factor-κB (NF-κB) [37,38]. Phase I and IIa clinical trials suggested that tumor necrosis factor-α inhibitors might slow down cognitive decline and improve daily activities in AD patients [39].

Unlike in AD and PD, the precise role of neuroinflammation in glaucoma is yet to be identified. The RGC axons at the optic nerve head were thought to be the site of initial insult, as evident by the

infiltration of leukocytes into the optic nerve head [40]. Although the initial trigger is unknown, mechanical alterations at the lamina cribrosa, direct pressure on RGC, and activation of glial cells (astrocytes and/or microglia) are potential factors to drive this damage. Blood samples from patients with glaucoma have indicated abnormal T-cell subsets and increased cytokines levels [41,42]. Compared with nonglaucoma controls, higher levels of pro-inflammatory cytokines have been found in the aqueous humor of glaucoma patients [43,44]. Further advancement in the understanding of the role of neuroinflammation in glaucoma may eventually open up an opportunity for future treatment in this aspect.

Oxidative stress and mitochondrial dysfunction

Because of the high oxygen consumption of human brain and neurons, the central nervous system is especially susceptible to oxidative stress. Mitochondrial dysfunction and overproduction of reactive oxygen species (ROS) are common pathogenic mechanisms in AD, PD, ALS, and HD. Oxidative stress is associated with amyloid β accumulation in AD and played an important role in PD. RGC also are susceptible to oxidative stress, as they are very thin and yet metabolically demanding, which is a disadvantage should available ATP diminish rapidly. Over time, light exposure to RGC promotes photo interactions, resulting in accelerated breakdown of endogenous antioxidant repair machinery of the mitochondria. There is cumulating evidence to support the involvement of oxidative stress as a component of glaucomatous neurodegeneration [45]. It has been shown that increased generation of ROS within RGCs from mitochondrial stress and DNA damage occurs early in glaucoma. Without altering IOP, oral administration of vitamin B3 (NAD + precursor nicotinamide) has been shown to be protective both prophylactically and interventionally against glaucoma development and RGC soma loss [46]. A prospective population-

based study in a glaucoma cohort of 3500 individuals revealed an association between low dietary intake of antioxidant (including retinol equivalents and vitamin B1) and a higher risk of open-angle glaucoma [47]. The exact pathogenic mechanism of oxidative stress in RGC loss was not fully understood. Besides direct cytotoxic effect, it is now thought that ROS can cause secondary RGC death via modulation of signaling pathway, dysfunction of glial cells, and activation of immune responses.

Dysregulation of calcium dependent process

Another important component of axonopathy across neurodegenerative disease is increased influx of extracellular Ca^{2+}, which triggers cytoskeletal degradation through enzymatic activity and eventually cell death. In glaucoma, cleavage of calcineurin (a Ca^{2+}-dependent protein phosphatase) occurs in response to elevated IOP, and calpains (a class of Ca^{2+}-dependent protease) are activated in RGC in experimental models [7,48], resulting in the breakdown of protein substrates. Delineating the role of specific Ca^{2+}-dependent neurochemical cascades in neurodegeneration in glaucoma IS important for future development of interventions [49].

Alterations of autophagy machinery

Autophagy is important for the clearance of intracellular components and recycling of anabolic resources. Excellent reviews have uncovered the emerging relationship between autophagy and various neurodegenerative diseases, including AD, PD, HD, ALS, and frontotemporal dementia [50]. Recent literature has shown that acute IOP elevation can induce a reduction of LC3II and beclin 1, 2 specific markers of autophagy, suggesting the role of IOP in disrupting autophagic mechanism [51].

Misfolding of proteins

Error in protein conformation is one of the common features in the pathogenesis of neurodegenerative disease. Examples include Lewy bodies in PD and Pick bodies in frontotemporal dementia. In AD, tau protein is abnormally phosphorylated to form extracellular β-amyloid plaques, which now are the current target component for drug development. Amyloid precursor protein (APP) is the most abundant protein in the optic nerve. Animal glaucoma models were able to demonstrate abnormal APP processing, and neurotoxic amyloid accumulation, while directly targeting the formation of amyloid-β, has shown promise in preserving RGC [52].

Activation of glia

The presence of A large number of activated microglia and astroglia (gliosis) is a hallmark of neurodegeneration. Over the years, in vivo and in vitro studies have characterized the changes in quiescent astrocytes that lead to reactive phenotype in glaucoma. In glaucomatous human eyes, there is immunohistological and immunohistochemical evidence of retinal glial cells activation when compared with controls [53]. It has been proposed that activated astrocytes at the optic nerve are capable of secreting matrix metalloproteases and signal a variety of cytokines that may result in optic nerve excavation in glaucoma [54]. Reactive astrocytes can cause remodeling of the optic nerve head and result in a nonsupportive environment for the survival of RGC axons and thus glaucomatous progression.

Glaucoma and cerebrospinal fluid

Almost a decade ago, a retrospective case control study identified glaucoma patients to have significantly lower cerebral spinal fluid (CSF) pressure in POAG and NTG patients, whereas CSF pressure is higher in ocular hypertension. The investigators suggested a contributory role of CSF pressure in the pathogenesis of open-angle glaucoma [55]. The low CSF pressure in glaucomatous eyes was later confirmed in a prospective interventional study, and translamina cribrosa pressure difference (TLCPD) (IOP minus CSF pressure) was higher in NTG than POAG patients [56]. The group was able to show a positive correlation between TLCPD and the extent of glaucomatous visual field loss and neuroretinal rim loss [56,57]. A recent meta-analysis has echoed the finding of high TLCPD in NTG and POAG patients [58]. This topic has been heavily reviewed, and it is hypothesized that an elevated TLCPD produces posterior bowing of the lamina cribrosa and disc excavation in some of the glaucoma patients [59]. Surely, there are other factors other than TLCPD in the pathogenesis of glaucoma, but it is becoming more acceptable nowadays that TLCPD is a contributory factor in glaucomatous development and progression. Interestingly, CSF pressure was shown to have a positive linear relationship with body mass index [60]. As low CSF pressure plays a contributory role in glaucoma, it has then put NTG as a conceptual opposite to idiopathic intracranial hypertension, which is a neurologic disease.

Looking into the future

An *N*-methyl-D-aspartate glutamate receptor antagonist was the first drug approved for use as a neuroprotective agent in moderate and severe Alzheimer dementia. Despite its protective effect against RGC loss in animal glaucoma models, unfortunately, a clinical trial in human glaucoma did not show a benefit. α2-Adrenergic activation was first shown to be neuroprotective in animal models of focal cerebral ischemia, and patients randomized to monotherapy of brimonidine (α2-agonist) were reported to have less visual field progression than patients being put on Timolol despite a similar IOP-lowering effect [61]. However, topical administration of brimonidine is accompanied with high incidence of local side effects and poor compliance rate. A novel delivery system of brimonidine using a surgical implant has been developed and was approved by the Food and Drug Administration for intracameral administration. Several other clinical trials are underway exploring novel therapies to improve RGC survival, protect, or rebuild RGC connections, and enhancing RGC function [62]. Antioxidant treatment or gene therapy, such as administration of adenoviral vector modified with neuroprotective candidate, may become important future adjunctive strategies for cytoprotection against apoptotic RGC body death in early or advanced glaucoma [63].

No doubt neuroscience-based approaches in understanding the pathogenesis of glaucoma have opened up the opportunity for new therapies. Upcoming imaging techniques for detecting RGC apoptotic cells are important in the evaluation of these new neuroprotective therapies. Cordeiro and colleagues [64] have reported in vivo visualization of neuronal apoptosis in glaucoma patients using intravenous injection of an infrared fluorescently labeled dye followed by retinal imaging using specific wavelengths. This new imaging technique DARC (detection of apoptosis of retinal cells) can serve as a potential surrogate marker in detecting and monitoring glaucomatous neurodegeneration.

In the past decade, gene therapy has been represented as a potential tool in terms of neuroprotection and neuron regeneration

via modulation of key molecular pathways dictating RGC survival. As there are heterogenic factors contributing to RGC death in glaucoma, gene therapy has the advantage of tackling multiple pathways simultaneously. Preclinical studies have demonstrated success in the modulation of neurotrophic factor or antioxidant expression and blockade of intrinsic apoptotic pathway using recombinant viral vectors, such as adeno-associated virus. As the list of candidate genes continues to expand, better patient stratification in future glaucoma practice is expected to enable more personalized and effective treatment [65].

Summary

Although high IOP is no longer required in the diagnosis of glaucoma, it remains the only modifiable risk factor proven to decrease risk of onset and progression. Studies have revealed that despite aggressive IOP lowering, glaucomatous progression appeared inevitable in some patients. Acknowledging glaucoma as a neurodegenerative disease and understanding the neuropathological processes are crucial in the development of complementary glaucoma treatment.

Clinics care points

- Early recognition and treatment of glaucoma patients are important in preventing irreversible neurodegeneration as well as brain insult. Better imaging techniques are needed to detect and monitor apoptosis of retinal ganglion cells.
- By acknowledging glaucoma as a neurodegenerative disease, clinicians must be aware of intraocular pressure as an independent risk factor when managing a patient with progressive glaucomatous loss despite good intraocular pressure control.
- Clinicians should watch out for the latest developments in neuroprotection and gene therapy for glaucoma patients.

Disclosure
The authors have nothing to disclose.

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Neuro-Ophthalmologic Manifestations of Novel Coronavirus

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Keywords

Neuro-ophthalmology; COVID-19; Coronavirus

Key points

- COVID-19 has been found to have many neuro-ophthalmologic associations, including cranial nerve palsies, Miller Fisher and Guillain-Barré syndromes, optic neuritis, intracranial hypertension, and sequelae from cerebrovascular events.
- Management of neuro-ophthalmology patients during the COVID-19 pandemic has brought about interesting discussions, including use of immunosuppressive agents, increasing usage of telehealth, and prone positioning as it relates to ischemic optic neuropathy.
- More research needs to be done to better characterize the relationship between COVID-19 and rare neuro-ophthalmologic presentations.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found to have many systemic manifestations. Of these, ocular presentations associated with COVID-19 have been identified as clinicians' familiarity with the disease has increased since the start of the pandemic in early 2020, with a rapidly evolving body of literature. Neuro-ophthalmology has been affected, because of neuro-ophthalmic manifestations of COVID-19, and adaptations in delivery of health care and treatment of preexisting conditions.

Literature emerging on the topic of COVID-19-related thrombotic events has highlighted the relationship between coronavirus infection and hypercoagulability. The increased risk of arterial and venous thrombosis is thought to be caused by inflammation, platelet activation, endothelial dysfunction, and stasis [1]. Patients with COVID-19 infections have been found to have elevated D dimer levels, thrombocytopenia, and prolonged prothrombin time/international normalized ratio [2–7]. These patients can develop venous thromboembolism, myocardial infarction, stroke, and limb ischemia, even when anticoagulated [1,8–11]. It is possible that a similar mechanism may account for some of the suspected neuro-ophthalmologic associations, such as cranial neuropathies, which often occur in the context of ischemia.

Beyond the neuro-ophthalmic conditions that have been associated with COVID-19 infection, neuro-ophthalmologists care of uninfected patients also has been drastically altered, with a significant shift toward telemedicine and optimizing the management of preexisting conditions given the concern regarding immunosuppression during the current COVID-19 pandemic.

Article body

Neuro-ophthalmic presentations

Cranial nerve palsies

Cranial nerve abnormalities, including anosmia and hypogeusia, have been reported in association with COVID-19, and are accepted symptoms of infection. Based on these findings, it is postulated that the olfactory bulb may serve as an entry point for SARS-CoV-2 into the nervous system [12]. Although less common, there have been reports of isolated oculomotor, trochlear, and abducens nerve palsies in patients with COVID-19.

Faucher and colleagues [13] documented an isolated, partial left oculomotor nerve palsy (impaired adduction and supraduction of the left eye without ptosis or mydriasis) in a 21-year-old man with no other comorbidities that developed 16 days after developing respiratory symptoms. He had a positive polymerase chain reaction (PCR) testing to SARS-CoV-2. His clinical course involved 6 days of intubation and intensive care unit care. MRI showed a few arterial microectasia, but no involvement of the oculomotor nerve. Extensive serologic testing was negative. His symptoms of diplopia resolved within 7 days. Belghmaidi and colleagues [14] described a similar presentation with a partial left oculomotor nerve palsy (lacking ptosis or mydriasis) in a 23-year-old women with no medical comorbidities, preceded by 3 days of fever, anosmia, and cough. Her MRI/MR angiography imaging and serologic testing for a cause was unremarkable apart from positive PCR testing for SARS-CoV-2. She recovered within 6 days of onset. Fitzpatrick and colleagues [15] reported a 67-year-old man with no medical comorbidities who developed a pupil-sparing oculomotor nerve palsy 4 days after being diagnosed with COVID-19. His MRI brain showed only nonspecific microvascular changes and serology was noncontributory. His diplopia improved over 1 month, and the nerve palsy had completely resolved by 2 months. Similarly, Wei and colleagues [16] reported a 62-year-old man who presented with a 5-day history of an

isolated pupil-sparing oculomotor nerve palsy with complete ptosis and loss of adduction and supraduction. His medical history was significant for well-controlled type 2 diabetes mellitus, hypertension, and a prior lacunar infarct, but he did not have any respiratory symptoms on presentation. MRI/MR angiography imaging did not show any acute infarct or aneurysmal cause. He developed dyspnea on Day 2 of his admission and was confirmed to have COVID-19 before rapidly deteriorating and passing away on Day 12.

Paresis of the trochlear nerve also has been reported. Oliveira and colleagues [17] report a case of a 69-year-old White man with a history of hypertension who presented with fever, abdominal pain, chest pain without cough or dyspnea, and a mild occipital headache. Eleven days after the onset of symptoms, he woke with worsening headache and acute onset of binocular diplopia. His neurologic examination was consistent with bilateral trochlear nerve palsies. PCR testing was positive for COVID-19. An MRI with angiography and vessel wall imaging showed findings consistent with vasculitis affecting the vertebrobasilar system and fourth cranial nerve nuclei. His diplopia resolved after a 5-day course of intravenous (IV) methylprednisolone.

Likewise, isolated, unilateral abducens nerve palsies have been reported in patients with active SARS-CoV-2 infections. One case involved an otherwise healthy 32-year-old man, who developed binocular horizontal diplopia after 3 days of progressively worsening upper respiratory tract infectious symptoms [18]. He was ultimately hospitalized for treatment of acute respiratory failure and tested positive for SARS-CoV-2. Five weeks after the onset of diplopia, an ocular examination confirmed a complete left abducens nerve palsy, and MRI imaging at that time showed atrophy of the left lateral rectus consistent with denervation of the muscle. The remainder of his ophthalmologic examination was within normal limits.

Another case involved a 71-year-old woman who presented with cough and fever several days before developing diplopia [19]. She was found to have a complete abducens nerve palsy of the right eye. Nasal swab for SARS-CoV-2 PCR was positive. Axial T1 fat-

saturated postcontrast MRI sequences showed bilateral enhancement of the optic nerve sheaths and Tenon capsule. She was treated with hydroxychloroquine. On follow-up 2 weeks after her initial presentation, she reported subjective improvement in her diplopia.

Two additional brief reports documented isolated abducens nerve palsies in SARS-CoV-2 PCR-positive patients: one in a 43-year-old woman who had negative serologic studies for other infectious and inflammatory causes and a normal contrast-enhanced MRI study of the brain and orbits; and the other a 52-year-old man who was only seen via telehealth consultation and declined further investigations [20]. Follow-up was not provided for the 43-year-old patient, but the 52 year old had a resolution of his abducens nerve palsy 14 days after onset.

All but one of the patients with cranial nerve palsies had developed upper respiratory tract infectious symptoms several days before the onset of diplopia. MRI findings were varied, making establishment of a potential mechanism for SARS-CoV-2 causing cranial nerve palsies somewhat challenging. Current hypotheses include direct viral invasion and injury of the nervous system verses indirect autoimmune and neuroinflammatory pathways [21,22]. The speed of recovery seems to be rapid: 2/3 of the patients with CN3 palsies recovered within 2 weeks (and the third by 2 months); the patient with the central nervous system vasculitis and bilateral CN4 palsies recovered within 5 days; and 2/3 of the patients with CN6 palsies with reported follow-up had rapid recovery within 14 days of symptom onset. This is comparable with the speed of recovery from anosmia and ageusia, suggesting a common underlying pathophysiology [23].

Guillain-Barré and Miller Fisher syndrome

The first case of a patient presenting with Guillain-Barré (GB) associated with SARS-CoV-2 infection occurred in January 2020, after the patient returned from travel in Wuhan, China [24]. This 61-year-old woman first developed symptoms of bilateral lower limb weakness and generalized fatigue before she developed fever and

cough 7 days later. The temporal relationship suggested a parainfectious process, rather than the postinfectious onset of GB classically associated with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, or other viral and bacterial triggers [25].

A second case of ascending muscle weakness developed in a 54-year-old woman who had been diagnosed with COVID-19 3 weeks prior, after experiencing anosmia and hypogeusia. Electrophysiologic studies demonstrated segmental demyelinating polyneuropathy. Cerebrospinal fluid (CSF) analysis showed albuminocytologic dissociation, consistent with GB. Her neurologic symptoms significantly improved with IV immunoglobulin [26].

Dinkin and colleagues [19] reported a 36-year-old man with a history of infantile strabismus who presented with diplopia, left ptosis, and mydriasis, consistent with a left oculomotor nerve palsy. He also had bilateral abduction deficits suggestive of abducens nerve palsies, lower limb hyporeflexia and hypesthesia, and gait ataxia. He had experienced self-limited cough, myalgias, and fever 4 days prior, and was positive for COVID-19. His MRI showed enlargement and enhancement of the left oculomotor nerve. He was admitted to the hospital and treated for presumed Miller Fisher syndrome (MFS; ganglioside antibody negative) and COVID-19, with IV immunoglobulin for 3 days and hydroxychloroquine for 5 days, respectively. His neurologic deficits had improved at the time of discharge.

Gutierrez-Ortiz and colleagues [27] described two cases of COVID-19 associated with MFS and polyneuritis cranialis. The first was a 50-year-old man who presented with MFS. PCR was positive for SARS-CoV-2. His neurologic findings consisted of a right internuclear ophthalmoplegia, anosmia, ageusia, ataxia, and areflexia that developed 5 days after developing fever, malaise, and cough. He was positive for anti-GD1b ganglioside antibodies, rather than anti-GQ1b, which is more commonly associated with MFS. He was treated with IV immunoglobulin and made a near complete neurologic recovery. The second case occurred in a 39-year-old man who was diagnosed with polyneuritis cranialis and COVID-19 after presenting with diarrhea, fever, and malaise, followed 3 days later

by bilateral abducens nerve palsies, ageusia, and areflexia. Ganglioside antibody testing was not performed. He was treated with acetaminophen and had complete resolution of symptoms. Both patients had albuminocytologic dissociation on initial work-up.

Of the five cases described, four developed neurologic symptoms after the onset of viral upper respiratory symptoms, within a range of 3 days to 3 weeks. One presented with physical examination findings consistent with GB before the onset of any symptoms known to be associated with SARS-CoV-2 infection. All had favorable outcomes despite their diagnoses of COVID-19. It is suspected that these cases of GB and MFS represent a similar immune response to other postviral cases of GBS/MFS because of molecular mimicry from the COVID-19 spike protein [27,28]. The short time frame between onset of COVID-19 symptoms and GBS/MFS may be caused by an underestimation of the actual date of infection because of the asymptomatic incubation period between SARS-CoV-2 infection and development of respiratory symptoms.

Optic neuritis

There have been several reports of optic neuritis in patients with concomitant SARS-CoV-2 infection and no known prior history of autoimmune or demyelinating disease. Two cases of inflammatory optic neuritis have occurred in the setting of panuveitis. One involved a 60-year-old woman who presented with left eye pain, redness, and blurred vision 2 weeks following a respiratory infection with associated sinusitis and conjunctivitis [29]. On examination, she was found to have panuveitis and optic disk swelling. Work-up for toxoplasmosis, human immunodeficiency virus, and syphilis were negative. She developed worsening respiratory symptoms 10 days after initial presentation and ultimately was diagnosed with COVID-19 after confirmatory PCR testing. Although her visual acuity significantly improved after treatment with hydroxychloroquine and systemic steroids, she had significant optic nerve atrophy at the time of discharge.

A second report described a woman in her late 50s who was admitted for bilateral COVID-19-positive pneumonia and developed a red eye with decreased vision (hand motion acuity), pain with extraocular movements, and a relative afferent pupillary defect [30]. On slit lamp examination, she had nongranulomatous anterior chamber reaction and keratic precipitates, mild vitritis, disk edema with peripapillary hemorrhages, and vessel narrowing in the inferior retina. MRI brain and orbits with contrast, CSF analysis, and serologic investigations for other inflammatory or infectious causes were negative. Despite treatment with topical and oral steroids, on Day 30, she had persistent papillitis and retinal vasculitis on fluorescein angiography. By Day 48, the panuveitis had resolved and the patient was left with optic atrophy and unchanged hand motion visual acuity.

Reports also exist of demyelinating optic neuritis in patients presenting with decreased vision and pain with extraocular movements, with and without other focal neurologic symptoms and signs. Zhou and colleagues [31] reported a case of 26-year-old man presenting with severe, sequential bilateral optic neuritis preceded by several days of dry cough. On examination, his Best Corrected Visual Acuity (BCVA) was hand motion OD and 20/250 OS with a right afferent pupillary defect and bilateral disk edema with retinal perivenous hemorrhages. MRI brain and orbits showed bilateral enhancement of the optic nerves and patchy T2 hyperintensities in the lower cervical and upper thoracic spinal cord. Myelin oligodendrocyte glycoprotein (MOG) antibody testing and PCR for SARS-CoV-2 were positive. His visual acuity recovered, and his fundus abnormalities resolved with a 5-day course of IV solumedrol with no pulmonary compromise.

A second report of MOG-optic neuritis has been described in a 44-year-old man, 2 weeks after developing symptoms of dyspnea and cough with a positive COVID-19 PCR test [32]. He reported pain with eye movements and was found to have BCVA 20/200 OD and 20/30 OS, a right afferent pupillary defect, generalized reduction in his visual field OD, and a superior arcuate visual field defect OS. Extensive investigations were significant for positive anti-MOG

antibodies and bilateral postcontrast enhancement of the optic nerves with no other radiographic evidence of demyelination.

A third report of optic neuritis as a presenting symptom of multiple sclerosis (MS) in association with COVID-19 infection has also been documented [33]. A 29-year-old woman presented with painful right eye movements and decreased vision, BCVA 20/200, and a right afferent pupillary defect on her initial examination. She also was found to have signs of pyramidal tract dysfunction on examination. Her MRI demonstrated right optic nerve enhancement, nonenhancing and enhancing supratentorial periventricular demyelinating lesions, and a normal spinal cord MRI. She was found to also have oligoclonal bands in the CSF, meeting the MacDonald criteria for a diagnosis of MS.

A case of acute disseminated encephalomyelitis was diagnosed in a 64-year-old woman who presented to care with bilateral hand motion vision loss after having flulike symptoms with anosmia and ageusia 2 weeks prior [34]. She had poorly reactive pupils bilaterally, a right abdominal sensory level, and left-sided lower limb hyperreflexia with a positive Babinski sign. She had multiple enhancing lesions on MRI brain, including bilateral optic nerve involvement, and a spinal cord lesion at T8 (not longitudinally extensive). CSF analyses showed lymphocytic pleocytosis and mild hyperproteinorachia with no oligoclonal banding. NMO and MOG antibodies were negative. She responded well to IV solumedrol and immunoglobulins with improvement to visual acuity of 20/30 OU within 14 days and had improving radiographic findings.

It has been previously established that SARS-CoV-2 enters cells by binding to the ACE2 receptor [35,36]. Given that ACE2 has been found on choroidal cells and neurons, direct viral invasion has been proposed as a mechanism for the development of uveitis and optic neuritis. The optic nerve atrophy that was found in the patients who recovered from panuveitis with optic neuritis could potentially be explained by an ischemic event, because the virus has a documented prothrombotic effect and endotheliumtropism [29]. In the case of patients with MOG-associated and MS-associated optic neuritis, and acute disseminated encephalomyelitis, the relationship between viral

prodrome and parainfectious or postinfectious demyelinating syndromes has been well established in the literature [37,38]. Molecular mimicry is the most widely accepted mechanism, whereby viral antigens initiate a robust immune response against endogenous central nervous system proteins, including MOG and myelin [38]. However, the patient who was diagnosed with MS after developing optic neuritis had radiographic evidence of active and inactive demyelinating lesions, suggesting that her MS disease likely preceded her SARS-CoV-2 infection, although one cannot exclude that the infection did not trigger the episode of optic neuritis.

Intracranial hypertension

Intracranial hypertension attributed to idiopathic (IIH) and secondary causes has been associated with COVID-19. Noro and colleagues [39] reported a nonobese 35-year-old woman who presented with fever, dyspnea, headache, and fatigue. A lumbar puncture showed an elevated opening pressure of 40 cm H_2O. No evidence existed of thrombosis or secondary causes on MRI/MR venography. She also tested positive for SARS-CoV-2, and ultimately was admitted to hospital for worsening headache and confusion. Her symptoms resolved within 2 days of supportive care.

Secondary intracranial hypertension caused by multisystem inflammatory syndrome in children was reported in a 14-year-old girl who presented with fever, rash, dyspnea, headache, and diarrhea [40]. She was admitted to the hospital for respiratory decline and septic shock. During her admission, she developed a right abducens nerve palsy and bilateral papilledema with disk hemorrhages. Lumbar puncture confirmed elevated intracranial pressure and MRI/MR venography was supportive of the same. Although her nasopharyngeal PCR was negative, qualitative IgG was positive for SARS-CoV-2. Two months postdischarge, after poor compliance with acetazolamide, her disk edema and nerve palsy had resolved.

Silva and colleagues [41] published a cross-sectional study investigating the characteristics of headache and CSF analysis in

COVID-19 patients. They included patients who underwent lumbar puncture over a defined period of 2 months for neurologic signs and symptoms that had a confirmed diagnosis of COVID-19. Of the 56 participants, 13 (23.2%) underwent lumbar puncture as part of the work-up for a new and persistent headache. Most of those patients (11/13) had complete or partial improvement in their headache. CSF analysis was normal in all patients, and six patients had opening pressures greater than 25 cm H_2O.

Cerebral venous sinus thrombosis (CVST) is a rare cause of secondary intracranial hypertension but is a significant concern given that SAR-CoV-2 induces a hypercoagulable state and the risk of significant morbidity if CVST is unrecognized or untreated [42]. Multiple reports exists of CVST associated with COVID, but there is a paucity of ophthalmic examinations in the reports to assess for papilledema and other findings of neuro-ophthalmic interest. This may reflect that these patients were admitted to high-acuity COVID-19 wards with reduced access to ophthalmology consultations [43–45]. Practitioners should have a high index of suspicion to rule out CVST with venography and ensure appropriate anticoagulation is instituted.

Beyond the direct causative effect of SARS-CoV-2 inducing intracranial hypertension through the aforementioned mechanisms, changes in health care delivery and biopsychosocial effects of pandemic restrictions have been associated with more severe presentations or worsening disease in patients with new or previously diagnosed IIH, respectively [46]. A tertiary center in Birmingham, UK found a 4.7-times increase in their rate of CSF diversion procedures, which included 21% of their patients with newly diagnosed IIH. Conclusions were limited because of the retrospective nature of the report, but it is likely a combination of decreased or delayed access to emergency care, limited clinical examinations (because guidelines have suggested minimizing fundoscopy and visual field testing to minimize exposures for health care workers), and weight gain caused by pandemic lockdowns and increased anxiety and depression in patients. This highlights the

importance of ensuring that clinical care for non-COVID-19-related presentations is not compromised as health care systems evolve and adapt to COVID-19 restrictions.

Other manifestations

In addition to the ischemic and hemorrhagic cerebrovascular complications of COVID-19, there is a higher rate of posterior reversible encephalopathy syndrome (PRES) in the setting of acute SARS-CoV-2 infections [47]. PRES is a disorder of presumed vascular dysregulation commonly associated with hypertension, and with severe infections/sepsis, autoimmune disease, and immunomodulator use, many of the features that exist in COVID-19 patients. Of the COVID-19 associated cases with PRES, transient visual loss has been reported and a hallucinatory palinopsia, a completely novel presentation of PRES [48,49].

Management changes

Prone positioning

In light of the number of SARS-CoV-2 cases requiring ventilation and prone positioning to improve oxygenation, there has been discussion on the multisystem side effects of maintaining such a position for extended periods [50,51]. One such complication is orbital compartment syndrome, which can develop secondary to direct pressure on the globe and orbit in a patient lacking cushioned eye protection. Sun and colleagues [50] reported two cases of orbital compartment syndrome in patients who had between four and nine sessions of 18-hour prone positioning while admitted under the critical care service. Both patients had periorbital edema and a two- to three-fold increase in intraocular pressure while laying prone versus supine. They also had indistinct optic disk margins and retinal hemorrhages, which was believed to be most consistent with papillophlebitis from a combination of coagulopathy secondary to COVID-19 infection and the prolonged prone positioning.

Other concerns with prone positioning include ocular surface disease, acute angle-closure glaucoma, vascular occlusion, and ischemic optic neuropathy [51]. Ischemic optic neuropathy can result from a combination of prone positioning and systemic hypotension from sepsis or iatrogenic causes. Although there have not been any documented cases of ischemic optic neuropathy attributed to prone positioning in COVID-19 patients, heightened awareness has been recommended, given the risk of significant morbidity.

Immunosuppression

The COVID-19 pandemic posed a dilemma among patients and health care staff alike in regard to the use of immunosuppressive agents. Early in the pandemic, there was concern regarding increased risk of SARS-CoV-2 infection in patients with neuromyelitis optica spectrum disorders and other autoimmune conditions being treated with immunosuppressive agents, because of the associated increased susceptibility to infection. This concern was speculative and given that no data existed at the time to support this hypothesis, it was not recommended to prophylactically change treatment regimens [52]. As the pandemic has progressed, these concerns have not been borne out, and evidence suggests patients on immunosuppressive agents are not at higher risk of COVID-19 [53].

Salama and colleagues [54] conducted a survey that was distributed among 186 randomly selected patients with neuromyelitis optica spectrum disorders to gain more understanding of patient perspectives surrounding use of immunosuppressive therapies during the COVID-19 pandemic. Most patients (85%) had not considered stopping their medication, although some had delayed rituximab infusions. Approximately one-third of patients were maintaining in-person clinic visits, whereas the remainder were communicating with their health care provider via telephone, email, or telemedicine. Overall, it was concluded that most patients did not alter their medication schedule despite concern about acquiring COVID-19.

Telehealth

In light of the current pandemic, physicians are turning to telehealth as a safer alternative to providing in-person visits. However, the practice of neuro-ophthalmology poses an interesting challenge to this transition, given the benefit of physical examination findings and timely diagnostic testing on differentiation of benign from sinister underlying etiologies [55]. Certain aspects of the physical examination, such as visual acuity and a testing for an afferent pupillary defect, are performed by the patient via videoconferencing with detailed instruction [56,57]. However, fundoscopy and quantification of strabismus currently requires in-person assessment and subtle findings, such as nystagmus, may be missed depending on the quality of the video connection. Practical considerations, such as lack of access to appropriate technology, may preclude the use of telehealth visits in some patients. Remote visual field testing has shown similar reliability to Humphrey visual fields in pilot studies but is not yet readily available [55]. Artificial intelligence optic disk analysis and digital fundus photography are on the horizon, but currently cannot replace clinic visits [58].

Although consultations often are best served by an office visit, appropriate triaging and prescreening of appointments (eg, to appropriately arrange laboratory testing or imaging by the referring physician) allows telemedicine to reduce the need for in-person visits [55,58]. Videoconferencing has gained popularity in medical education and research, with entire large-scale conferences being held via online platforms. As technology evolves and matches the demand for online visits, it certainly is possible that these innovations will propel the field into an era where comprehensive virtual visits become commonplace, pandemic notwithstanding.

Relevance

As more time passes, clinicians are seeing an increasing number of neuro-ophthalmologic conditions presenting in patients with SARS-CoV-2. However, true associations and mechanisms are theoretic and based on extrapolations from a limited, although increasing, number of cases. As more data are accumulated, these relationships will become better characterized. One also has to consider the possibility that the timing of COVID-19 infection and the various neuro-ophthalmologic presentations have overlapped coincidentally, rather than because of the SARS-CoV-2 virus being a causative factor. However, given the restrictions and attempts to limit exposure to COVID-19 patients with abbreviated physical examinations or lack of manpower because of hospital capacity issues, there may also be underreporting of subtle neuro-ophthalmic presentations.

This review summarizes what is known about the relationship between SARS-CoV-2 and neuro-ophthalmology, in hopes that clinicians will have a higher index of suspicion to investigate for concomitant COVID-19 infection in patients, because many of the patients had little or no respiratory symptoms when they developed their neuro-ophthalmic concerns. Given the extensive contact tracing and isolation associated with testing positive for COVID-19, it is also conceivable that patients may underreport these symptoms. Thus, health care providers must remain vigilant and informed on the conditions that may be associated with SARS-CoV-2 infection.

Immunosuppressive medications are still being widely used during the pandemic. There has been no evidence to date to suggest preemptively stopping or changing a patient's immunosuppressive therapy during this time. Even those with proven SARS-CoV-2 infection are assessed on a case-by-case basis, taking into account the patient's comorbidities and severity of the sequelae associated with undertreating their neuro-ophthalmologic disease.

In regard to the changes in patient care, telehealth has been well received by health care providers and patients alike. There is a need for further research on the topic to analyze cost-effectiveness and

overall efficacy, and validate tools, such as visual field testing, to allow their implantation in a clinical setting.

Summary

Although these neuro-ophthalmic findings may be unrelated to SARS-CoV-2 infection, health care providers should still consider them as potential manifestations of infection and exercise caution when seeing patients who present with these findings. As more reports of neuro-ophthalmic presentations in the setting of COVID-19 infections are published, the body of evidence from which to draw from will be become more robust. In turn, the quality of data on the topic of neuro-ophthalmology and COVID-19 will improve, such that more definitive conclusions can be drawn about underlying mechanisms of these associations.

Clinics care points

- Optic nerve and other cranial nerves can be affected in COVID-19 infections, but these cranial neuropathies may spontaneously recover.
- Clinicians should have a high index of suspicion for central venous sinus thrombosis in patients at risk for COVID-19 infections, especially in patients with atypical features for idiopathic intracranial hypertension.
- While tele-ophthalmology cannot replace in person examinations, its use in the appropriate clinical settings can improve patient access while minimizing risk of exposure to the patient and clinician.

Disclosure
The authors have nothing to disclose.

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Cornea and External Diseases

OUTLINE

Advances in Endothelial Keratoplasty Surgery

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Keywords

Corneal transplant; Endothelial keratoplasty; Penetrating keratoplasty; Descemet's stripping endothelial keratoplasty; Descemet's membrane endothelial keratoplasty

Key points

- Endothelial keratoplasty is a novel approach for treating corneal endothelial disease, which selectively transplants the posterior layers of the cornea.
- Compared with penetrating keratoplasty, endothelial keratoplasty has a lower intraoperative risk, faster visual recovery, and elimination of suture and wound junction complications.
- Descemet stripping endothelial keratoplasty and Descemet's membrane endothelial keratoplasty are the most common types of endothelial keratoplasties that are performed.
- Future avenues for treatment of endothelial disease includes Rho-associated kinase inhibitors, bioengineered corneal grafts, and gene therapy.

Introduction

Numerous visually devastating pathologies such as corneal dystrophies, infections, and autoimmune processes require corneal transplants to restore visual function. The first successful corneal transplant was performed by Dr Eduard Zirm in 1905 [1], and more than a century later, corneal transplants are the most common type of transplantation in humans [2]. Although corneal transplants were a groundbreaking step in medicine, traditional penetrating keratoplasties have a number of challenges. Intraoperatively, the "open sky" method of penetrating keratoplasties has the risk of expulsive suprachoroidal hemorrhage and vitreous prolapse. Postoperatively, visual the stability of penetrating keratoplasties required months to plateau, given the changes in corneal power and refraction from each suture removal [3]. Furthermore, the avascular graft to host interface causes lower globe stability and the risk of wound dehiscence, particularly after trauma [4].

Although penetrating keratoplasties replace all layers of the cornea, the leading indications for corneal transplants in the United States are Fuchs' endothelial dystrophy (FED) (Fig. 1) and pseudophakic bullous keratopathy (Fig. 2), both of which are diseases of corneal endothelial dysfunction [5]. Thus, ophthalmologists recognized there was a need to selectively transplant the corneal endothelial layer, which could potentially mitigate some of the complications seen with traditional penetrating keratoplasties. A partial thickness posterior lamellar keratoplasty through a 180° anterior lamellar flap was published in 1956 [6]; however, this idea of selectively transplanting corneal layers was not further developed or adopted until decades later.

In 1999, corneal transplant surgery was revolutionized when Melles and colleagues [7] introduced a novel technique of posterior lamellar keratoplasty, which was the first time a partial thickness corneal endothelial transplant was performed without a large full-thickness penetration of the host corneal tissue. Given that most corneal transplants were for endothelial dysfunction, this novel surgical technique had the potential to transform treatment methods for patients with vision limiting endothelial pathology requiring corneal transplants.

Posterior lamellar keratoplasty, as pioneered by Melles and colleagues [7], was the inaugural technique for the newly created field of endothelial keratoplasty. Endothelial keratoplasty, when clinically indicated, as compared with penetrating keratoplasty, has the advantages of a shorter

recovery time, better visual outcomes, a lower risk of wound dehiscence, and less foreign antigen exposure. Additionally, the absence of sutures reduces the number of postoperative visits for suture removal and eliminates the risk of suture-induced vascularization. Since the introduction of posterior lamellar keratoplasty, there have been newer surgical techniques created including Descemet's stripping endothelial keratoplasty (DSEK), Descemet's membrane endothelial keratoplasty (DMEK), and Descemetorhexis without endothelial keratoplasty (DWEK) (also known as Descemet stripping alone), which are outlined in Table 1. The advent of endothelial keratoplasty has transformed the field of ophthalmology. In this article, we describe the advances in endothelial keratoplasty and future directions of this field.

Significance

Lamellar keratoplasty

Given the complications related to penetrating keratoplasties for corneal endothelial pathology, ophthalmologists sought to invent a new surgical approach that would only require replacing the posterior corneal layers. The aim was to decrease some of the challenges of full-thickness corneal transplants such as high astigmatism, suture-related visual fluctuation, and graft–host junction weakness.

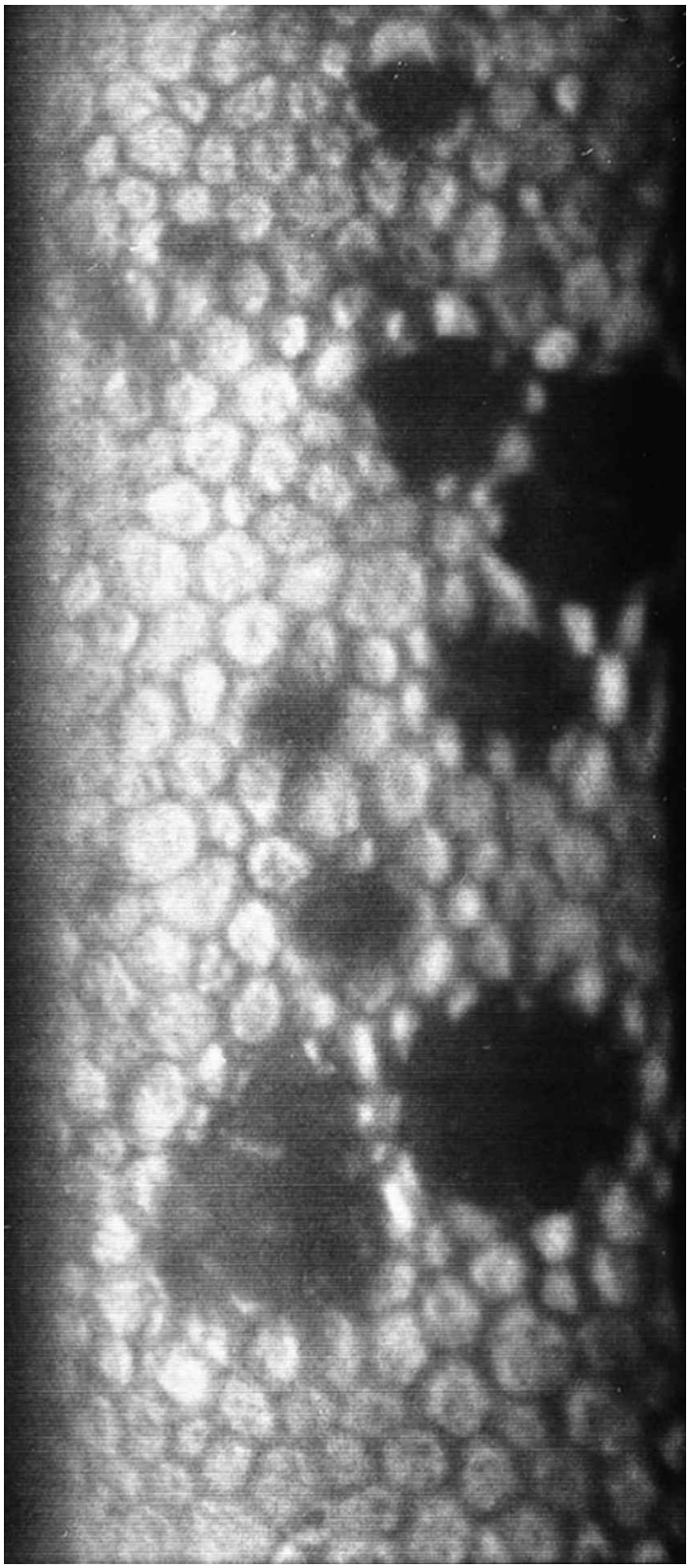

FIG. 1 Specular microscopy of the endothelium of a Fuchs' endothelial corneal dystrophy patient with dark punched out areas consistent with corneal guttata and variations in cell size and shape.

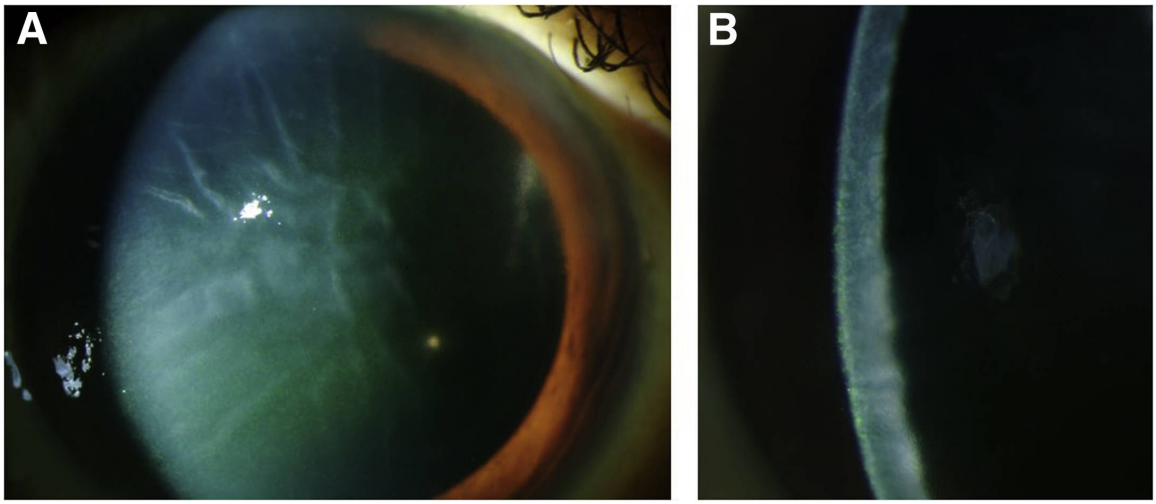

FIG. 2 Slit lamp photograph of pseudophakic bullous keratopathy with (*A*) a diffuse beam and (*B*) a slit beam.

In 1999, Melles and colleagues [7] published a new technique termed posterior lamellar keratoplasty for a patient with pseudophakic bullous keratopathy from numerous intraocular surgeries. To prepare the host tissue for grafting, a midstromal corneal pocket was dissected through a 9.0-mm scleral tunnel incision. The graft tissue was prepared with a 7.0-mm trephine and the posterior lamella was dissected off the graft with curved micro-scissors. The graft was then inserted from a spoon-shaped slide and positioned on the host pocket with an air bubble in the absence of any suture fixation. The scleral incision was sutured closed. This technique required no corneal wounds. The authors postulated that the graft adhered to the host through the "stickiness of the stromal tissue" or the donor endothelial pump created negative pressure allowing the graft to hold in place [7]. One month after surgery, the patient had a best-corrected visual acuity of 20/80 owing to preexisting maculopathy; corneal pachymetry was 0.44 mm.

Table 1 Endothelial keratoplasty methods based on corneal layers of host tissue removed and graft tissue implanted

Technique	Host tissue removed	Graft tissue implanted
Deep lamellar endothelial keratoplasty (DLEK)	Posterior stroma Descemet's membrane Endothelium	Posterior stroma Descemet's membrane Endothelium
Descemet stripping endothelial keratoplasty (DSEK)	Descemet's membrane Endothelium	Posterior stroma Descemet's membrane Endothelium
Descemet membrane endothelial keratoplasty (DMEK)	Descemet's membrane Endothelium	Descemet's membrane Endothelium
Pre-Descemet endothelial keratoplasty (PDEK)	Descemet's membrane Endothelium	Pre-Descemet's layer Descemet's membrane Endothelium
DWEK	Descemet's membrane Endothelium	None

This surgery was revolutionary; it was the first time that the posterior corneal layers were selectively transplanted without full-thickness penetration of host tissue at the graft–host junction or sutures to secure the graft. This technique was adopted by Terry and colleagues [8] in the United States and termed deep lamellar endothelial keratoplasty (DLEK). Terry and colleagues successfully performed this new surgical approach on 2 patients with FED and found that DLEK preserved the preoperative corneal topography.

Although Melles and colleagues [7] demonstrated a technique with the potential to be superior to penetrating keratoplasties, the patient in Melles and colleagues from 1999 had a 3.5+diopter astigmatic error from the scleral suture. Thus in 2002, Melles and colleagues [9] published a modified sutureless technique for posterior lamellar keratoplasty. This was achieved through a 5.0-mm self-sealing scleral tunnel incision and an 8.5-

mm posterior lamellar graft that included stroma, Descemet's membrane, and endothelium. The graft was folded and placed underneath the host tissue using a custom inserter. This modified technique was also known as small incision DLEK [10]. Despite the necessity of folding the graft tissue to accommodate a smaller incision, the relative postoperative endothelial cell loss from preoperative donor graft measurements were similar to what was observed for penetrating keratoplasty and the large incision DLEK [10]. This sutureless technique resolved the issue of suture-induced astigmatic error.

Overall, the results from Melles and colleagues and Terry and colleagues proved that endothelial keratoplasty was clinically feasible [7–11]. These novel surgeries paved the way for further innovations to treat corneal endothelial dysfunction.

Descemet stripping endothelial keratoplasty

The next advancement in endothelial keratoplasty was DSEK and Descemet-stripping automated endothelial keratoplasty, as seen in Fig. 3. The innovation of DSEK was how the host tissue was prepared. In contrast with prior techniques for lamellar keratoplasty, DSEK eliminated the tedious dissection and removal of a stromal pocket from the host tissue; rather, the removal of Descemet's membrane only (descemotorhexis) was performed and the graft tissue was simply additive to the host stroma [12,13]. The posterior lamella of the graft was prepared manually and then inserted in a similar fashion as DLEK. Descemet-stripping automated endothelial keratoplasty used the descemetorhexis step from DSEK; however, the graft tissue was prepared with microkeratome dissection instead of manual dissection [14]. For the remainder of this article, we refer to the modern iteration of this technique as DSEK.

Lee and colleagues [15] conducted a large review on studies published on DSEK. After analysis of 34 articles, the most common complications seen with DSEK were graft dislocation, endothelial rejection, primary graft failure, iatrogenic glaucoma from steroids, and air bubble–induced pupillary block. Dislocations usually occurred in the first week in an average of 14.5% of cases. DSEK grafts had an average rejection rate of 10%. Primary graft failure is when the donor tissue does not clear as expected and occurs owing to suboptimal conditions from various graft factors, host factors, or surgical technique. Primary graft failure was observed for an average of 5% of DSEK cases. For refractive error, DSEK

patients had an average induced hyperopia of 1.1 diopter, which was found to occur owing to nonuniform donor thickness that was thinner centrally and changed the posterior corneal radius of curvature. Average astigmatism was 0.11 diopters, which was minimal compared with penetrating keratoplasties.

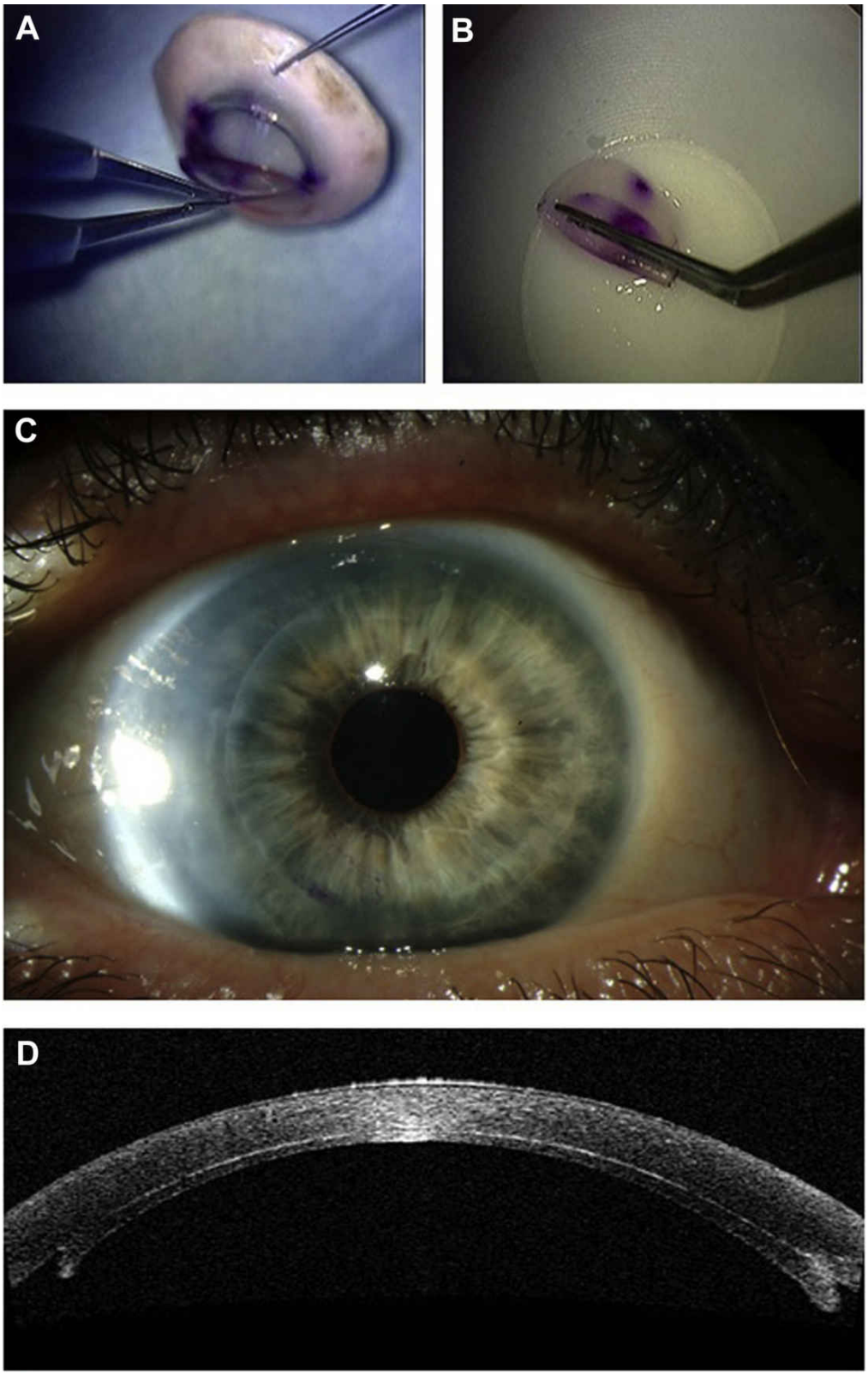

FIG. 3 Descemet stripping endothelial keratoplasty (DSEK). (*A*) The precut stromal cap is removed from the corneoscleral rim. (*B*) This surgeon elects to use specifically made forceps to insert the folded graft into the anterior

chamber. There are many techniques for inserting the DSEK graft into the eye through a corneal or scleral incision. (*C*) A clear and compact cornea after DSEK. The circular edge of the graft is subtly visible. (*D*) Anterior segment optical coherence tomography demonstrating a fully adhered DSEK graft. The lenticule of stromal tissue is additive to the host stroma. The peripheral edges of the graft are thicker than in the center, which is typical.

Although DSEK had promising short-term postoperative outcomes, the long-term results were also comparable with penetrating keratoplasties. For DSEK, the average endothelial cell loss at 6 months was 37%, which was greater than results previously seen for penetrating keratoplasties; however, the results were similar at 12 months [15]. Price and colleagues [16] reported 5-year DSEK outcomes for 165 eyes and found graft survival of 95% for patients treated for FED and 76% for patients treated for pseudophakic or aphakic corneal edema, comparable with long-term outcomes of penetrating keratoplasties. Overall, DSEK or Descemet-stripping automated endothelial keratoplasty had similar outcomes to penetrating keratoplasty for graft survival and vision without the wound and suture-related complications. Given the advantages of DSEK, it became the most common type of corneal transplantation performed in the United States, and by 2014 there were more than 23,000 of these procedures performed annually [17].

Descemet's membrane endothelial keratoplasty

In 2006, Melles and colleagues [18] proposed a variation to endothelial keratoplasty called DMEK. In contrast with DSEK where the donor tissue involves endothelium, Descemet's membrane and part of the posterior stroma, DMEK involves only endothelium and Descemet's membrane. Melles and his colleagues proposed that replacing a patient's endothelium and Descemet's membrane with a graft containing the same constituents would result in a faster and more complete visual recovery and, in theory, is the perfect anatomic replacement. Moreover, because donor DMEK grafts could be stripped directly from the donor corneoscleral rim instead of dissecting a posterior lamellar disc as in the case of DSEK, DMEK was suggested by the authors to be more accessible to corneal surgeons [18].

Since the introduction of DMEK, several studies have compared the visual outcomes and complication rates of DMEK versus DSEK. Stuart and colleagues [19] conducted a review of all studies published 2017 and earlier comparing DMEK with DSEK. Although no randomized control

trials were identified at the time of that publication, 4 retrospective studies were found that compared outcomes in patients who had received DSEK in 1 eye followed by DMEK in the fellow eye with the follow-up of patients ranging between 6 and 24 months. The review showed that DMEK was associated with a slightly improved visual acuity of 1 to 2 lines compared with DSEK and also had a statistically significant higher rate of corneal graft dislocation (relative risk, 5.4). DMEK dislocation is shown in Fig. 4. The final endothelial cell density count in the 4 studies were equivocal, because 2 studies showed no difference and 2 studies found a better final endothelial cell count for DMEK [19]. Other studies have showed that DMEK has a lower immunologic rejection rate and has the advantage of using a smaller incision than DSEK [20]. Overall, patients seemed to demonstrate statistically significant increased satisfaction with their outcomes from DMEK over DSEK owing to the quicker recovery time and slightly improved visual outcomes [21].

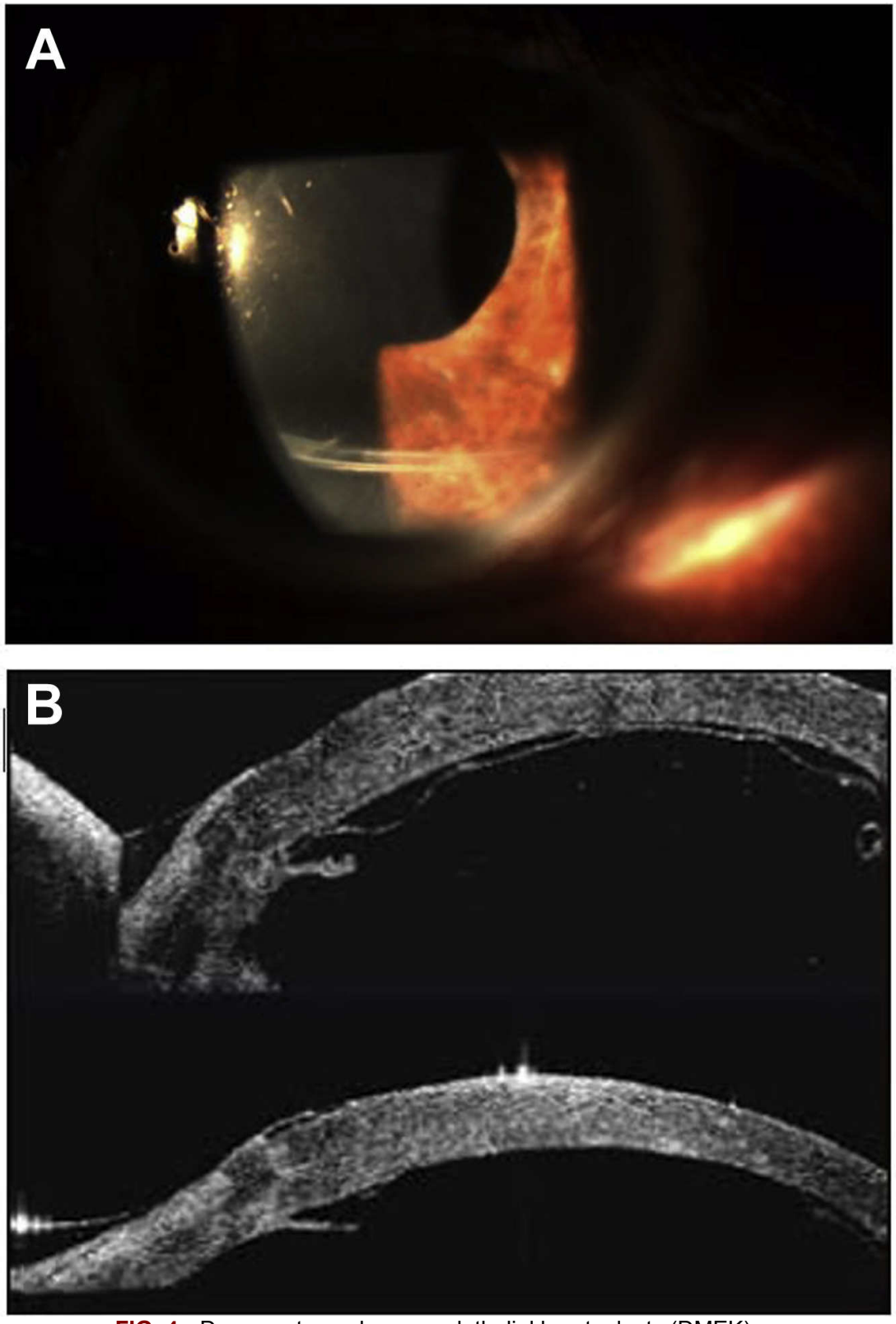

FIG. 4 Descemet membrane endothelial keratoplasty (DMEK) complications. (*A*) Slit lamp photograph of a DMEK graft with chronic inferior

scrolling, but with preservation of central cornea clarity. (*B*) Anterior segment optical coherence tomography of a detached DMEK graft.

Regardless of the benefits of DMEK, some surgeons still prefer to perform DSEK because DMEK is felt to be a greater technical challenge with a marginal benefit over DSEK compared with the innovation that DSEK was to penetrating keratoplasty. The main surgical steps of DMEK are shown in Fig. 5. In response to DMEK, ultrathin DSEK grafts with less stroma were introduced, which theoretically allows better clarity but with potentially easier graft manipulation over DMEK [22]. However, in a randomized control trial by Chamberlain and colleagues [23] comparing ultrathin DSEK with DMEK in 216 patients, DMEK still had superior visual acuity results at 3, 5, and 12 months with similar complication rates. Additionally, in a follow-up report from the same trial, it was found that higher order aberrations were decreased postoperatively in the DMEK group compared with preoperatively, whereas higher order aberrations were actually increased in patients who underwent ultrathin DSEK compared with preoperatively [24].

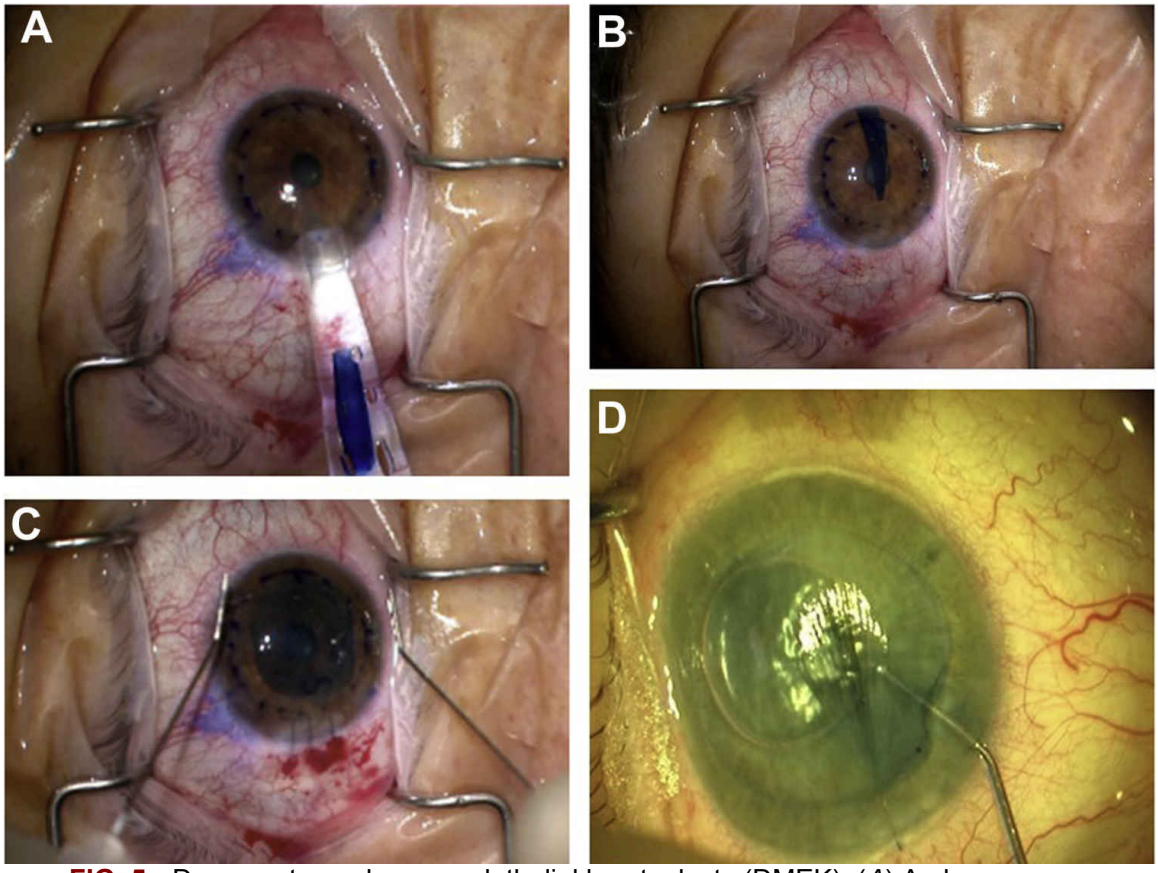

FIG. 5 Descemet membrane endothelial keratoplasty (DMEK). (*A*) A glass tube is used to inject the scrolled DMEK graft that has been prestained blue for visualization. (*B*) The graft is inserted is in the anterior chamber in a scrolled configuration. (*C*) The anterior chamber is shallowed and directing tapping motions on the anterior surface of the cornea with cannulas are used to unscroll the graft. (*D*) When the graft is unscrolled, centered, and confirmed to be in the correct orientation, air or gas is injected posterior to the graft to tamponade it against the host stroma.

According to the 2019 Eye Bank of America Statistical report, the number of endothelial keratoplasties continues to increase, with more than 30,500 of these procedures performed in the United States in 2019 alone. Because of the increase in expertise and popularity with DMEK, the number of DMEK procedures increased by 23% to approximately 13,000 per year, whereas DSEK decreased by 11% to 17,500 in 2019 [25].

Pre-Descemet endothelial keratoplasty (PDEK) is another novel procedure, but it has yet to gain traction in mainstream practice. For PDEK, the pre-Descemet layer along with Descemet's membrane and endothelium are transplanted. PDEK has the major advantage of better graft maneuverability and less tissue loss, at the cost of additional thickness to the graft and a more complicated tissue preparation [26]. The

developers of PDEK advocate that this procedure can be more cost effective, technically easier than DMEK, and have favorable visual outcomes compared with DSEK [27]; however, further research is needed.

Descemetorhexis without endothelial keratoplasty

For a certain subset of patients with FED, DWEK (also known as Descemet stripping alone) may be a viable alternative to DSEK or DMEK. DWEK involves surgically removing Descemet's membrane without subsequent endothelial transplantation. DWEK aims to clear the central guttae causing visual symptoms for patients with FED and allow peripheral endothelial cells to migrate and repopulate the central cornea with potentially healthier endothelium [28,29]. As such, the ideal candidate for this procedure is a patient who is mainly symptomatic from central guttae and central edema and otherwise has a normal peripheral cornea with a robust endothelial cell count of more than 1000 cell/mm^2 on confocal or specular microscopy [30]. Huang and colleagues [31] conducted a retrospective study that compared DWEK to DMEK in 27 eyes with mild to moderate FED with corneal guttae and edema limited to the central cornea and showed that visual outcomes were similar in both groups, although the time to achieve similar outcomes in the DWEK group was about 5 weeks longer. Adjunctive therapy with Rho-associated kinase (ROCK) inhibitors to stimulate the proliferation of human corneal endothelial cells have been shown to enhance corneal clearing in DWEK surgery [32,33], although not yet approved in the United States for this purpose (see the detailed description elsewhere in this article). The advantages of DWEK include the absence of graft procurement, intraoperative graft manipulation, postoperative dislocation or repositioning, potential for rejection, or long-term steroid requirements. However, DWEK remains a controversial technique with insufficient literature to support a more prominent role of DWEK in supplanting traditional endothelial keratoplasty for a majority of patients with endothelial corneal dystrophy.

Relevance and future avenues

Since the introduction of endothelial keratoplasty in 1999, significant advances have been made in improving patient visual acuity and decreasing the rate of complications. Endothelial keratoplasties have become the standard for treating endothelial disease. In 2019, the number of penetrating keratoplasty grafts done in the United States was approximately 17,000, whereas the number of endothelial keratoplasties far surpassed penetrating keratoplasties at more than 30,000 [25]. As the popularity of endothelial keratoplasty increases, future avenues of improving treatment for patients with corneal endothelial disease continue to be explored.

Recent advances in the treatment of endothelial cell dysfunction have shown promising results. One avenue of exploration is the use of ROCK inhibitors to stimulate the proliferation of human corneal endothelial cells. The Rho/Rho-kinase pathway is thought to be involved in regulating the proliferation and apoptosis of corneal endothelial cells and thus could serve as a therapeutic target for inducing endothelial cell proliferation [33]. Okumura and colleagues [32] looked at ROCK inhibitor Y-27632 eye drops in rabbit corneal endothelial cells and found that the drops promoted proliferation of the endothelial cells in a dose-dependent manner. Similar results were subsequently found for in vivo studies of primates' corneal endothelial cells [34]. In a small study looking at 8 eyes with 4 eyes that had diffuse corneal edema caused by bullous keratopathy or pseudoexfoliation syndrome and 4 eyes that had central corneal edema caused by FED, the patients underwent transcorneal freezing followed by 1 week of ROCK inhibitor Y-27632 eye drops. The drops decreased central corneal edema in the patients with FED [33]. The authors proposed that ROCK inhibitor drops could be used in early corneal dystrophy to prevent the future need for corneal transplantation [33]. In a follow-up landmark study published in *The New England Journal of Medicine*, Kinoshita and colleagues [35] injected human corneal endothelial cells with a ROCK inhibitor into the anterior chambers of 11 patients with bullous keratopathy. The process involved making a small 1.6-mm incision at the corneal limbus and using a silicone needle to remove any abnormal extracellular matrix on Descemet's membrane or the endothelial layer of the central cornea. They then injected a solution containing cultured human corneal endothelial cells mixed with the ROCK inhibitor Y-27632 into the anterior chamber. The patients subsequently lay in a prone

position for 3 hours to facilitate the adhesion of the injected corneal endothelial cells. At 24 weeks after the procedure, the investigators found a statistically significant increase in endothelial cell density, decrease in corneal edema, and improvement in visual acuity [35]. Moreover, corneal transparency was maintained in all 11 patients at their 2-year follow-up. This study was monumental in that it demonstrated the possibility of shifting the treatment of patients with corneal endothelial disease away from very technical anatomic keratoplasty procedures and toward a less invasive injection.

Another avenue of exploration is the use of bioengineered corneal endothelial grafts instead of cadaveric corneal grafts to address a global shortage of donor cornea. In a survey conducted by Gain and colleagues [2] interviewing eye bank staff and corneal surgeons across 148 countries, the authors concluded that there is a worldwide shortage of corneal donor grafts with only 1 cornea available for every 70 that are needed. A tissue-engineered endothelial–keratoplasty graft would at minimum include a monolayer of cultivated corneal endothelial cells supported on a basement membrane-like substrate [36]. Sources of corneal endothelial cells include culturing of primary human corneal endothelial cells, as well as deriving the cells from related adult cell types [36]. It has been shown that it is possible to induce the differentiation of corneal endothelial cells from adult skin-derived precursor cells because they both share the same neural crest cell origins [37]. Possible candidates for membrane substrates that are being investigated include anterior lens capsules [38], decalcified fish scales [39], and synthetic materials such as compressed collagen gels [40]. One of the main theoretic advantages of bioengineered grafts over the injection of endothelial cells into the anterior chamber is the decreased risk of endothelial cells migrating into improper areas including the trabecular meshwork [36]. Moreover, using a bioengineered graft with corneal cells produced from autologous precursors from the patient's own cell lines should decrease the risk of rejection after transplantation.

Finally, the use of gene therapy to target specific deleterious mutations remains at the forefront of new treatment modalities being studied for patients with endothelial dystrophies. In FED, a large majority of patients have an unstable CTG trinucleotide repeat sequence in the TCF4 gene in chromosome 18q21 that leads to abnormal post-transcriptional splicing of genes important for the function of corneal endothelial cells [41]. Broadly, gene therapy uses the transfer of genetic material or enzymes into cells to drive expression of a gene or silence the expression of a damaged gene.

One genome editing technique involves the use of antisense oligonucleotides that consist of nucleotides complementary to the messenger RNA target of interest. Binding of the antisense oligonucleotide to the partner messenger RNA prevents downstream translation, thereby silencing the culprit gene that is harboring the mutation of interest. Another gene therapy technique involves using clustered regularly interspaced palindromic repeat (CRISPR) nucleases and CRISPR-associated protein (Cas9) to form a ribonucleoprotein complex that recognizes and binds to specific DNA sequences of choice. Once the complex binds to the target DNA, alterations such as double-stranded breaks, can be initiated. In mitotically inactive cells such as corneal endothelial cells, double-stranded breaks trigger endogenous DNA damage responses that lead to frame shifts or deletion of the disrupted DNA sequence, thereby silencing the gene of interest [36]. Available delivery systems of gene therapy include viral vectors [42] and nanoparticles [43], both of which have been successfully shown to be used for gene delivery in the anterior segment of animal models. Ophthalmologic diseases that have been treated successfully in animal models or humans using the CRISPR-Cas9 system include retinitis pigmentosa, Leber congenital amaurosis, and proliferative vitreoretinopathy [44]. Uehara and colleagues [45] showed in a murine model that an intraocular injection of the CRISPR–Cas9 system can prevent corneal endothelial cell loss in early onset FED. In addition to focusing on silencing the harmful gain-of-function mutations, other gene therapy studies have looked at using the CRISPR system to promote transcription and regeneration of human corneal endothelial cells. Chang and colleagues showed that activation of the SOX2 gene in rat corneal endothelial cells in vivo led to regeneration of the endothelial cells [46]. Although gene therapy serves to be a promising therapeutic modality for corneal endothelial disease, further studies looking into efficacy and safety, especially regarding the potential for genomic editing at unintended sites, need to be pursued before gene therapy becomes a viable alternative to endothelial keratoplasty.

Summary

Since the initial introduction of posterior lamellar keratoplasty 20 years ago, the treatment of patients with corneal endothelial disease has made numerous advances leading to improved patient visual outcome and satisfaction. Initial groundbreaking work from Melles and colleagues and Terry and colleagues involved the creation of a stromal pocket in the host cornea and implanting a donor graft consisting of stroma, Descemet's membrane, and endothelium by using an air bubble to promote adherence of the graft to the host cornea [7,8]. This technique offered numerous advantages over the prior standard of penetrating keratoplasty by decreasing intraoperative and postoperative risks and promoting faster visual recovery. Further advances came in the form of DSEK, which used selectively peeling Descemet's membrane from the host cornea before implanting the donor graft. Studies comparing DSEK to penetrating keratoplasties showed that DSEK had similar outcomes to the latter without the wound and suture-related complications [15,16]. The field of endothelial keratoplasty further evolved with the introduction of DMEK, a technique where the donor graft consists of only Descemet's membrane and endothelium [18]. Studies comparing DMEK to DSEK showed improved visual outcomes in DMEK, although there is a higher rate of corneal graft dislocation and detachment [19]. Although DMEK offered slightly improved visual outcomes, some cornea surgeons prefer to use DSEK because the thicker graft in DSEK is easier to manipulate and the presence of posterior stroma in the graft leads to lower detachment rates, particularly in eyes with abnormal anterior segment anatomy. Ultrathin DSEK has also been adopted, but seems to be inferior in terms of visual outcomes compared with DMEK [22]. PDEK is a newer iteration of EK that selectively transplants the pre-Descemet's layer, Descemet's membrane, and endothelium, but has yet to reach widespread adoption [26].

Although DSEK and DMEK remain as the standard procedure for endothelial keratoplasty, the quest for increasingly minimally invasive strategies led to the introduction DWEK, a technique involving descemetorhexis without an endothelial transplant [30]. DWEK relies on the host's own peripheral corneal endothelial cells to migrate and repopulate the central cornea. The efficacy of DWEK remains controversial and has a limited therapeutic role for a subset of patients with only central corneal endothelial disease [31].

Future avenues of exploration include ROCK inhibitors, bioengineered corneal endothelial grafts, and gene therapy. ROCK inhibitors modify the Rho/Rho-kinase pathway that is thought to be involved in regulating the proliferation and apoptosis of corneal endothelial cells. Initial studies have shown that ROCK inhibitors are a valuable adjunct in DWEK/Descemet stripping alone and may be a useful treatment modality when used early in patients with FED to prevent the need for future transplantation [33]. Bioengineered corneal endothelial grafts also have been researched as a possible alternative to human cadaveric cornea [36]. The grafts consist of cultivated endothelial cells, either cultured from primary human corneal endothelial cells or induced from related adult cells, on top of a basement membrane-like substrate. Bioengineered grafts should minimize adverse immune reactions from corneal transplants as well as help to address the global shortage of donor cornea. Finally, gene therapy is perhaps the most exciting area of innovation in treating corneal endothelial disease. Genome editing techniques using antisense oligonucleotides and CRISPR–Cas9 complexes to promote or silence genes implicated in various corneal endothelial diseases could supplant the need for endothelial keratoplasties in many patients [44]. Recent studies looking at the delivery of gene therapy via viral vectors or nanoparticles have shown promising results in preventing corneal endothelial loss and promoting endothelial cell regeneration in animal models [42,43]. All these therapeutic innovations could play an integral role in augmenting or even replacing endothelial keratoplasty as the standard of care for the treatment of corneal diseases.

Clinics care points

- Endothelial keratoplasty is an optimal technique for surgical treatment of corneal endothelial disease, which has fewer intraoperative risks and postoperative complications compared with penetrating keratoplasty with better visual outcomes and similar long-term survival.
- DMEK has improved visual outcomes compared with DSEK; however, DMEK has a higher rate of corneal graft dislocation and detachment. DSEK grafts are also surgically easier manipulate and place.
- DWEK in conjunction with ROCK inhibitors is a novel technique that has promising early results and may be a useful treatment modality.
- Future avenues for treatment of corneal endothelial disease includes bioengineered corneal grafts, cultivated endothelial cells, and gene therapy.

Disclosure
The authors have nothing to disclose.

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Update in the Management of Keratoconus

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Keywords

Keratoconus; Corneal cross-linking; Scleral contact lens; Intrastromal corneal ring segments; Deep anterior lamellar keratoplasty

Key points

- The management goals for keratoconus are 2-fold: to halt disease progression and to provide visual rehabilitation.
- Corneal cross-linking with UV-A light and riboflavin has become the standard treatment of preventing the advancement of mild to moderate keratoconus.
- Scleral contact lenses and intrastromal ring segments are effective visual and refractive interventions for keratoconus.
- Deep anterior lamellar keratoplasty has become the preferred initial surgical treatment of keratoconus, unless there is significant scarring in which case penetrating keratoplasty is preferred.

Introduction

Keratoconus (KCN) is a common corneal degeneration characterized by progressive, noninflammatory changes in collagen structure that results in corneal thinning and ectasia [1]. The exact etiology remains unknown and likely is multifactorial. Certain genes, such as VSX1, DOCK9, or TGFβ1, may play a role in the disease [1]; between 8% and 10% of cases present with a hereditary component [1]. KCN can occur as an isolated condition or in association with ocular and systemic conditions, including Leber congenital amaurosis, Down syndrome, connective tissues disorders, and allergic eye disease [1–3]. No significant gender or ethnic predilection exists [1,2]. Initial studies conducted in the United States in the 1980s demonstrated a prevalence of approximately 1 in 2000 (54.5 per 100,000), with a mean incidence of 2 new cases per 100,000 per year [4]; however, newer studies have noted that these values may be 5-fold to 10-fold higher [5].

Most patients present in adolescence with features of progressive myopia and astigmatism, with eventual involvement of both eyes by the third or fourth decade of life [1]. Numerous clinical signs have become synonymous with moderate to advanced KCN, including Munson and Rizzuti signs, Vogt striae, Fleischer ring, central or paracentral stromal thinning, conical protrusion with apical steepening (Fig. 1), epithelial nebulae, and anterior stromal scarring [2]. Direct ophthalmoscopy may demonstrate a Charleux oil droplet reflex, and retinoscopy is characterized by a scissoring reflex [2]. Patients with advanced disease may develop painful acute hydrops, caused by breaks in Descemet membrane, with resulting corneal edema and eventual scarring [2].

Numerous systems have been developed to better characterize the severity of KCN. The Amsler-Krumeich system is one of the oldest, in which the severity of KCN is graded from stages I to IV based on a patient's refractive error, central keratometry readings, central corneal thickness, and presence or absence of scarring [6]. It does not account, however, for posterior corneal changes nor does it utilize corneal topographic/tomographic values, which now are standard in diagnosing KCN. The newer Scheimpflug imaging–based Pentacam system (Oculus, Wetzlar, Germany) utilizes the Belin/Ambrósio Enhanced Ectasia Display to screen for KCN using maximal keratometry, anterior/posterior elevation, and tomographic thickness data (Fig. 2) [7]. In general, topographic parameters that should arouse suspicion for KCN include

astigmatism greater than 5 diopters (D), and/or keratometry values (K1/K2) greater than 48 D, maximum keratometry (K_{max}) reading greater than 49 D, central corneal thickness less than 470 μm, asymmetric bowtie pattern with a skewed radial axis, and cornea asphericity greater than −0.50 μm [1].

There has been a dramatic shift in how KCN is diagnosed, followed, and treated over the past few decades. Newer treatment strategies can delay or prevent the need for corneal transplantation, which long has been considered the endpoint in the treatment of KCN when vision can no longer can be corrected with refraction. Currently, the goal of treatment of KCN is 2-fold: to halt disease progression (currently via CXL) and to provide visual rehabilitation though a variety of methods, including traditional spectacles and contact lenses (CLs), scleral CLs, intrastromal ring segments, and corneal transplantation.

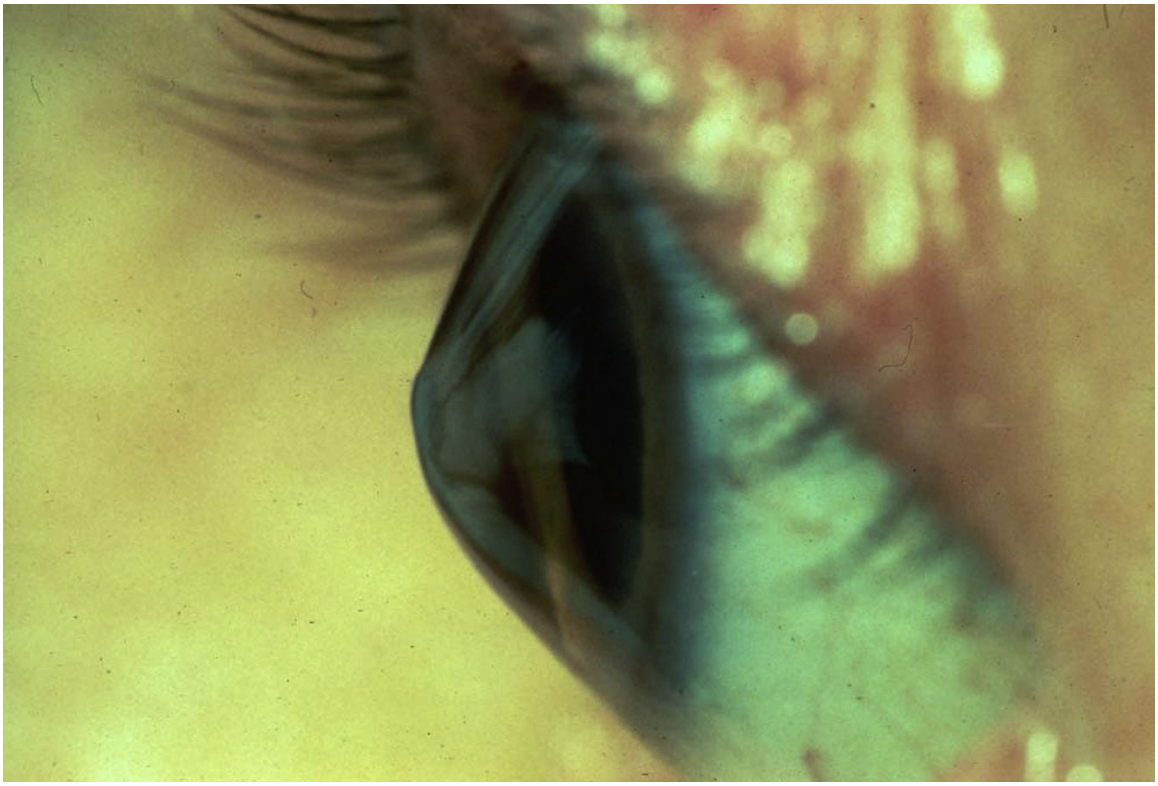

FIG. 1 Slit lamp image of a KCN eye demonstrating apical steeping.

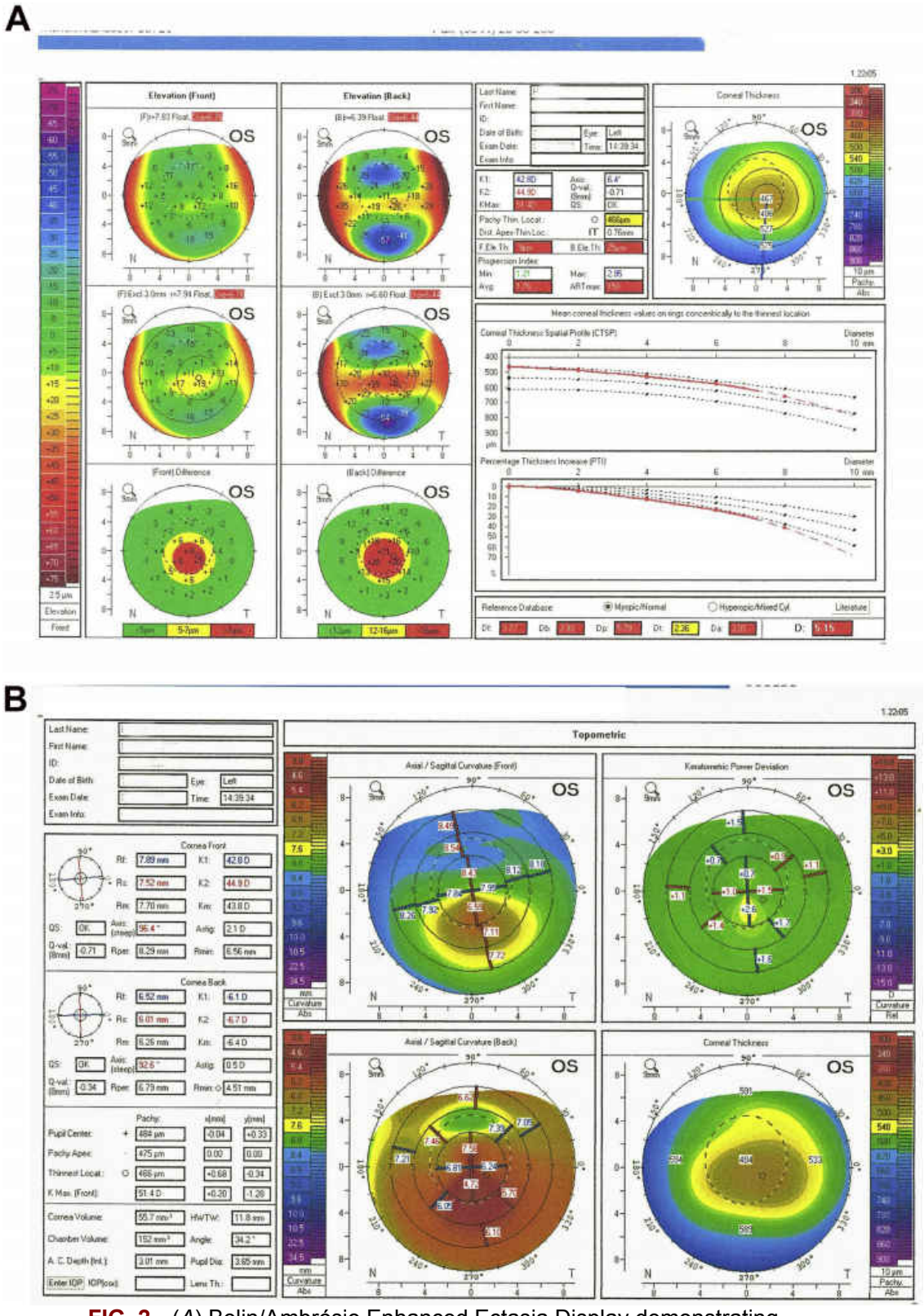

FIG. 2 (*A*) Belin/Ambrósio Enhanced Ectasia Display demonstrating posterior corneal steepening in a KCN eye. (*B*) Topographic map demonstrating inferior corneal asymmetry and steepening in a KCN eye.

Corneal cross-linking

CXL with UV-A light and riboflavin (vitamin B_2) has become a revolutionary treatment in preventing the advancement of KCN. CXL uses riboflavin as a photosensitizer, which, when exposed to longer wavelength UV-A, induces chemical reactions in the corneal stroma and results in the formation of covalent bonds between the collagen molecules [8]. This collagen cross-linking increases the tensile strength and rigidity of the cornea, preventing further thinning and ectasia [9].

CXL currently is Food and Drug Administration (FDA) approved for KCN with evidence of progression. Although no definite criteria exist to precisely define progression, many practitioners consider an increase in K_{max} value, change in spherical and astigmatic refraction, mean central K-readings, and a decrease in mean central corneal thickness to signify advancing disease [8]. According to the Global Delphi Panel of Keratoconus and Ectatic Diseases, 2 of the follow 3 parameters should be taken into account when considering progression: steepening of either the anterior or posterior corneal surfaces or corneal thinning [3]. These changes should be demonstrated over time (typically with tomography). CXL is not indicated for KCN that is stable. Other relative contraindications to CXL treatment include a corneal thickness of less than 400 μm, prior herpetic ocular infection, current ocular infection, severe scarring, severe dry eye, neurotrophic keratopathy, history of prior epithelial wound healing, autoimmune disorders, and pregnancy [8].

The Dresden protocol, initially described by Wollensak and colleagues in 2003, is considered to be the conventional CXL (C-CXL) protocol. Known as the epi-off protocol, it entails removal of the central 8-mm to 9-mm epithelium followed by the application of 0.1% riboflavin solution every 5 minutes for 30 minutes [9]. This is followed by 30 minutes of UV-A radiation (wavelength 370 nm and power 3 mW/cm^2) with the application of riboflavin solution every 5 minutes during exposure (Fig. 3) [8]. Short-term and medium-term results have demonstrated favorable improvement of topography measures with halted progression of KCN [7,9,10]. C-CXL has proved to be relatively safe with improved uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) (often due to a reduction of irregular astigmatism) [11]. In their 10-year follow-up of 34 eyes, the Dresden group demonstrated long-term stability of KCN after CXL [12].

Complications secondary to C-CXL are rare but include persistent epithelial defect or delayed epithelial closure and frequently reported postoperative pain [8]. Keratitis has been reported to occur following C-CXL because of the presence of an epithelial defect, although the use of soft bandage CLs and topical corticosteroids in the immediate postoperative period also may serve as risk factors [13]. Postoperative microbial keratitis from bacterial, herpetic, protozoal, and fungal sources have been described in the literature [13], which can lead to stromal scars and poor visual outcomes.

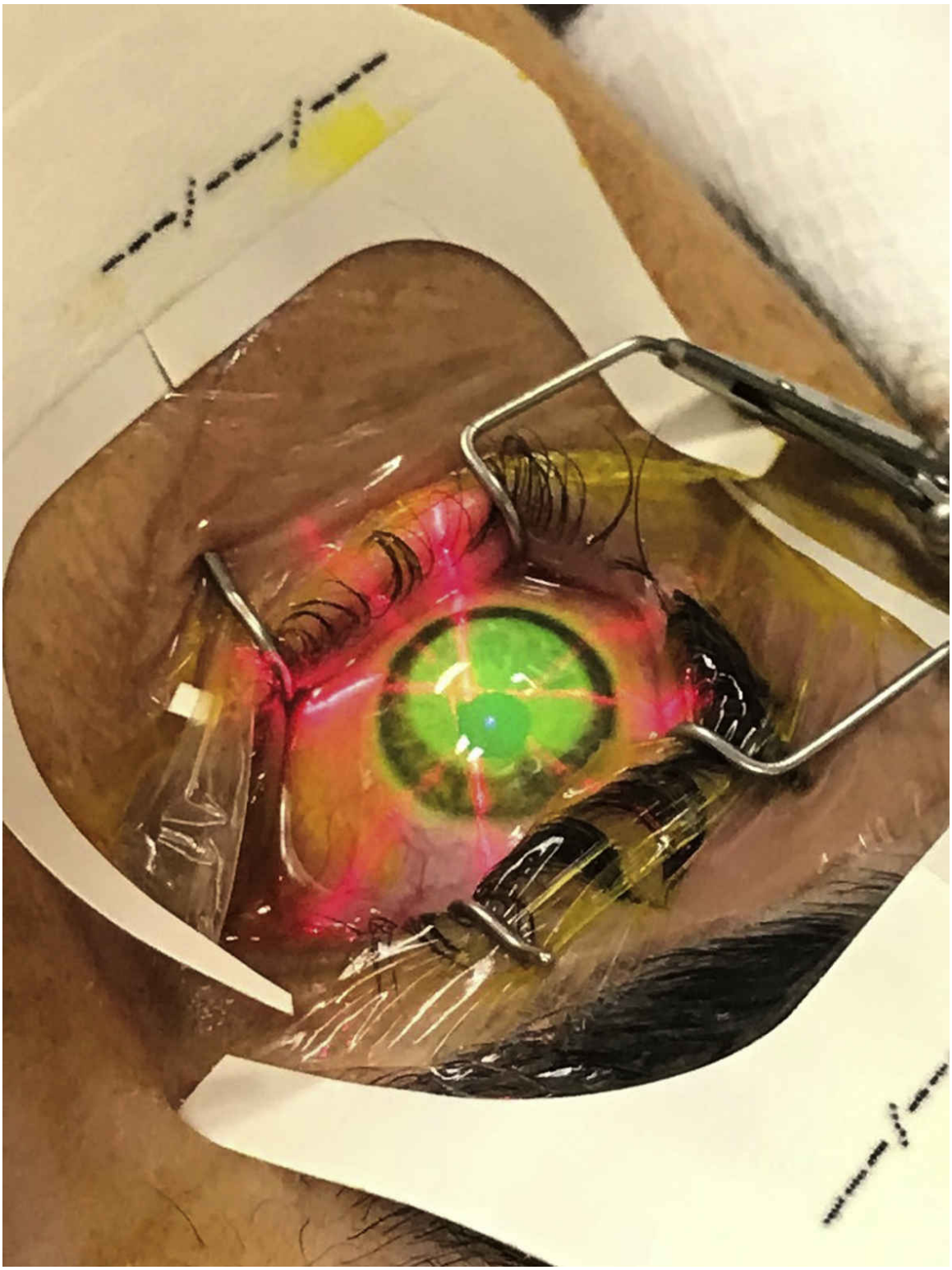

FIG. 3 Photograph demonstrating the application of UV-A radiation during an epi-off CXL procedure.

To minimize these complications, epi-on or transepithelial CXL (T-CXL) protocols, which retain the epithelium, have been developed. Initial studies of T-CXL demonstrated limited diffusion of riboflavin through corneal epithelial tight junctions [8]. The extent of the cross-linking effect and UV-A interaction with riboflavin was found to be decreased by the limited riboflavin penetration into the corneal stroma. Riboflavin penetration through epithelial tight junctions, however, since have been increased by a variety of techniques, including the use of chemical enhancers, such as ethylenediaminetetraacetic acid, D-α-tocopherol polyethylene glycol 1000 succinate, tetracaine/proparacaine, ethanol, gentamicin, and benzalkonium chloride [11]. Other strategies to increase riboflavin penetration without epithelial débridement include mechanical disruption of the corneal epithelium, increasing the application time of riboflavin, ultrasound enhanced penetration of riboflavin, use of intrastromal channels or microneedles to introduce riboflavin and bypass the corneal epithelium, intrastromal administration of riboflavin via femtosecond laser-generated corneal pockets, and nanotechnology-based T-CXL [11,14]. Although these techniques have overcome some of the immediate postoperative complications of C-CXL, their effectiveness seems to be less than that of C-CXL, thus their utility still is a matter of debate [11].

A newer CXL technique, iontophoresis CXL, does not require epithelium removal and shortens riboflavin penetration time and duration of irradiation [11]. A generator that delivers a small electric current is connected to 2 corneal electrodes that generate a low-intensity electric field that in turn facilitates the penetration of riboflavin through the cornea [15]. It has been shown to provide better riboflavin saturation than other T-CXL approaches, and clinical studies have shown good results in halting KCN progression and improvement in topographic and visual parameters; however, the biomechanical tissue effect and stromal remodeling are inferior compared with C-CXL [11,13].

Despite their limitations, some investigators argue that T-CXL protocols should be considered in thin corneas (<400 μm). These patients typically are not candidates for C-CXL given an increased likelihood of radiation damage to the endothelium [8]. The T-CXL protocols, however, are able to conserve corneal morphology and reduce the risk of endothelial damage, while making the procedure more comfortable for patients. For both epi-on and epi-off procedures, additional protection can be provided to the endothelium by using hypo-osmolar riboflavin or isotonic solutions with

hydroxypropyl methylcellulose to induce iatrogenic corneal swelling and to increase the stromal thickness to greater than 400 μm before the radiation exposure stage [8,16].

Accelerated CXL (A-CXL) protocols have been adopted to reduce the exposure time of the de-epithelialized cornea to sources of infection and to minimize patient discomfort by shortening the procedure length [11]. This concept works on the Bunsen-Roscoe law of photochemical reciprocity: the same photochemical effect is achieved with a shorter irradiation time by a corresponding increase in irradiation intensity [16]. There are no uniform protocols for A-CXL, but the irradiation time typically is shortened from 30 minutes to 3 minutes, 5 minutes, 10 minutes, or 15 minutes with UV-A intensities ranging from 7 mW/cm^2 to 30 mW/cm^2 and various riboflavin soaking times (5–30 minutes) [16]. Due to the variability in surgical protocols, however, it is difficult to deduce a reliable conclusion about the success of the procedure. Many studies seem to indicate that A-CXL is effective at halting the progression of KCN at 12-month follow-up, with reductions in K_{mean} and K_{max} values, and a similar safety profile to C-CXL [16]. Yet, the degree of flattening and remodeling of the cornea is less than with C-CXL and may not be as long lasting [8,11,14,16]. On the other hand, because of the shallower effect of A-CXL with less riboflavin penetration, it generally is safer in thin corneas and is beneficial in preventing endothelial cell damage [16]. Another limiting factor in A-CXL is that the biochemical effect of CXL might be oxygen dependent, and accelerating the procedure results in a relatively hypoxic environment that can diminish the efficacy of the procedure [17].

CXL-plus has become an increasingly popular way of combining CXL with adjuvant refractive procedures to both halt the ectatic process and enhance functional visual outcomes. Several combined protocols have been studied to various degrees in conjunction with CXL, including photorefractive keratectomy (PRK), transepithelial phototherapeutic keratectomy, conductive keratoplasty, intrastromal corneal ring segments (ICRSs) implantation, phakic intraocular lens implantation, or multiples of these techniques together [14]. One of the more well-known protocols, the Athens protocol, involves sequential excimer laser débridement of epithelium and partial topography-guided excimer laser stromal ablation, followed by high-fluence CXL (10 mW/cm^2 for 10 min) [14]. Ten-year follow-up using the Athens protocol has demonstrated persistent flattening/stabilization of pachymetric and topographic indices, with

improvement in average UCVA and BCVA [18]. Further investigation still is necessary to delineate optimal treatment conditions for this combined procedure and to identify specific disease subgroups who are more likely to benefit [14].

Increased risk of stromal haze after simultaneous combined procedures remains a substantial barrier to generalized adoption of this treatment method [14], especially because between 10% and 90% of patients may develop stromal haze with CXL procedures of any kind [13]. The stromal haze usually is temporary and appears to be due to increased edema, keratocyte activation, and corneal remodeling, and can occur for 1 month to 3 months postoperatively [13]. Patients who develop long-term steroid-resistant haze appear to have more advanced KCN, older age, grade III or grade IV KCN by the Amsler-Krumeich classification system, and preoperative reticular pattern of stromal microstriae [13]. Rarer but more serious side effects of CXL include infectious infiltrates (discussed previously), sterile infiltrates, corneal scars, corneal melts, and endothelial failure [11].

Treatment failure is a possible complication of CXL. This can be defined as progression of the condition with an increase in K_{max} values of 1.0 D over the preoperative value or greater than a 10% decrease in pachymetry readings 6 months postoperatively [19]. This may occur in up to 10% of patients [19]. Risk factors for CXL failure include a preoperative patient age of 35 years or older, a spectacle-corrected visual acuity better than 20/25, and a K_{max} reading greater than 58.00 D [13]. The possibility of requiring an additional CXL should be considered when progression is found after the procedure [8].

Spectacles and contact lenses

CXL thus far is the only FDA-approved intervention to prevent the progression of KCN. The first-line treatment of corneal ectasia and visual compromise resulting from KCN is refraction and optical correction. This, however, masks an important but subtle point, in that although better-corrected vision may be achievable with certain modalities, it may not be tolerated by the patient. Patients may not be able to tolerate CLs or they may not be able to access specialty CLs [3].

Much of the evidence-based understanding of the natural history of KCN and the role of CLs has been elucidated by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study. The CLEK study of 1200 patients with KCN followed over 8 years found that a vast majority (74%) of patients were corrected with CLs, of whom 65% of patients wore rigid gas-permeable (RGP) lenses. This cohort consisted largely of patients who exhibited moderate to severe disease based on keratometric readings, with steep K greater than 45.00 D [20].

Soft CL quickly can become inadequate for progressive KCN. In contrast, RGP CLs long have been a preferred initial treatment modality for patients with unsatisfactory vision with glasses or soft CLs. Patients who fail conventional corneal RGP lenses now have an armamentarium of alternatives to choose from, among them hybrid lenses (rigid center and soft skirt), toric lenses, and piggyback lenses that overlay a rigid lens over a soft CL.

It is important to discuss some basic principles of CL fitting. Lenses vary with respect to lens clearing and bearing. Clearing refers to an area where the lens is directed away from, whereas bearing refers to where the lens support is directed. Flat fitting lenses touch the apical cornea whereas steep fitting lenses are designed to vault over the corneal apex. Given the concern that CLs may induce further ectasia or corneal scarring, the issue of CL fit assumes greater importance than initially may be realized.

Soft lenses and soft toric lenses may be indicated in early KCN. These lenses fit centered over the cornea. Advantages of soft CL include good comfort and lower cost given their greater commercial availability [21]. They are less likely, however, to be successful with moderate to severe astigmatism.

RGP lenses have been shown to provide better vision than glasses. Gas-permeable lenses range in size and can be custom fitted. The goal is to vault minimally over the corneal apex to prevent epithelial disruption and

provide midperipheral bearing and moderate peripheral clearance [21]. A major advantage of RGP lenses is that they provide a smooth regular surface that masks underlying corneal irregularity. They also provide good tear exchange. Their disadvantage is stability, in that they are more likely to decenter. One study comparing flat fit lenses with steep fit lenses for keratoconus patients found that a greater proportion of corneas wearing flat fitting contact lenses were scarred [22]. Again, however, the study investigators found that after controlling for corneal curvature, the association of rigid contact lens fit and corneal scarring at baseline did not persist. The linking of advanced disease and flat fit renders it difficult to statistically discriminate between the effect of flat CL fit and disease severity on visual acuity, CL comfort, ocular pain, and incident corneal scarring. It would be useful to have prospective data to determine the presence of any causal relationship between lenses fit and apical corneal scarring.

As KCN advances, CL fit can be more difficult due to peripheral corneal irregularities. Intralimbal lenses are larger and good alternative for fitting moderate KCN. They have a central corneal vault or light touch with midperipheral bearing. Piggyback lenses consist of a soft lens underneath an RGP lens. This is helpful in cases of intolerance to RGPs or significant epithelial disruption with them. It has the advantage of soft CL in providing better comfort, whereas the gas-permeable material provides better oxygen permeability and thereby helps prevent corneal edema and hypoxia. The base curve of the soft lens can be modified to alter the fitting relationship of the RGP lens, with a plus-powered soft lens used to flatten the RGP fit, and a minus-powered soft lens used to steepen the RGP fit [21]. Hybrid CLs have a gas-permeable center and a soft skirt and can be used in early to advanced KCN to improve BCVA while preventing endothelial cell damage [23]. A hybrid lens is a preferred lens if there is poor centration or poor stability with GP lenses [21].

CL use in KCN patients has been associated with various structural changes, such as decreased basal epithelial cell density, stromal keratocyte density, and endothelial cell count, especially with lenses that have low oxygen permeability, but RGP lenses have not been demonstrated to reduce endothelial cell count [24].

Scleral contact lenses

Although CLs are superior to spectacles for advanced KCN and are important for visual rehabilitation, they do not slow or halt disease. Retrospective studies have shown, however, that CLs, specifically scleral CLs, can prevent or delay corneal transplant surgery in KCN patients. A cohort study of patients with advanced KCN with maximal keratometry value greater than 70 D found that these patients were able to achieve better vision with scleral CLs compared with spectacles, even with corneal scarring [25]. Only after a trial lens fitting can a determination be made whether patients can tolerate or achieve satisfactory visual correction with CLs. Failure with traditional RGPs, piggybacks and hybrids, and onset of neovascularization with other types of lenses are reasons to use scleral CLs. A contraindication to use, however, is significant edema from reduced endothelial cell count. Scleral lenses can be adapted to fit almost any degree of corneal ectasia by changing the vault of the optic zone. The basic design philosophy when fitting a scleral CL is to vault over the cornea, thereby creating a post–lens tear reservoir between the lens and the cornea [26]. The ideal fit of a scleral lens is to completely vault the cornea and limbus and to rest on the sclera [21]. Full scleral lenses range from 18.1 mm to 24.0 mm and have scleral bearing and maximum corneal clearance. Semiscleral lenses and miniscleral lenses have both corneal and scleral bearing to varying degrees. They have gained popularity due to being reengineered with gas permeability [26].

The prosthetic replacement of the ocular surface ecosystem (PROSE) device is a custom-designed scleral CL used to treat ocular surface diseases as well as corneal ectasia. The degree of customization in the fitting process and the lens design make it possible to fit eyes with severely ectasias or eyes that are status post–penetrating keratoplasty (PK) [27]. It also has been demonstrated to be efficacious in eyes with advanced KCN. In 1 retrospective study comparing 36 eyes fitted with PROSE and 37 eyes that underwent PK, visual acuity was better in the PROSE cohort, even when comparing eyes with the most advanced ectasia [28]. Of those eyes with the most severe ectasia, more eyes achieved 20/25 visual acuity after PROSE than after keratoplasty.

A barrier to scleral CL use is the difficulty in handling compared with corneal lenses, which are easier to use but have less scope in advanced disease. A study by Barnett and colleagues [29] assessing scleral CL use in a cohort of patients with a history of PK—mostly for KCN—found more than 40% of patients discontinued use due to difficulty with lens use. Similarly, miniscleral lenses have been shown to improve vision and

quality of life for patients with KCN, but 1 study showed that approximately 20% of patients abandoned their use due to difficulty with lens handling [30].

Deloss and colleagues [28] and Koppen and colleagues [25] have shown through retrospective cohort studies that patients who are able to be fitted with SCLs can avoid undergoing PK for years, despite having advanced ectasia, although some who initially are fit eventually still do require PK given that CLs do not halt the progression of disease. Both studies evaluated groups of patients with advanced KCN and found comparable visual acuity outcomes between those patients who underwent keratoplasty and those who deferred keratoplasty by adopting scleral CLs.

Building on this theme, a retrospective study from Michigan found scleral CL or RGP use significantly lowered the hazard of undergoing keratoplasty when compared with no CL use [31]. Although the investigators were unable to conclude whether those who underwent keratoplasty would have achieved good outcome with scleral CLs given the retrospective nature of the data set, their results did show that black race, younger age, and living in a neighborhood with more socioeconomic deprivation was associated with increased risk of keratoplasty [31]. This is relevant insofar as it demonstrates the existence of a cohort of patients who may possibly achieve good outcomes with scleral CLs but, due to possible downstream effects related to access to specialty care and affordability of CLs, endured a higher risk of undergoing avoidable keratoplasty. In a similar vein, Sarezky and colleagues [32] showed that patients with a household net worth of $150,000 to $249,000 and greater than $500,000 were significantly less likely to undergo PK than those with household net worth less than $25,000.

The most important consideration in managing KCN is that spectacle and CL correction never stop being relevant in the management of the disease. In many cases, especially with progressive disease, CLs still are required, including after CXL, intrastromal corneal ring procedures, and keratoplasty [33]. Certainly, if the cornea becomes too scarred or too steep to tolerate CL, then a transplant is indicated, but whether the disease is stable or progressive or whether treatment has been done to halt disease progression with novel procedures, such as CXL, or to reverse the disease with lamellar or PK, visual rehabilitation with CLs still is a mainstay of disease treatment. Different types of lenses have been investigated not only in treatment-naïve KCN patients but also in those who have undergone ICRS, CXL, or PK; these lenses show good efficacy in the

treatment of KCN post-ICRS implantation [33] as well as after CXL [34] and with PK [33].

Intrastromal corneal ring segments

Originally developed to correct mild myopia, ICRSs (Fig. 4) now are used as a method of visual rehabilitation in KCN and other corneal ectasias. A tunnel is created in the corneal stroma, either with a steel dissector or a femtosecond laser, and the rings are inserted in the midperipheral deep stroma on each side of the pupil. The insertion of the segments improves myopia and astigmatism in KCN via an arc-shortening effect that flattens the steep area of central cornea and reduces visual distortion [35]. ICRSs are indicated in mild to moderate stages of KCN with a clear optical zone (ie, unscarred corneas) and CL intolerance [35,36]. Given their success, they can be used as an alternative to penetrating or lamellar keratoplasty and can be used on an off-label basis as a purely refractive option to improve UCVA or BCVA in KCN [36].

Four main variations of ICRS are available internationally: Intacs SK (Addition Technology, Inc, Des Plaines, IL), Ferrara Ring (Ferrara Ophthalmics, Belo Horizonte, Brazil), KeraRing (Mediphacos, Belo Horizonte, Brazil), and MyoRing (DIOPTEX GmbH, Austria). Intacs SK are at present the only variations available in the United States since their approval in 2004 by the FDA [35,36]. ICRS are made of polymethyl methacrylate and come in a variety of arc lengths, cross-sectional shapes, thickness, and diameters [35]. Generally, a greater flattening effect can be acquired with thicker segments and closer positioning of the ring segments to the visual axis [35]. In a review of published studies from 2014 to 2018 on the outcomes of KCN patients who received various types ICRS implantation, Park and colleagues [35] found that the mean changes in spherical equivalent ranged from 1.064 D to 7.6 D, the gain of lines of BCVA ranged from 34% to 100% of eyes, and the average change in mean keratometry ranged from −6.4 3 D to −2.16 D. Overall, most studies, conducted largely in adult eyes, demonstrate ICRS to be an effective visual and refractive intervention in the treatment of KCN.

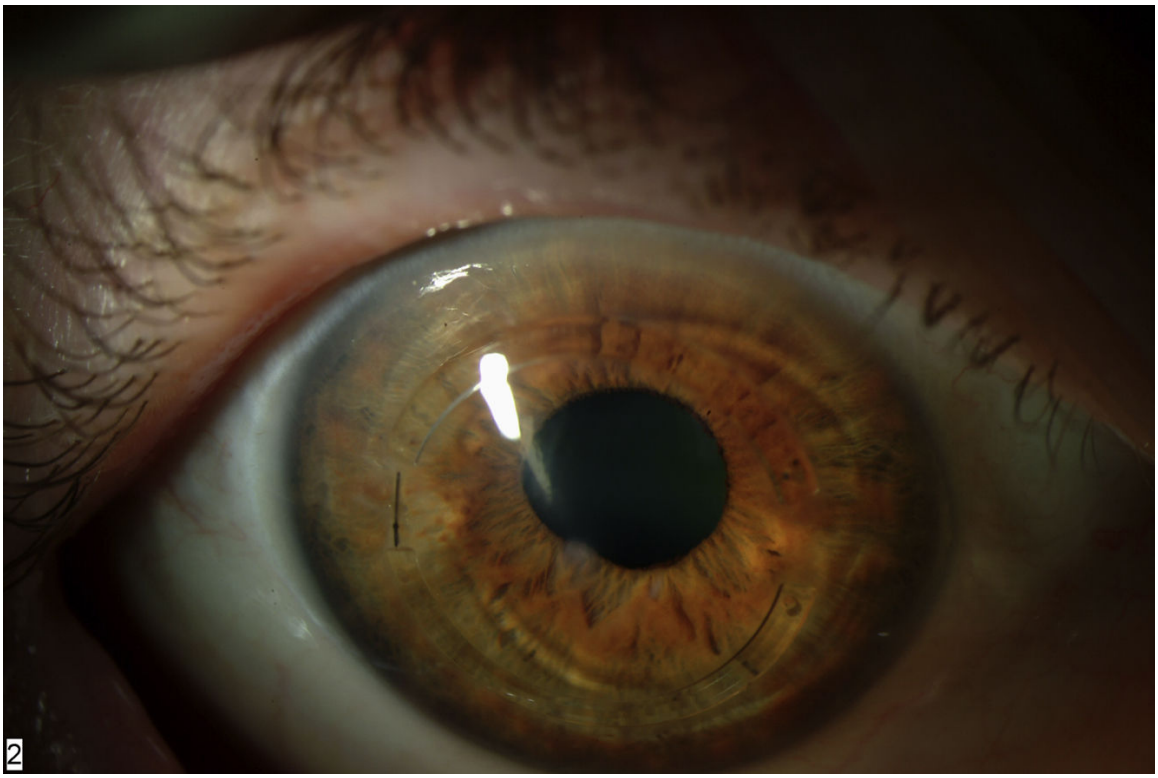

FIG. 4 Slit lamp image of a KCN eye implanted with ICRSs.

ICRS are not preferred in young children due to the rapid progression of their KCN, eye rubbing tendencies, and noncompliance with postoperative instructions [35]. Other poor candidates for ICRS include those with advanced KCN (grade III or grade IV based on the Amsler-Krumeich classification) [37], steep preoperative corneas (mean K values > 55.0 and/or steep K values > 57.0 D–58.0 D) [36,38], and corneal thickness less than 450 μm at the central optic zone [37]. The newest models of ICRS (including Keraring 355°, 320° Ferrara ICRS, and Intacs SK), however, have been demonstrated to improve distance visual acuity in moderate to severe KCN patients [35,37].

Surgical success and visual improvement ultimately depend on several factors, including proper ring placement, accurate implantation depth, and the diameter of the optical zone [36]. Improper positioning of the ring (including superficial or deep placement of the ring) can lead to over-correction or under-correction. Anterior segment imaging can help surgeons plan the appropriate depths for the intrastromal tunnels (often 70%–80% of the peripheral corneal thickness) with increased precision and decreased risk of anterior chamber perforation or incomplete tunnel creation [35]. Other rare intraoperative complications include epithelial

defects and wound gape, both of which can increase the risk of infection [36]. Rotating the ICRS so that the ends of the 2 segments are in contact with one another also can result in erosion through the corneal stroma [36].

Segment migration or ring extrusion always remains a potential postoperative complication, with reported rates up to 10% [14]. Other possible postoperative complications include incision opacification, corneal edema, infectious keratitis, corneal melt, corneal deposits, crystalline sterile keratitis, and vascularization of the wound [35,36]. Patients may experience inflammation, fluctuation of vision, and photophobia, which may necessitate removal of the ICRS [36]. Patients with large pupils receiving ICRS may complain of halo and glare, but often this can be managed with brimonidine tartrate to decrease the pupil size [36].

Although ICRSs are effective in improving visual acuity in KCN via a mechanical flattening effect, they do not stop the disease. As a result, ICRSs have been used as an adjunctive treatment before or after CXL for mild to moderate KCN. Studies have demonstrated significant reductions in K values, although with variable improvement in visual acuity over ICRS implantation alone [14]. There have not been enough large studies with extended follow-up to fully determine the ideal technical protocol (including optimal sequence and timing) and long-term outcomes for combined ICRS with CXL [14,35].

Other adjuvant therapies have been found to be effective in optimizing KCN treatment with ICRS. PRK has been performed after ICRS to reduce the residual refractive error and/or to reduce the astigmatism enough to make patient's CL tolerant [35]. Simultaneous PRK and CXL also have been performed after ICRS implantation with a statistically significant decrease in Ks, sphere, and cylinder after PRK/CXL compared with baseline ICRS treatment [39]. UCVA and BCVA improved from baseline though the stability of visual gain after PRK/CXL/ICRS was variable compared with after ICRS alone [35,36,39]. Sequential ICRS and IOL implantation also can be a well-tolerated and effective option in patients with KCN and cataracts [35].

Penetrating keratoplasty

The historical literature on KCN and the findings of the CLEK study indicate a 10% to 20% lifetime chance of needing a corneal transplant [20,40]. The Global Consensus on Keratoconus project, in its determination of the indications for PK, found the main indication to be the presence of significant corneal scarring, such as from acute hydrops that has previously occurred [3]. Inability to improve vision with CLs also is an indication for PK [3], although deep anterior lamellar keratoplasty (DALK) has become the leading treatment of patients unable to tolerate CLs. Severe KCN and potential risk of acute hydrops as well as a very thin cornea (<200 μm) also constitute reasons, as per the global consensus, for proceeding with a full-thickness corneal graft [3].

PK often is an effective long-term treatment method for KCN as demonstrated by a retrospective study of patients who underwent PK at University of California, Davis. Of 123 eyes of 94 patients who underwent PK, at 12 months postoperatively 84% of patients achieved 20/40 or better BCVA, and at 18 months, the number reached 87% of patients. At 18 months, 47% of eyes were fit with CLs and 30%, with spectacles. Although nearly 18% of eyes had at least 1 graft rejection, rejection episodes did not significantly influence the incidence of 20/40 vision. Combined nonrejection complications did not significantly influence incidence of 20/40 or better vision at 18 months, and with time spherical correction and astigmatism stabilized, allowing more effective and long-lasting visual rehabilitation with spectacles and CLs [40].

The strength of PK is its well-established profile and well-documented success in treating KCN. Rates of graft survival with PK are high, typically 90% or higher at 10 years [41]. In the United States, even though the total number of annual corneal transplants has increased steadily, the rates of PK have decreased markedly relative to all corneal transplant (from 95% to 42% as a percentage of total corneal transplants from 2005 to 2014), and PK increasingly has been replaced by various lamellar keratoplasty techniques (from 5% to 58% as a total of all corneal transplants) [42]. This is reflected in trends specific to corneal transplantation for KCN as well, with rates of PK for KCN decreasing significantly from 2001 to 2012 [32].

Early data from Norway and the Netherlands have demonstrated a decrease in rates of keratoplasty 3 years to 6 years after the introduction of CXL nationally in those countries, although definitive evidence supporting the reduction in need for corneal transplantation secondary to CXL

requires much longer follow-up [5,43]. A retrospective review from Canada of corneal transplantation rates since the introduction of CXL found a substantial and statistically significant decrease in the proportion of keratoplasties performed for KCN in the decade prior to the introduction of CXL compared with 8 years thereafter, albeit with no significant change in the absolute numbers of grafts for KCN since the introduction of CXL [44].

Deep anterior lamellar keratoplasty

DALK has emerged as a leading alternative to PK, except for in eyes that have suffered significant corneal scarring. It is not a uniform procedure. Rather, there are many different techniques, with DALK with big bubble technique the most common [3]. DALK is associated, however, with a significant surgical learning curve.

Systematic reviews and meta-analysis of clinical trials, cohort studies, and prospective studies comparing outcomes with DALK and PK have found DALK to be superior in terms of lower rates of rejection, less incidence of intraocular pressure spike, and lower rates of cataract formation, whereas with respect BCVA, DALK and PKP are equivocal [45,46]. Presumed corticosteroid-related elevation of intraocular pressure has been reported in up to 35% of KCN eyes after keratoplasty; thus, the ability to decrease time of steroid coverage is not an insignificant consideration [20]. DALK is associated with fewer postoperative complications [47]. One retrospective interventional nonrandomized clinical study specifically assessing outcomes in patients with moderate to severe KCN who underwent either PK or DALK found comparable visual outcomes [48]. Another study found DALK to be particularly effective in patients who have severe KCN with respect to improvement in astigmatism and BCVA [49]. To date, there have been only 2 randomized controlled trials comparing the 2 procedures, both performed in Iran, which show no difference in outcomes [50]. These various studies also suggest that DALK is less damaging to the endothelium than PK, with PK cases exhibiting higher rates of sight-threatening endothelial rejection [41].

A report by the American Academy of Ophthalmology evaluating published evidence comparing DALK to PK reviewed findings from 11 studies that compared the results of DALK and PK procedures in 481 DALK eyes and 501 PK eyes. With respect to postoperative BCVA, spherical equivalent refraction, and astigmatism, the 2 groups were equivalent. Eyes in the DALK group, however, demonstrated higher endothelial cell density at study conclusion, being significantly higher relative to PK eyes starting at 6 months after surgery, remaining so at all time points thereafter [51].

Based on published literature and expert consensus, DALK is in many cases considered the first treatment of choice, unless there is significant scarring or previous corneal hydrops or the clinician has limited experience with DALK. In patients without endothelial compromise, it is a

wholly effective surgical treatment. Conclusive evidence demonstrating the superiority of DALK over PK, however, still is lacking, and visual and refractive results remain equally variable and unpredictable with both procedures.

Summary

Management of KCN is focused primarily on stabilizing the disease and preventing progression, while optimizing visual outcomes though surgical and nonsurgical means. Future avenues for exploration likely will include new diagnostic techniques to identify KCN. For instance, epithelial thickness, derived from optical coherence topography and very-high-frequency digital ultrasound machines, quickly is becoming another modality for detecting early KCN changes. Additionally, future therapeutic innovations likely will be aimed at preventing and/or reversing changes in stromal collagen structure; in addition to optimizing current techniques by minimizing adverse outcomes. For instance, corneal allogenic intrastromal ring segments (CAIRSs), which are semicircular pieces of donor corneal tissue inserted into channels dissected within the recipient corneal stroma, recently have emerged as an alternative to ICRS [52]. From preliminary results, CAIRSs appear to offer improved visual acuity and decreased risk of progression via a flattening, stiffening, and stabilizing effect with decreased risks of rejection or extrusion [52]; however, further studies still are needed on this new technique. These and other innovations eventually may play an integral role in managing KCN in the future.

Clinics care points

- KCN presents initially with progressive myopia and astigmatism either unilaterally or bilaterally. Munson and Rizzuti signs, Vogt striae, Fleischer ring, central or paracentral stromal thinning, conical protrusion with apical steepening, epithelial nebulae, and anterior stromal scarring are signs of moderate to advanced KCN.
- In patients who have progression of KCN, CXL should be strongly considered. Progression can consist of steepening of either the anterior or posterior corneal surfaces or corneal thinning over time and can be monitored with corneal tomography.
- Refraction and optical correction are the front-line treatments of vision deterioration from KCN. Lens fitting with a CL specialist may be required to find optimal CL fit. RGP lenses and scleral CL have proved benefit in KCN patients.
- In patients with mild to moderate KCN who cannot tolerate CLs, ICRSs may be considered to improve CL fitting.
- In patients whose vision no longer is able to rehabilitated, corneal transplantation is indicated. Both PK and DALK are well-proved surgical options that achieve equivalent visual outcomes. DALK is preferred by many experts over PK, except in cases of corneal scarring, due to lower rates of rejection, less incidence of IOP spike, and lower rates of cataract formation.

Disclosure
The authors have nothing to disclose.

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Update on Refractive Surgery

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Keywords

Refractive surgery; PRK; LASIK; SMILE; Phakic IOL; Refractive lens exchange; Corneal inlay; Wavefront

Key points

- Corneal refractive surgeries including surface ablation, laser-assisted in-situ keratomileusis, and small-incision lenticule extraction remain the most commonly performed refractive surgeries with excellent visual and safety outcomes.
- Intraocular refractive surgeries including phakic intraocular lenses and refractive lens exchange represent excellent options for poor corneal surgery candidates.
- Active areas of research include advanced ablation profiles, advances in refractive lenticule surgery, and new intraocular lenses for presbyopia.

Introduction

Uncorrected refractive error is the most common cause of reversible visual impairment globally, contributing to 20.9% of blindness and 52.9% of moderate and severe visual impairment worldwide [1]. Given the growing global population and increasing rate of myopia, there is a pressing need for improved refractive surgery therapies to improve outcomes and expand eligibility for refractive surgery [2].

Corneal refractive surgeries, such as photorefractive keratectomy (PRK) and laser-assisted in-situ keratomileusis (LASIK), remain the most commonly performed refractive surgeries due to their excellent safety and efficacy profiles. Advances such as wavefront-optimized (WFO), wavefront-guided (WFG), and topography-guided (TPG) laser ablation have improved the visual outcomes of traditional laser ablation, especially for patients with higher degrees of refractive error and/or higher-order aberrations. Refractive lenticule techniques such as small-incision lenticule extraction (SMILE) represent a novel and increasingly popular approach to corneal refractive surgery that avoids the need to create a stromal flap, potentially leading to reduced incidence of postoperative dry eye and improved corneal biochemical strength.

Intraocular refractive surgery is gaining prominence as a therapeutic option for poor candidates for corneal surgery. Phakic intraocular lenses have excellent efficacy and safety outcomes, especially for pre-presbyopic patients. Conversely, patients with presbyopia or emerging cataracts may benefit from refractive lens exchange (RLE) or early cataract surgery. Improvements in understanding of the lens aging process and advances in diagnostics have taught us that just because a patient can see the 20/20 line in our office does not necessarily mean they are good candidates for corneal refractive surgery. The understanding of optical scatter coming from the aging lens has led to improvements in history taking (eg, How is your nighttime image quality?) and diagnostics that quantify lens density and optical scatter, which could have led to an unhappy corneal refractive laser patient. This has helped patient education around the decision to either continue with optical devices or consider early lens replacement surgery.

Beyond achieving emmetropia, new surgical techniques and lens technologies are available for the treatment of presbyopia. Corneal inlays using different mechanisms of action have been designed to improve near vision. Advanced intraocular lens (IOL) technology using multifocality,

extended depth of focus, and pseudoaccommodation allow for higher rates of spectacle independence following RLE or cataract surgery.

We begin by reviewing currently established surgical techniques for correcting refractive error and astigmatism, including both corneal and intraocular procedures. We then review current strategies of presbyopia correction, including corneal inlays, monovision, multifocal, and extended depth-of-focus intraocular lenses. The authors conclude this article by discussing newer technologies, such as advanced ablation profiles, refractive lenticule surgery, and accommodative intraocular lenses.

Significance and in-depth analysis of the topic

Corneal refractive surgery

Surface ablation: photorefractive keratectomy, laser subepithelial keratomileusis, and epipolis laser in-situ keratomileusis

Surface ablation techniques, in which laser ablation is performed without the creation of a stromal flap, include PRK, laser subepithelial keratomileusis (LASEK), and epipolis laser in-situ keratomileusis (Epi-LASIK) [3]. PRK was developed in 1983 by Dr Steven Trokel and approved by the Food and Drug Administration (FDA) in 1995. PRK involves the removal of epithelium followed by laser ablation of Bowman layer and superficial stroma. There are several methods for removing the epithelium, including mechanical debridement, loosening with alcohol, and transepithelial application of the excimer laser (transepithelial PRK). PRK initially supplanted incisional keratotomy as the preferred method of refractive correction, but its popularity decreased in the late 1990s with the introduction of LASIK. Various laser platforms are currently FDA approved for the correction of myopia up to −12.0 D, hyperopia up to +5.0 D, and astigmatism up to 6.0 D [4].

LASEK and Epi-LASIK are epithelial-preserving techniques. In LASEK, the epithelium is loosened using 20% alcohol and folded back in an intact sheet. In Epi-LASIK, an epikeratome is used to create an epithelial flap [3]. A 2016 Cochrane review of studies comparing LASEK and PRK did not find clear evidence of differences in efficacy, accuracy, or adverse effects [5].

Advantages of surface ablation techniques compared with LASIK include lower incidence of postoperative dry eye, better preservation of corneal biomechanics, and the avoidance of flap-related complications such as flap dislocation, epithelial ingrowth, or buttonholing. Surface ablation is preferred for situations such as thin or irregular corneas, epithelial basement membrane dystrophy, prior corneal surgery, or LASIK flap complications. Disadvantages include prolonged healing time and increased incidence of corneal haze, although the risk has been reduced with the use of topical mitomycin-C [3].

Laser-assisted in-situ keratomileusis

LASIK involves the creation of a stromal flap followed by excimer laser stromal ablation [3]. Various platforms are FDA approved for the correction of myopia up to −15.0 D, hyperopia up to +6.0 D, and astigmatism up to 6.0 D [6]. Demand for LASIK peaked in 2007 at 1.4 million procedures yearly and has since declined in volume but still it remains the most commonly performed refractive surgery procedure in the United States today [7].

Studies have generally shown comparable outcomes between LASIK and surface ablation techniques. A 2013 Cochrane review of studies comparing LASIK and PRK found faster visual recovery with LASIK but no differences in accuracy or safety [8].

There are 2 main methods of creating the stromal flap: microkeratome and femtosecond laser. In microkeratome flap creation, an oscillating microkeratome blade attached to an applanation plate is advanced to create a flap of predetermined depth. In femtosecond flap creation (femto-LASIK), a femtosecond laser is used to create a lamellar dissection within the stroma [3]. A 2013 American Academy of Ophthalmology systematic review comparing microkeratome with femtosecond flap creation found mixed evidence for visual outcomes, with some studies showing better uncorrected visual acuity (UCVA), mean spherical equivalent, and improvements in best-corrected visual acuity (BCVA) for femtosecond laser flap creation [9].

Refractive lenticule surgery

Refractive lenticule surgery techniques involve the selective removal of a lenticule of stroma to alter the refractive power of the cornea. The initial refractive lenticule extraction technique used a picosecond laser to create an intrastromal lenticule that was removed manually from under a flap, but this was associated with suboptimal results. In 2007, femtosecond lenticule extraction was introduced and was shown to have similar refractive results to LASIK and PRK but with slightly longer visual recovery times compared with LASIK and faster recovery times compared with PRK. In 2016, the FDA approved SMILE, in which the lenticule is removed through a pocket rather than a flap. It is approved for treatment of myopia of −1.00 D to −10.00 D and astigmatism of 0.75 D to 3.00 D [4].

SMILE has emerged as a promising alternative to LASIK due to several potential advantages, including avoiding the need to create a corneal flap,

less incidence of dry eye, and potential improvements in biomechanical stability. Studies have found generally comparable visual acuity, predictability, and safety outcomes between SMILE and LASIK, with greater than 60% to 80% of patients achieving UCVA greater than or equal to ≥20/20 after either procedure [10].

Intraocular refractive surgery

Phakic intraocular lenses

Phakic intraocular lens (PIOL) implantation refers to the implantation of a synthetic intraocular lens without the removal of the natural crystalline lens of the eye (Fig. 1). The first PIOL implantations were attempted in Europe in the 1950s but did not gain widespread use until the 1990s due to complications such as endothelial cell loss, uveitis, pupillary block, and glaucoma. Improvements in PIOL design have led to decreased rates of complications and improved visual outcomes, leading to their increased popularity [3,11].

PIOLs can be placed in the posterior chamber (sulcus-supported), fixated to the iris (iris-supported), or positioned in the anterior chamber angle (angle-supported). Currently in the United States there are 3 FDA-approved PIOL models. The Visian Implantable Collamer Lens (STAAR, Monrovia, CA, USA) is a sulcus-supported foldable collamer lens that is approved for the treatment of myopia from −3.0 to −20.0 D with up to 2.5 D of astigmatism. The Verisyse (also known as the Artisan lens internationally) phakic intraocular lens (Abbott Medical Optics, Santa Ana, CA, USA) is an iris-fixated nonfoldable polymethyl methacrylate lens available in 2 models with differing optic sizes (VRSM5US, VRSM6US) and approved for the treatment of myopia from −5.0 to −20.0 D with up to 2.5 D of astigmatism [11].

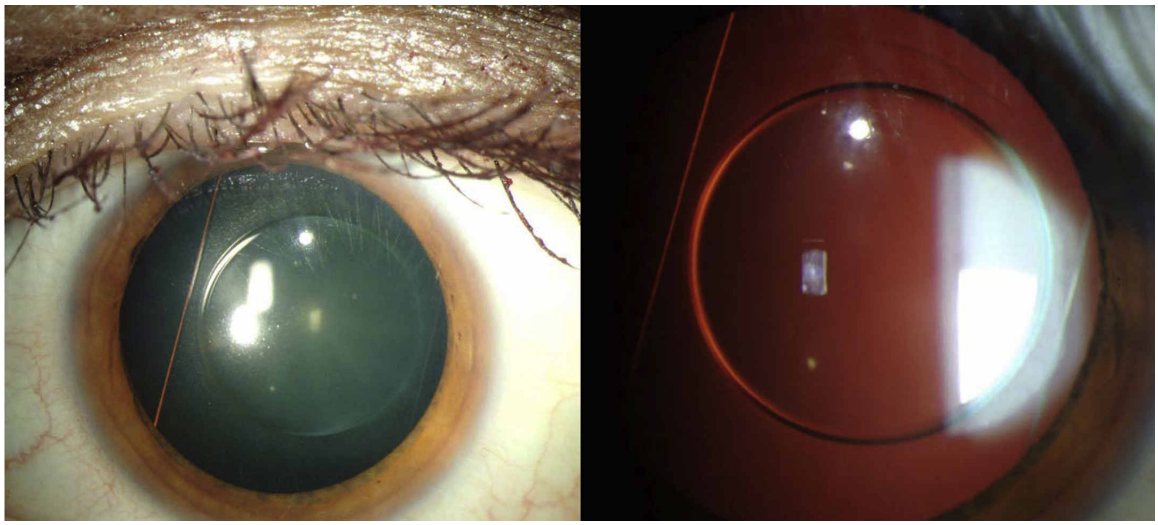

FIG. 1 Examples of phakic intraocular lens placed in the sulcus.

Currently, most surgeons use PIOLs for patients with extreme levels of refractive error or who are otherwise poor candidates for laser refractive surgery (eg, keratoconus or other corneal ectasias). Advantages of PIOLs over laser refractive surgery include better image quality and visual outcomes at higher corrections, wider range of refractive correction, less need for expensive equipment, and reversibility with PIOL removal. Disadvantages include risks associated with intraocular surgery (endothelial cell loss, uveitis, pupillary block, cataract formation, endophthalmitis) and need for a relatively large wound with the nonfoldable Verisyse PIOL [3,11].

Studies of the Visian and Verisyse PIOLs have shown good long-term efficacy, stability, and safety outcomes, with generally comparable outcomes between the 2 types of lenses [12,13]. A Cochrane systematic review of studies comparing PIOL with laser refractive surgery (PRK or LASIK) for the treatment of moderate-to-high myopia found no significant difference in UCVA at 12 months between the 2 approaches but better safety, contrast sensitivity, and patient satisfaction outcomes for PIOLs [14].

Refractive lens exchange

RLE refers to the removal of the natural crystalline lens and replacement with a synthetic lens to correct refractive error. The concept of clear lens surgery for myopia may have been proposed as early as 1776, but modern day RLE became more widespread in the late twentieth century with the development of foldable intraocular lenses, multifocal and extended depth

of focus lenses, and accommodating lenses. Currently all intraocular lenses are only FDA approved for implantation at the time of cataract removal, and thus RLE remains an off-label use [3].

RLE is generally considered for the treatment of refractive error in patients who are presbyopic or in whom lens opacity is expected to progress quickly. Studies have shown that RLE can achieve excellent outcomes for myopia, hyperopia, and astigmatism up to 2.5 D [15–17]. Young patients who retain natural accommodation may be better served with PIOLs, although new technologies in multifocal and accommodative lenses may allow RLE to provide similar high-quality vision across a broad range of focus. Furthermore, technologies such as intraoperative aberrometry and postoperative lens adjustment (eg, light-adjustable lens) allow surgeons to achieve targeted refraction with even more precision while maintaining excellent long-term safety outcomes.

One important complication of RLE is retinal detachment, especially in myopic eyes with longer axial length. Studies have shown an incidence of retinal detachment of 1.5% to 8.1% after RLE, which is higher than the rate of 0.68% in unoperated eyes with myopia greater than −10.0 D [15]. Risk factors for retinal detachment after RLE include increased axial length, age less than 50 years, male sex, white race, peripheral retinal degenerations, intraoperative capsular tear with vitreous loss, and Nd:YAG for posterior capsule opacification [18]. In contrast, hyperopic eyes with shallower anterior chambers are more predisposed to developing pupillary block, uveal effusion syndrome, and postoperative choroidal detachment.

Treatment of presbyopia

Presbyopia, defined as the age-related reduction in amplitude of accommodation, is a global phenomenon affecting 1.8 billion people in 2015 and projected to affect 2.1 billion people by 2030 [19]. Presbyopia correction has been referred to as the “holy grail of vision correction” and would ideally restore accommodation to prepresbyopia levels across the normal dioptric range, with a suggested minimum amplitude of accommodation of 5.0 D. There are 2 main theories of accommodation: the Helmholtz theory, which postulates that ciliary muscle contraction causes relaxation of the zonules and an increase in lens curvature and power, and the Schachar theory, which postulates that ciliary muscle contraction causes a selective increase in zonular tension pulling the lens outward toward the sclera. Presbyopia correction based on the Schachar theory

such as scleral expansion surgery has fallen out of favor, although new methods such as scleral expansion bands and the LaserACE procedure remain under study [3].

Current methods of presbyopia correction include spectacles, contact lenses, corneal surgery (corneal inlays and laser refractive surgery including multifocal ablations and intrastromal ablations), and intraocular lenses (including multifocal and extended depth of focus lenses). Newer approaches still under investigation include accommodative lenses, lenticular softening with laser or pharmaceuticals, and flexible polymers designed for injection into an intact capsular bag following lens extraction [3].

Corneal inlays for treatment of presbyopia

Corneal inlays involve the placement of synthetic biocompatible lenticules of varying designs under a stromal flap or pocket to improve near vision. Corneal inlays have been designed based on several different mechanisms of action, including using a small central aperture based on the pinhole principle; increasing the central radius of curvature of the cornea; or altering the corneal refractive index [3,20]. Of these, only the small-aperture inlay approach is currently available in the United States.

The KAMRA corneal inlay (AcuFocus Inc., Irvine, CA) is a small aperture inlay made of polyvinylidene fluoride that improves near vision based on the pinhole principle. The original model (ACI7000) was 10 μm thick with 1600 microperforated holes and implanted under a corneal flap 170 to 180 um deep. The newer model (ACI7000PDT) is 6 μm thick with 8400 microperforated holes and implanted within a stromal pocket created by a femtosecond laser at a depth of 200 to 250 um or 100 to 110 um beneath a previous LASIK flap. It was approved for use in the European Union in 2005 and approved by the FDA in 2015 for the treatment of presbyopia in nondominant phakic eyes with refractive error between +0.5 D and −0.75 D and up to 0.75 D of astigmatism [3,20].

Studies of the original ACI7000 model have shown excellent mean uncorrected near, intermediate, and distance visual acuity (UDVA) outcomes that remained stable for up to 3 years. About 27% to 45% of patients lost one or more lines of corrected distance visual acuity (CDVA), but mean binocular CDVA remained greater than or equal to 20/20 in all studies [21–23]. Complications included dry eye, halos and glare, epithelial ingrowth, interface haze, flap striae or buttonholing, and inlay

misalignment requiring recentration. Approximately half of the patients developed epithelial iron deposits with overlying corneal flattening but without visual or refractive effects. Studies of the newer ACI7000PDT model have shown better outcomes, with only one case of epithelial iron deposits reported to date [24–26].

Multifocal and extended depth of focus intraocular lenses

Multifocal IOLs, available since the 1980s, provide simultaneous distance and near vision by focusing light at 2 or more loci. Currently there are 2 categories of multifocal IOLs: refractive and diffractive. Refractive IOLs use zones with different refractive powers to create multiple focal points. Diffractive IOLs use concentric rings to create a diffraction gradient. Some diffractive IOLs are apodized, meaning the diffractive heights are gradually tapered to yield a more even distribution of light that theoretically provides a smoother image transition from intermediate to near viewing. Bifocal models currently available in the United States include the TECNIS multifocal lens (Johnson & Johnson, New Brunswick, NJ, USA) and the AcrySof ReSTOR multifocal lens (Alcon, Geneva, Switzerland) [3,27]. Studies of multifocal IOLs implanted for both cataract surgery and RLE have found excellent visual outcomes with greater than 95% achieving monocular UDVA greater than or equal to 20/40 and 80% achieving spectacle independence [28].

Trifocal IOLs add a third focus point to theoretically provide good distance, intermediate, and near vision. The PanOptix trifocal IOL (Alcon, Geneva, Switzerland) is currently the only trifocal IOL available in the United States. Ninety-five percent of patients with the PanOptix lens achieved spectacle independence for all activities, compared with 73% to 80% of patients with bifocal lenses. Furthermore, greater than 90% of patients receiving the PanOptix lens stated they would choose the same IOL again and recommend it to others, compared with 70% of patients receiving a bifocal lens [27].

Extended depth of focus (EDOF) lenses are designed to create a longitudinal extended plane of focus rather than discrete focal points. The TECNIS Symfony lens is currently the only EDOF lens available in the United States (Fig. 2). Compared with bifocal and trifocal lenses, EDOF lenses have comparable distance vision but inferior intermediate and near vision, with 70% of patients with EDOF lenses achieving spectacle independence. However, applying a mini-monovision or blended

approach with 2 EDOF lenses can improve uncorrected intermediate and near vision and achieve spectacle independence in 95% of patients. Most studies report similar rates of photic phenomenon (eg, glare, halos, starbursts) between EDOF and multifocal lenses. Similar to trifocal lenses, EDOF lenses were associated greater than 90% patient satisfaction rate [27].

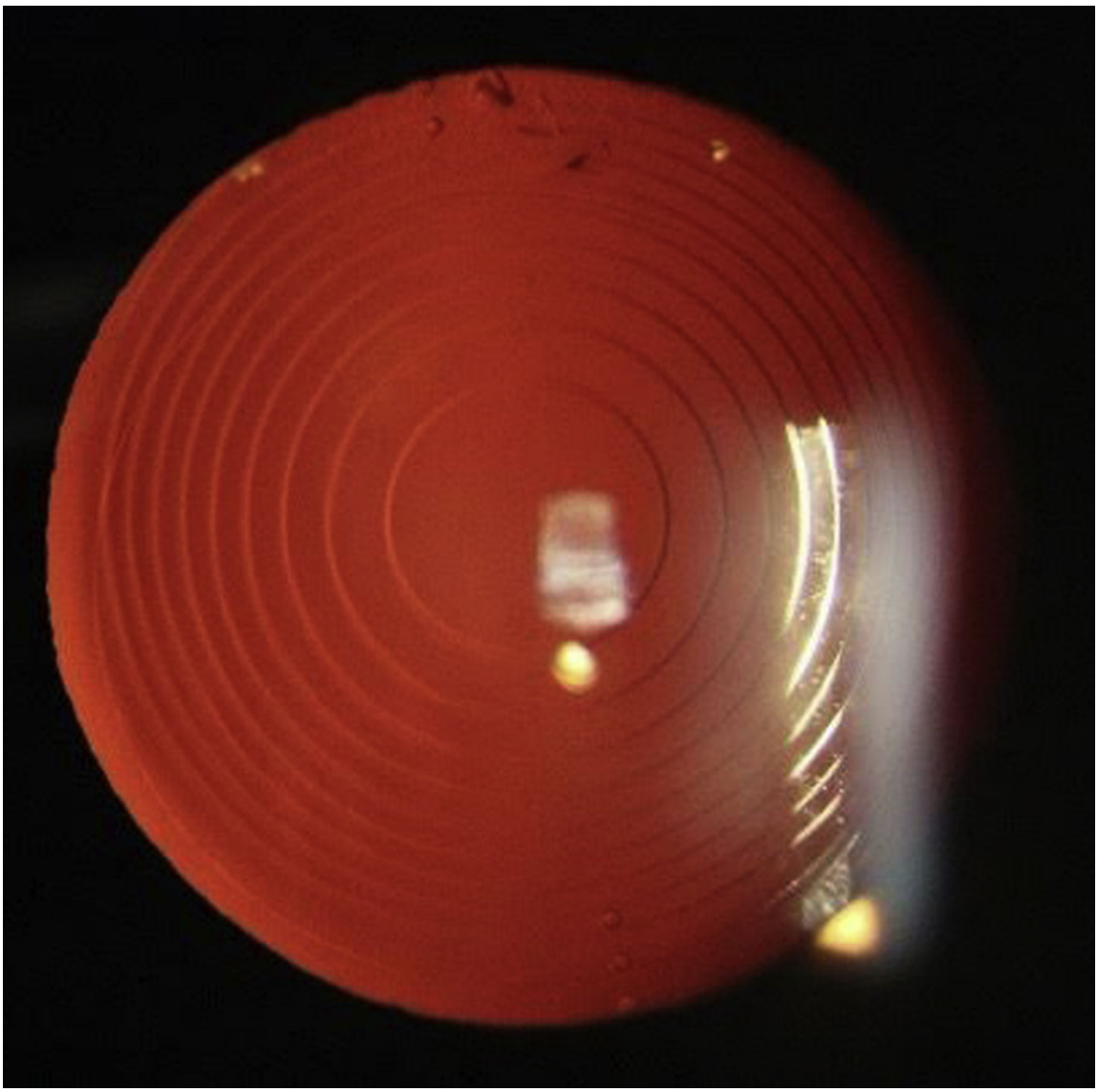

FIG. 2 Extended depth of focus intraocular lens.

Current relevance and future avenues to investigate the topic

Management of higher-order aberrations: wavefront-optimized, wavefront-guided, and topography-guided laser ablation

Conventional laser treatments have been shown to induce higher-order aberrations (HOAs) such as spherical aberration, coma, and trefoil because of the small blend zones and oblate corneas following myopic correction. Newer technologies attempt to reduce HOAs by incorporating measurements of the preoperative corneal surface into treatment algorithms. WFO laser ablation uses population average aberrometry data to reduce the induction of spherical aberration. WFG laser ablation incorporates patient-specific data from a wavefront-sensing aberrometer into the treatment algorithm to reduce preexisting HOAs. TPG laser ablation incorporates data from corneal topography into the treatment algorithm and has been shown to be beneficial for highly aberrated corneas when wavefront data cannot be easily acquired [3].

A comparison of submitted FDA data for the Visx iDesign (WFG), Alcon CONTOURA (TPG), and Nidek CATz (TPG) platforms showed that all 3 achieved excellent efficacy, safety, stability, and accuracy outcomes. However, when outcomes were stratified by preoperative spherical equivalent and cylinder, the Alcon CONTOURA had a greater percentage of eyes with BCVA greater than or equal to 20/20 for eyes with greater degrees of myopia and a greater percentage of eyes within 0.5 D of emmetropia at all levels of astigmatism [29]. Thus, TPG laser ablation may be advantageous for eyes with higher degrees of myopia or astigmatism.

Future studies on WFO, WFG, and TPG refractive surgery may help answer the following:

- What characteristics of eyes are most likely to benefit from these enhanced ablation techniques?
- How do the individual aberrometry platforms compare with each other, especially considering the development of newer high-resolution aberrometers?
- How do cost-effectiveness and workflow impact factor into decisions to use these platforms, given the need for additional

preoperative imaging and acquisition of new technology?

Advances in refractive lenticule surgery

Although refractive lenticule techniques such as SMILE already are widely used as an alternative to surface ablation and LASIK, ongoing research is investigating advantages of SMILE and ways to overcome its current limitations.

One advantage of SMILE over LASIK is that because SMILE does not involve creation of a flap. SMILE is associated with less damage to the subbasal nerves and a theoretically lower risk of postoperative dry eye symptoms [30]. A meta-analysis of prospective trials comparing SMILE with femto-LASIK found that SMILE was associated with higher corneal sensitivity and subbasal nerve density, higher tear breakup time, and better ocular surface disease index scores [31]. Another proposed advantage of SMILE is that it may result in greater corneal biomechanical strength than LASIK due to avoidance of the creation of a flap. A systematic review found that SMILE was superior to LASIK and comparable with PRK/LASEK in its effect on corneal biomechanics as measured by corneal hysteresis and corneal resistance factor [32]. Finally, some studies have found that SMILE induces fewer higher-order aberrations than LASIK, possibly due to less induction of a corneal wound-healing response [10,30].

On the other hand, early observations found that SMILE was associated with a relatively delayed visual recovery compared with LASIK of up to 3 months, possibly due to inflammation associated with manual extraction of the lenticule [33]. Other limitations of SMILE include the inability to use cyclotorsion control or eye-tracking technology for correction of astigmatism, the lack of an established method of postoperative enhancement, and limited data for hyperopic correction. SMILE for hyperopia involves creation and extraction of a negative lenticule, which is thinner in the middle and thicker in the periphery. Limited studies have shown comparable visual outcomes, stability, and safety between hyperopic SMILE and hyperopic LASIK, although higher rates of visual regression and loss of BCVA were reported for hyperopic SMILE compared with myopic SMILE [34]. Novel refractive lenticule techniques for treatment of hyperopia currently under investigation include lenticule intrastromal keratoplasty and small-incision lenticule intrastromal

keratoplasty, which involve implantation of a minus lenticule under a stromal flap or pocket, respectively [35].

Complications of SMILE are similar to those reported after LASIK and include epithelial defects, epithelial ingrowth, microstriae, and diffuse lamellar keratitis. SMILE avoids the flap-related complications of LASIK but is associated with unique cap-related complications such as cap tear or perforation. It has been hypothesized that SMILE may be associated with lower rates of ectasia due to less effect on biochemical strength, although studies have had mixed outcomes as noted earlier, and a few cases of ectasia after SMILE have been reported [30].

Future studies on refractive lenticule surgery may help answer the following:

- What is the clinical significance of proposed advantages of SMILE over LASIK on outcomes such as dry eye, corneal biomechanical strength, and higher-order aberrations?
- What technologies or techniques can be used to improve the accuracy of SMILE for astigmatism?
- What methods can be reliably and safely used for enhancement after SMILE?
- What is the long-term efficacy, safety, and reliability of SMILE for hyperopia?

Accommodative intraocular lens

Accommodative IOLs are lenses that are by definition designed to increase in dioptric power with accommodative effort. Current accommodative IOLs use several accommodative and pseudoaccommodative mechanisms to achieve this. Accommodative mechanisms include single-optic forward motion, dual-optic opposite motion, lens-shape changing, lens filling, and refractive index changing. Pseudoaccommodation refers to mechanisms that increase depth of focus without producing objectively measurable accommodation, such as miosis, lens tilt, and induction of higher-order aberrations [3,36].

The Crystalens (Bausch and Lomb, Rochester, NY, USA) is the only accommodative IOL currently available in the United States (Fig. 3). It is a single-optic accommodative IOL that theoretically works by inducing forward optic movement with accommodative effort. However, studies using ray-tracing aberrometry have found that the Crystalens can only

produce up to 0.4 D of accommodation in vivo, suggesting that it functions primarily through pseudoaccommodative mechanisms [37]. Other single-optic accommodative IOLs available outside the United States include the Tetraflex KH-3500 (Lenstec, Inc., St. Petersburg, FL, USA), the Akkommodative 1CU lens (HumanOptics AG, Erlangen, Germany), and the Tek-Clear lens (Tekia, Inc., Irvine, CA, USA) [36].

Dual-optic accommodative IOLs are designed with 2 optics separated by spring haptics that allow the optics to move in opposite directions with accommodative effort. Current dual-optic accommodating IOLs under development include the Synchrony accommodating IOL (Abbott Medical Optics Inc., Santa Ana, CA, USA), Lumina Lens (AkkoLens International BV, Breda, The Netherlands), and the Sarfarazi Elliptical IOL (Bausch and Lomb, Rochester, NY, USA). Unlike single-optic accommodating IOLs, dual-optic accommodating IOLs have been shown to demonstrate more than 1 D of objective accommodation when measured with aberrometry devices [36].

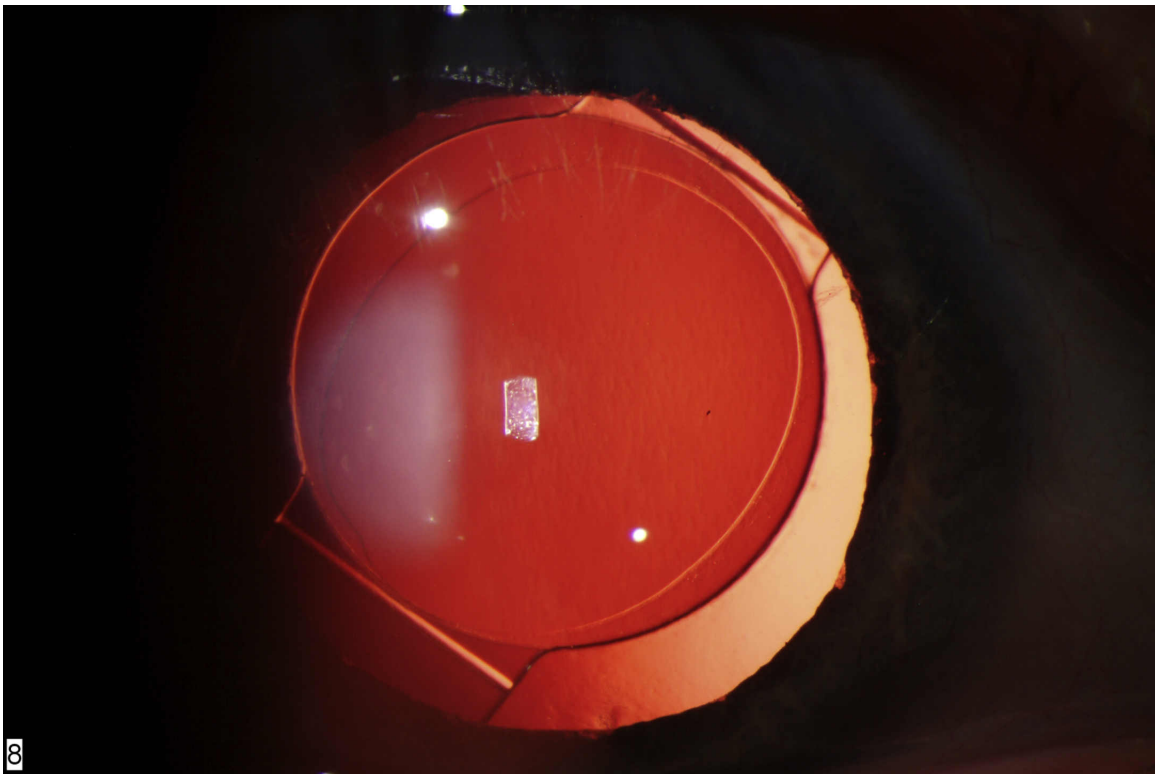

FIG. 3 Pseudoaccommodative intraocular lens.

Shape-changing accommodating IOLs are designed to mimic changes in the curvature of the natural lens to change dioptric power. The NuLens Dynacurve accommodative IOL (NuLens, Ltd., Herzliya Pituah, Israel) is composed of a posterior piston with a central aperture that compresses a silicone gel with contraction of the ciliary muscle, causing the silicone gel to bulge through the aperture and change the dioptric power of the lens unit. The Wichterle Intraocular Lens-Continuous Focus (Medicem, Kamenne Zehrovice, Czech Republic) is a haptic-less lens made of 42% pHEMA copolymer hydrogel designed to change shape with ciliary body contraction. The FluidVision accommodating IOL (PowerVision, Inc., Belmont, CA, USA) consists of a drop of silicone oil that flows back and forth between a hollow acrylic optic and oversized haptics with accommodative effort. The Juvene accommodating IOL (LensGen, Irvine, CA, USA) is a 2-component lens composed of a fixed outer lens and a fluid inner lens that changes curvature based on accommodative forces. Small scale studies of these shape-changing lenses are promising, but more research needs to be done before they are ready for large scale trials [38].

Lens-filling accommodative IOLs aim to replicate the shape changes of the natural crystalline lens by filling the capsular bag with a soft polymer. Surgical techniques proposed for filling the capsular bag include making a small anterior capsulotomy, placing a silicone plug in the anterior capsulotomy area to prevent leakage, and injecting a silicone polymer between an anterior and posterior IOL. Current challenges with lens-filling accommodative IOLs include leakage of refilling materials, capsular opacification, and insufficient refractive index of refilling materials. Studies of lens-filling accommodative IOLs in nonhuman primate eyes have achieved up to 74% of natural accommodative amplitudes, but human trials still are pending [39].

Finally, some technologies under investigation attempt to modulate the refractive index of the lens to achieve accommodative power. The LiquiLens (Vision Solutions Technologies, Inc., Rockville, MD, USA) is an accommodative IOL containing 2 immiscible solutions of differing refractive index. When the patient looks down at a 60° to 70° angle, the 2 fluids mix to produce a composite index of refraction that creates accommodative power. Studies also are underway to develop electroadaptive IOLs that change refractive index based on microsensors that detect physiologic changes with accommodative effort, such as miosis or ciliary muscle movement [36].

Summary

Refractive surgery has seen exciting developments over the past few decades. There is an expanding arsenal of novel techniques and technologies available to the refractive surgeon to help patients achieve emmetropia and overcome presbyopia.

Classic laser refractive surgeries such as PRK and LASIK continue to show excellent efficacy, predictability, stability, and safety outcomes over extended follow-up periods. These techniques can now be enhanced with WFO, WFG, and TPG ablations to reduce higher-order aberrations and improve outcomes.

Beyond PRK and LASIK, refractive lenticule techniques such as SMILE represent new promising options for correcting refractive errors at the corneal level while avoiding the need to create a stromal flap. Early outcomes are promising with lower incidence of dry eye and potential improvements in corneal biomechanical strength and induction of higher-order aberrations. However, future developments are needed to overcome current limitations of refractive lenticule techniques including lack of eye-tracking technology for astigmatism, limited options for postoperative enhancement, and limited data for hyperopic correction.

For patients whose refractive error falls outside of current limits for laser refractive surgery or who are otherwise poor candidates for laser refractive surgery, intraocular refractive surgery offers multiple therapeutic approaches with excellent outcomes. Phakic IOLs such as the Visian and Verisyse lenses represent excellent options for younger patients who still maintain natural accommodation. For older patients approaching presbyopia or cataract development, RLE may be the preferred treatment option, and new developments in multifocal, extended depth of focus, and accommodative IOLs bring us closer to achieving the "holy grail" of presbyopia correction.

As corneal and intraocular refractive techniques become more refined, more surgeons are exploring ways to combine the 2 to achieve even better visual and functional outcomes. "Bioptics," initially coined in 1996, refers to the combined use of corneal and intraocular refractive surgeries to treat large and complex refractive errors. To date, bioptics has most frequently consisted of intraocular surgery (PIOL or RLE) followed by corneal laser surgery once refractive outcomes have stabilized. However, promising outcomes have been reported for almost every combination of intraocular and corneal refractive surgery, including PRK/LASIK following PIOL

placement, PRK/LASIK following RLE, and "reverse bioptics" consisting of PIOL placement or RLE following PRK/LASIK [40].

The plethora of new developments within refractive surgery present multiple avenues for further research. Key areas of investigation include long-term and comparative outcomes of WFG/TPG laser treatment, refractive lenticle techniques, and novel phakic and intracapsular lens technologies. With the proliferation of new treatment options, more guidance is needed on which approach can be expected to provide the optimal outcomes for each individual patient. Given the burgeoning interest in achieving better visual outcomes and higher degrees of spectacle independence, it is an exciting and promising time for refractive surgery.

Clinics care points

- Consider surface ablation techniques over flap-associated techniques for patients with thin or irregular corneas, epithelial basement membrane dystrophy, prior corneal surgery, or LASIK flap complications.
- For patients who are poor candidates for corneal refractive laser surgery, consider phakic intraocular lens placement or RLE.
- When considering RLE, evaluate and discuss risks of surgery including retinal detachment, especially in patients with axial myopia.
- For patients with presbyopia, discuss advantages and disadvantages of different treatment options including spectacles, contact lenses, corneal inlays, multifocal/extended depth of focus lenses, and accommodative lenses.

Disclosure
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Oculoplastics

OUTLINE

Xanthelasma Palpebrarum: An Oculoplastic Viewpoint of Optimal Treatment

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Keywords

Xanthelasma palpebrarum; Reconstructive surgical procedures; Myocutaneous flap; Co2 laser; Eyelids

Key points

- Xanthelasma palpebrarum (XP) is the most common type of cutaneous xanthoma in middle-aged and older adults.
- Numerous treatment options and algorithmic approaches for XP treatment have been suggested, including surgical, laser, chemical compounds, radiofrequency, and cryotherapy.
- Most of the literature dealing with XP treatment offer nonsurgical solutions, and laser treatment has been advocated as an ideal therapy for XP because of its superficial location.
- We herein present our oculoplastic surgery approach for the treatment of XP. The surgical approach is based on the size of the lesion, its location in the eyelid, and the laxity of the skin.

Introduction

Xanthelasma palpebrum (XP), the most prevalent cutaneous xanthoma [1], is usually located on the medial aspect of the eyelids, more often on the upper than the lower lids. The prevalence of XP in different studies ranges between 0.3% and 1.54% in men and 0.82% and 3.4% in women [2]. The lesions, which appear as yellow flat or raised plaques, usually are soft but also may be firm on palpation. Lee and colleagues [3] classified the lesions into 4 grades according to lesion extension: Grade I, lesions on upper eyelids only; Grade II, lesions extend to medial canthal area; Grade III, lesions on medial side of both upper and lower eyelids; and grade IV, diffuse lesions that involve medial and lateral of both upper and lower eyelids.

Although XP is a benign condition, many patients seek treatment for improvement of cosmetic appearance. Treatment modalities include surgical excision, laser ablation, and introduction of chemical compounds, radiofrequency, and cryotherapy. In addition, there have been reports of a correlation between dyslipidemia and XP, so the diagnosis of XP itself may warrant further systemic evaluation to rule out treatable life-shortening conditions. Moreover, the differential diagnosis of XP includes life-threatening conditions such as Langerhans cell histiocytosis and Erdheim–Chester disease [4]. Thus, if a patient presents with atypical yellow eyelid lesions such as nodular lesions, diffuse eyelid involvement, extension to the neighboring skin, or association with induration or ulceration, it is important to rule out other diagnoses.

In this review, we organize the current knowledge about XP pathophysiology and treatment modalities with an additional focus on our XP management approach.

Significance (in-depth analysis)

Pathophysiology

Histologically, XP is composed of foam cells, which are lipid-laden histiocytes generally located in the upper dermis, often near the capillaries. Occasionally Touton multinucleated giant cells may be present [2,5]. The main lipid stored in xanthelasmas is cholesterol, most of it esterified cholesterol but the portion of esterified versus free cholesterol lowers as the lesion gets older [2]. A histologic study of surgically excised XP lesions revealed that in 42% of the lesions' lipid-laden macrophages either touched or infiltrated the muscle tissue underlying the dermis [6].

On average, approximately 50% of patients with XP are hyperlipidemic and the other half are normolipidemic (ranges from 25% to 70%), defined as normal cholesterol and triglyceride levels [2,7–9]. Among the hyperlipidemic patients, the most frequent Fredrickson hyperlipidemic phenotype is type IIa, which is expressed as elevated low-density lipoprotein (LDL) cholesterol [10]. Among the normolipidemic patients, although blood lipid profile is in the normal range, the levels of LDL cholesterol and very low density lipoprotein have been shown to be significantly higher, and high-density lipoprotein (HDL) cholesterol levels and HDL/LDL ratio lower, than that of healthy controls [10,11].

Because XP does not develop in most hyperlipidemic patients and because it can also develop in the normolipidemic population, blood lipid levels cannot solely explain the pathogenesis of XP. The exact pathophysiology of XP is not yet clear, but it appears to involve multiple pathogenetic factors. The first step for XP formation is leakage of LDL from tissue capillaries. Heat, physical movement, and friction increase LDL capillary leakage, which can explain why the eyelids are a primary location [2]. Another step of XP lesion formation is accumulation of LDL cholesterol in tissue macrophages. Most cells' uptake of LDL is via a designated LDL receptor that is inhibited by high intracellular cholesterol levels. Unlike most cells, macrophages have an additional scavenger receptor that uptakes oxidized LDL independent of intracellular cholesterol levels so that oxidized LDL can accumulate in them and convert them into foam cells [2,12]. In addition, unlike free cholesterol that is released from LDL after its normal internalization, the cholesterol caught by scavenger receptors does not inhibit de novo cholesterol synthesis [12]. Factors that take part in lipid oxidation include metal ions

and various enzymes secreted from macrophages, fibroblast, and endothelial cells [12]. An additional pathogenic factor for XP is low HDL levels, because HDL is a main player in reverse cholesterol transport, a process in charge of removal of superfluous cholesterol from peripheral tissues [2,12]. This can partially explain the formation of XP in normolipidemic patients with low HDL levels. More research is needed to clarify the exact pathogenetic pathway and to reveal other genetic and environmental factors that are involved in the pathophysiology of XP.

Treatment

Due to the correlation between XP and dyslipidemia, a blood lipid profile investigation is recommended in all patients. When indicated, commencement of lifestyle changes and medical treatment should be applied according to general or internal physician recommendations.

The lesions themselves do not regress without treatment. Because they pose no medical concern, it is not necessary to treat them. Nevertheless, their noticeable location on the face leads many patients to desire to undergo removal of the lesions for aesthetic reasons. The variety of treatment options implies there is no gold standard treatment, and that results are not perfect in any treatment modality. Several common side effects of the different treatments include lesion recurrence, hyperpigmentation or hypopigmentation, and eyelid ectropion and scarring.

Surgical excision

Surgical excision has been the traditional method for treating XP. Although it is a modality suitable for all XP lesions, it is the method of choice for diffuse or recurrent XP lesions. In addition, it is very suitable for patients with XP with dermatochalasis or skin laxity, who also can benefit from aesthetic treatment of the excess tissue. Lee and colleagues [3] reserve nonsurgical treatment only for grade I, II, or III lesions that are limited to the superficial dermis, lesion height of less than 5 mm, and lesion onset of less than 1 year (Figs. 1–3). To achieve complete excision and thus minimize recurrence, all other lesions including grade IV lesions, small but deeper lesions extending to the inner dermis or musculature, or long-standing lesions should be excised surgically. Patient preference also must be taken into consideration.

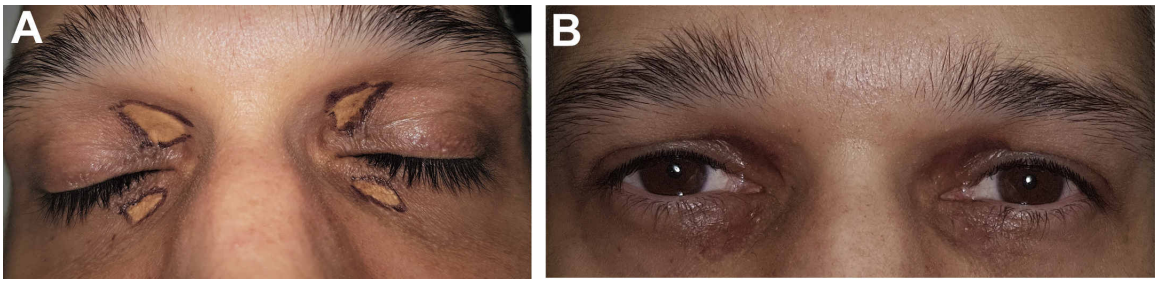

FIG. 1 A 36 year old man with four eyelids nasal xanthalasma. Preoperative photo of lesions involving the medial sides of both upper and lower eyelids. (*A*) Postoperative photo at 6 months after surgical excision and direct closure (*B*) Postoperative photos show complete excision of the lesions with relatively minimal scarring and no sign of recurrence (FU 24 months). The patient expressed satisfaction with the overall aesthetic result.

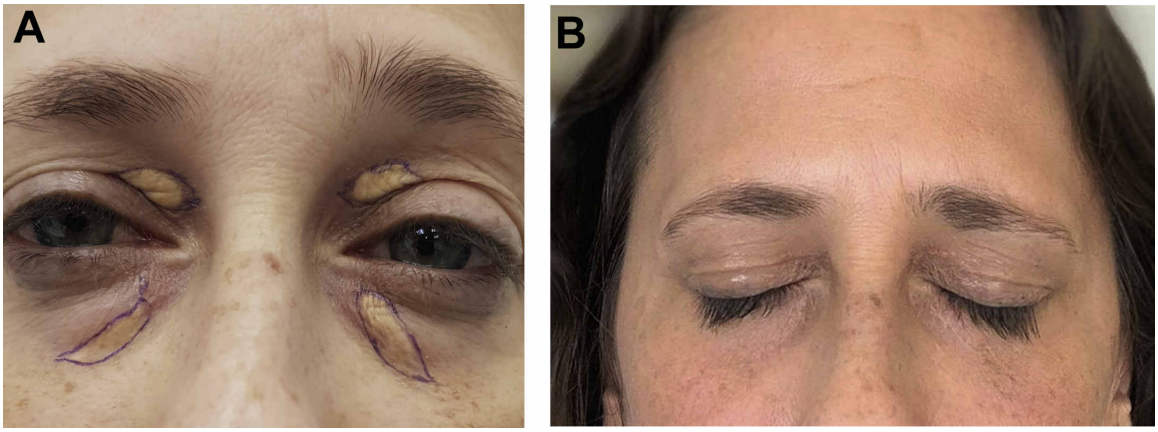

FIG. 2 A 44-year-old woman with 4 eyelids nasal xanthalasma. Preoperative photo of lesions involving the medial sides of both upper and lower eyelids. (*A*) Postoperative photo at 6 months after surgical excision and direct closure (*B*) Postoperative photos show complete excision of the lesions with relatively minimal scarring and no sign of recurrence (follow-up 18 months). The patient expressed satisfaction with the overall aesthetic result.

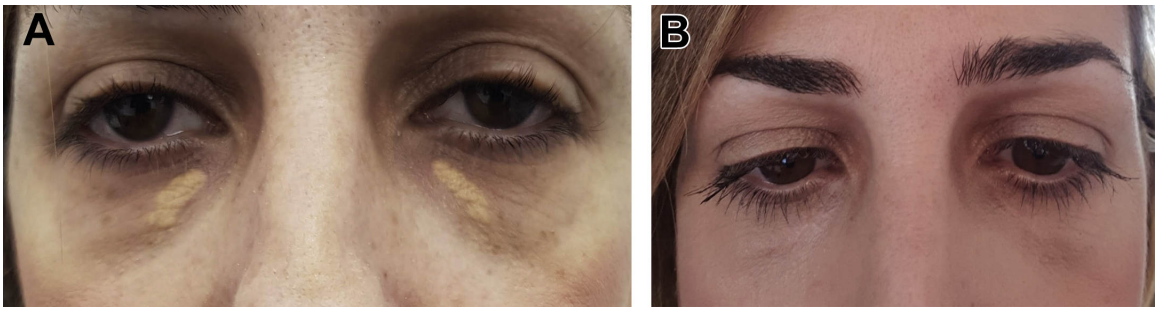

FIG. 3 A 41-year-old woman with lower eyelid nasal xanthalasma. Preoperative photo of lesions involving the medial sides of the lower eyelids. (*A*) Postoperative photo at 6 months after surgical excision and direct closure (*B*) Postoperative photos show complete excision of the lesions with relatively minimal scarring and no sign of recurrence (FU 20 months). The patient expressed satisfaction with the overall aesthetic result.

Simple excision with primary closure may be suitable for small XP lesions of grade I or II, not involving the lower eyelids. Medial epicanthoplasty (an orbicularis myocutaneous advancement flap), is needed for grade II lesions because they extend to the medial canthus. To avoid lid retraction or ectropion, larger lesions require more complex surgical manipulation such as "uncapping surgery," local skin or muscle flaps, or skin grafts [3]. "Uncapping surgery" was first introduced in 1997 by Doi and Ogawa [13] as a new microsurgical inverted peeling technique. In this surgery, an incision is made at the edge of the xanthelasma, the content is excised, and the skin is sutured without any skin loss. A disadvantage of this method is the training it requires, and recurrence can be seen more frequently in patients with hypercholesterolemia.

A more common surgical technique for large lesions is removal of the XP lesions by blepharoplasty and using the excised tissue as a donor site for a skin graft [3,14,15]. This is a simpler surgical technique to perform, and it allows good cosmetic results while both removing excess skin from the upper eyelid and using a perfect match as the skin graft in terms of skin color and tissue and dermal thickness. Another surgical option for large defects after XP excision is using a local flap. An elegant flap can be fashioned by incorporating a mucocutaneous flap from a blepharoplasty incision where the medial part of the excess skin of upper eyelid is not detached and is instead used as the pedicle of a rotational flap [16,17]. Obviously, although the first 2 techniques can be used for both upper and lower eyelid skin defects, this type of blepharoplasty rotational flap is only suitable for upper eyelids. In some cases after XP excision, the defect is so large that a combination of a skin graft and flap is needed [15]. In the

report of Lee and colleagues [3], the grafts were harvested by blepharoplasty, and different types of flaps, such as modified rhomboid flaps, local advancement flaps, and bilobed flaps, were used to complete the defects.

Recurrence of XP after surgical excision has been reported by Mendelson and Masson [18] in 1976 to be 40% after primary excision, 60% after recurrent excision, and 80% when involving all 4 eyelids. More recent studies reported a lower incidence of recurrence ranging from 0% to 37.5% [3,13–17]. According to these studies, risk factors for recurrence include incomplete excision: excision should include layers of the lesion in the deeper dermis and of muscle infiltration, primary closure of the incision (vs grafting), and underlying uncontrolled hypercholesterolemia. The side effect of dyspigmentation was rare.

Laser ablation

Since the 1990s, laser ablation of XP is another common treatment. Nguyen and colleagues [19] have presented a systematic review and compared the different laser modalities in XP treatment.

Precise photoablation and coagulation of the skin allow bloodless removal of lesions with minimal scarring, pain, and perilesional inflammation [20]. One of the downsides of laser treatment is its relatively high cost, especially ablative lasers.

Complications of laser therapy include persistent erythema, superficial depigmentation, scars, severe burns, transitory or permanent lower lid ectropion, and corneal injuries or ocular perforation if the procedure is undertaken in the periocular region [21,22].

Advantages of lasers include better patient acceptance, avoidance of surgery, minimal tissue loss, and good functional and cosmetic results. Moreover, the procedure is easy to perform and provides rapid results. Disadvantages include high cost and less predictable results. In addition, it is not possible to obtain a histopathological specimen [20,23,24].

CO_2 lasers are based on vaporization of water within cells, and are the most commonly reported lasers for XP lesion ablation. They offer excellent cosmetic results in 1 to 3 treatment sessions [19], but are reserved for treatment only in small lesions and lesions involving the superficial dermis [3]. In addition, treatment in the early stages of XP development is crucial to prevent recurrence [25]. Fractional CO_2 lasers deliver tiny pinpoints of laser light, leaving healthy skin between the ablated areas, to

allow more rapid healing. They require more sessions than standard CO_2 lasers but have a significantly shorter downtime and fewer complications, such as scarring and recurrence [26] (Figs. 4 and 5). Recurrence rate of XP after CO_2 laser ablation is reported to be 13% to 16% [25–27] but follow-up duration in these studies is short (less than a year). Longer follow-up is needed for better conclusions. Reported adverse events typically included transient dyspigmentation-hypopigmentation and hyperpigmentation, erythema, and scarring [25].

Ablation of XP with Er:YAG lasers is reported to achieve good results with 1 to 2 treatment sessions, with no recurrences by 1 to 12 months; dyspigmentation was the main side effect [19]. A comparison between CO_2 lasers and Er:YAG lasers for the treatment of XP showed that wound healing is much longer with CO_2 lasers but that they are more suitable for deeper lesions [24]. Treating XP with Nd:YAG lasers showed less success than with Er:YAG lasers. Although Nd:YAG lasers provided improvement of the lesion appearance, complete clearance of the lesion was not achieved [28,29], and are reported to induce greater swelling, bleeding, and crusting [29].

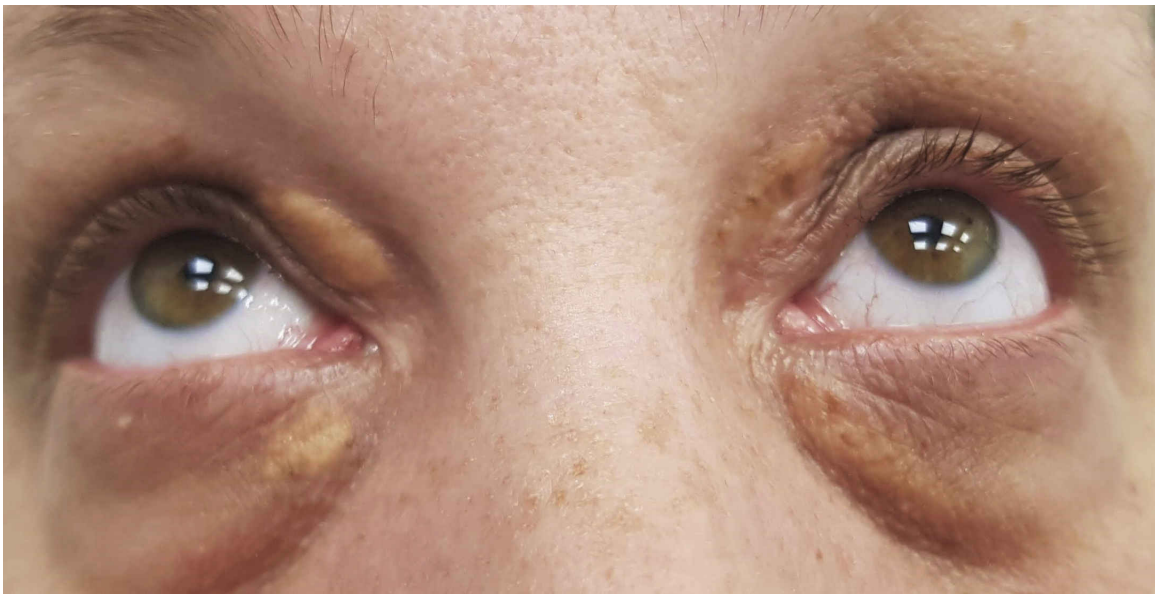

FIG. 4 A 34-year-old woman post laser treatment of lesions involving the medial sides of both upper and lower eyelids. The tissue is scarred and with no clear margin between the lesion and the skin.

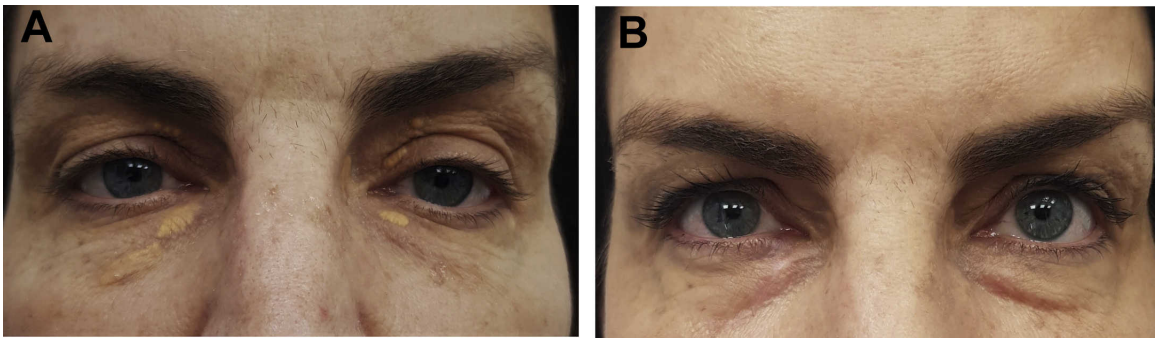

FIG. 5 A 39-year-old woman post laser treatment of lesions involving the medial sides of both upper and lower eyelids. The tissue is scarred and with no clear margin between the lesion and the skin (*A*). Postoperative photos show complete excision of the lesions with relatively minimal scarring and no sign of recurrence. (*B*).

Using a shorter wavelength absorbed mainly by hemoglobin, argon laser ablation also demonstrated good results when treating XP [30,31] with good cosmetic results in 72% to 85% of the patients. Other lasers that were less frequently used for treating XP lesions include pulsed dye laser [23], diode laser [32], and potassium titanyl phosphate laser [33]. All these lasers showed satisfactory results but more research is needed to confirm their efficacy and safety.

Chemical compounds

Chemical cauterization of XP lesions with chlorinated acetic acids is an inexpensive, simple method and has been available for many years. Their mode of action involves dissolving lipids and precipitating and coagulating proteins [21]. Although bichloracetic acid (BCA) also is used [34], trichloracetic acid (TCA) is a more common substance for this use [21,35–38]. TCA is topically applied over the lesion with caution not to touch the surrounding heathy skin or the eye. Haque and Ramesh [35] compared 3 concentrations of TCA (50%, 79%, and 100%) for treating XP lesions and concluded that the thicker the lesion is, the higher the concentration of TCA is required for clearing of the lesion with fewer applications. They experienced a complication of dyspigmentation in 31% of the patients and 1 of 51 patients had mild scarring. Nahas and colleagues [36] demonstrated that treatment with 70% TCA caused hypopigmentation and hyperpigmentation in nonwhite patients (38.8% and 16.6%, respectively) more often than in white patients (16.6% and 0%, respectively), suggesting that white patients will have a better cosmetic result with this treatment. The recurrence rate during a 9-month follow-up

was 25%. In a study by Cannon and colleagues [21], treatment of XP lesions with 95% TCA had a success rate of 70% at a mean follow-up of 14.3 months that dropped to 33% due to recurrence or persistence at a mean follow-up of 31.8 months, suggesting that the treatment effect may be only temporary. In a study that compared 70% TCA and Erbium:YAG laser for treatment of XP lesions, the 2 treatment methods were implemented for different lesions in the same patient [37]. There was no significant difference in efficacy or complications between the treatments 4 weeks after application; however, follow-up was short and recurrence rate was not reported in this study. A comparison between treatment with 70% TCA and treatment with CO_2 laser showed similar efficacy for both treatments, and they were both more efficient than lower concentrations of TCA (35% and 50%) [38]. This study showed a statistically significant improvement for patients older than 40 compared with younger patients and for patients without lipid profile abnormalities compared with patients with dyslipidemia. In conclusion, chemical peeling with TCA is a treatment method that has a rather high percentage of complications, mainly dyspigmentation, and of high rate of recurrence, but may be a suitable choice in settings where treatment cost is an issue.

Other chemical compounds have been used to treat XP by intralesional injections. In 2016 a Chinese group published their experience of a new treatment for XP with intralesional pingyangmycin [39]. Pingyangmycin, also known as bleomycin A5, is one of the 13 components of bleomycin, a cytotoxic drug with antitumor activity. It is used to treat lymphatic malformations, vascular malformations, and benign or malignant neoplasms. Three of their 12 patients received 2 sessions of treatment and the remainder only 1 treatment. Seventy-five percent of the patients had an excellent outcome defined by the researchers as a clearing of more than 75% of the lesions. Only 1 patient had a recurrence after 1 year. In 2020, the same group published another series of 24 patients who were treated with 2 concentrations of intralesional bleomycin [40]. They report satisfactory results with this treatment as well.

Intralesional injections of deoxychloric acid (DCA) are used for submental fat lipolysis. Patel and colleagues [41] injected DCA into 2 patients' recurrent XP lesions. Both patients needed reinjections: one received 4 treatment sessions and the second 3. They observed an improvement of size and thickness of the lesions in both patients but neither had complete resolution.

Radiofrequency

Electric cauterization with low voltage radiofrequency has been shown to be an effective treatment for XP in a 15-patient case series out of which 14 had good to excellent cosmetic results. Only 5 patients required a second session of treatment [42]. Posttreatment, mild to moderate pain and swelling subsided in 1 to 2 days. Three of the 15 patients had dyspigmentation after treatment that continued for 5 months of follow-up, but no recurrence of the remaining lesions was reported.

In recent years, aesthetic medicine has begun to use plasma generator devices for contraction and tightening of the skin. This is a nonsurgical superficial procedure that is used as an eyelid blepharoplasty substitute and for treating perioral wrinkles, improvement in the appearance of scars, face and neck lifts, tattoo removal, among other applications. Baroni [43] presented a series of 15 XP cases treated with a long-wave radiofrequency plasma generator. Each treatment consisted of 3 to 4 sessions at intervals of 30 days; all patients had optimal results with no dyspigmentation 3 months after the final treatment. A different plasma generator device was used by Rubins and colleagues [44] to treat another series of 15 patients with 27 XP lesions. In their series, after only 1 treatment, all lesions were resolved by 1 month and remained stable at 12 months with no recurrence or side effects, such as dyspigmentation or scarring.

Liquid nitrogen cryotherapy

In 1995, Dewan and colleagues [22] reported a series of 100 cases of XP treated with liquid nitrogen cryotherapy. In their series, each patient was treated only once with a freeze cycle of 15 seconds. They had 26% recurrence in 6 months and 6% incidence of hypopigmentation. A more recent report by Labandeira and colleagues [45] suggests a shorter treatment cycle but with more repetitions as needed according to lesion thickness. This method achieved better cosmetic results with no scarring and or recurrence. Unfortunately, the investigators did not report the number of patients they treated or the exact length of each cycle to draw definite conclusions.

Surgical or laser treatment

Surgical excision has been the treatment of choice of XP for decades [2,46]; however, most of the literature dealing with XP treatment offer solutions other than surgical treatment, and laser treatment has been advocated as an ideal therapy for XP because of its superficial location [47,48]. Some algorithmic approaches for XP treatment have been suggested, including surgical, laser, and peeling for different cases, taking into account the consistency, size, and locations of the lesion [21,32,44]. We herein present our approach for the treatment of XP.

Many patients with XP present to dermatologists and plastic surgeons for treatment and not to oculoplastic surgeons. Surgical excision is in the periorbital region and carries with it the risks of cosmetically unacceptable or functional scar with possible ectropion [38]. As a result of such potential complications, some practitioners prefer the use of laser therapy. However, for the oculoplastic surgeon, surgery may be a preferred solution for most of the cases of XP.

Disadvantages associated with surgery include a need of systemic or local anesthesia for the procedure. Surgical excision often is followed by slight scarring, regardless of whether wound closure is achieved through primary closure, full-thickness skin grafting [14,49], or granulation. Complications include ectropion and dyspigmentation [14]. However, considering the advantages and disadvantages of each method, it seems that for most XP cases, surgical treatment is a worthy solution.

With laser treatment, only eyelid defects that are smaller than 5 mm are amenable to healing by secondary intention [50]. A clinically large lesion (ie, lesions >5 mm in height), regardless of depth, when treated with lasers, resulted in a more blatant secondary deformity and is more susceptible to skin discoloration, scarring, and recurrence [3].

Mittelviefhaus and colleagues [51] found through histologic specimens that in 42% of the XPs, the lesion infiltrates the entire dermis and reaches the stratum musculare or even invades into this layer. In such cases, orbicularis muscle resection is required for complete excision of the lesion. This can be achieved only through surgical excision. In one study, muscular infiltration was seen in approximately 25% of patients [3]. Incomplete excision of the lesion leads to a higher incidence of recurrence [3]. Mendelson and Masson [18] found that 40% of patients had recurrence after primary surgical excision, 60% after secondary excision, and 80% when all 4 eyelids were involved.

Discussion

The surgical approach of XP is based on the concept that it should be treated as a tumor with surgically free borders, and all fatty tissue removed. The approach to surgery is based on the *size of the lesion, its location in the eyelid, and the laxity of the skin*. The pinch test is performed to detect the excess amount skin in the upper and lower eyelid and to perform lateral canthopexy or skin flap or graft accordingly.

Simple excision with or without blepharoplasty and medial myocutaneous flap or a skin graft can be conducted in grades I and II lesions, whereas, in advanced cases, like grade III, medial side of both upper and lower eyelids, and Grade IV, diffuse lesions that involve medial and lateral of both upper and lower eyelids, uncapping surgery, local flaps, and skin grafts can be carried out (Fig. 6). The most common method of surgery is full-thickness skin excision. In XP that infiltrates the muscle layer, muscle resection is required [51].

For lesions either in the upper or lower eyelids that are confined to the superficial dermis, less than 5 mm in vertical height undermining the skin and direct closure may be enough (Fig. 7).

If the skin is tight, additional lateral canthopexy may be performed. For long-standing lesions with an onset exceeding a year, or large lesions extending beyond 5 mm in height, local flaps and skin grafts may be necessary to preserve the aesthetic continuity of the eyelids, regardless of the lesion depth [3]. (Fig. 8) Also, simple excision by blepharoplasty may provide a more aesthetically pleasing result after surgery [17].

The location

Nasal upper eyelid

The nasal upper eyelid is a danger zone for creating a web. In the medial upper lid, we often leave to granulation. However in recurrent cases, in cases post-laser or peeling treatment, and in large XP, local skin advancement flaps or orbicularis oculi muscle flaps can be performed. Another option is using an orbicularis oculi muscle myocutaneous flap formed in blepharoplasty [17]. The skin can be closed by single or mattress Prolene or PDS 6 to 0 or 7 to 0 stiches.

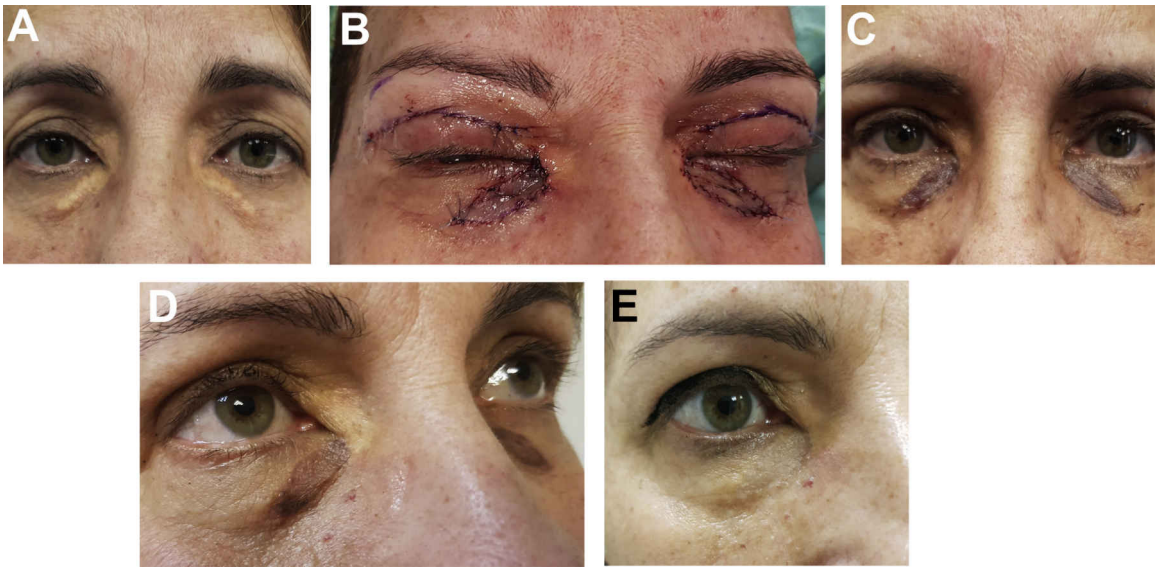

FIG. 6 Post laser treatment photo of lesions involving the medial sides of both upper and lower eyelids. The tissue is scarred, it involves the medial canthus and with no clear margin between the lesion and the skin. The lesion maximal width is 8 mm and there is a need for a flap or graft. (*A*) In this case *free skin graft was used for lower lid XP simultaneously with blepharoplasty*. (*B*) Postoperative photo at 2 weeks after surgery. The graft is accepted, however, it is hyperpigmented at this stage. (*C*) Six weeks postsurgery, the graft is still hyperpigmented. (*D*) Eight months postsurgery, the graft got a suitable color with no hyperpigmentation. The patient expressed satisfaction with the overall aesthetic result.(*E*).

Nasal lower eyelid-primary

In the lower eyelid, whenever the lesion is located in the nasal side of the eyelid, and there is some tissue laxity, primary closure can be performed. Undermining of the skin of at least 10 mm that can be a lot in the lids in the upper and lower edges should be performed. The skin can be closed by single Prolene or PDS 6 to 0 or 7 to 0 sutures.

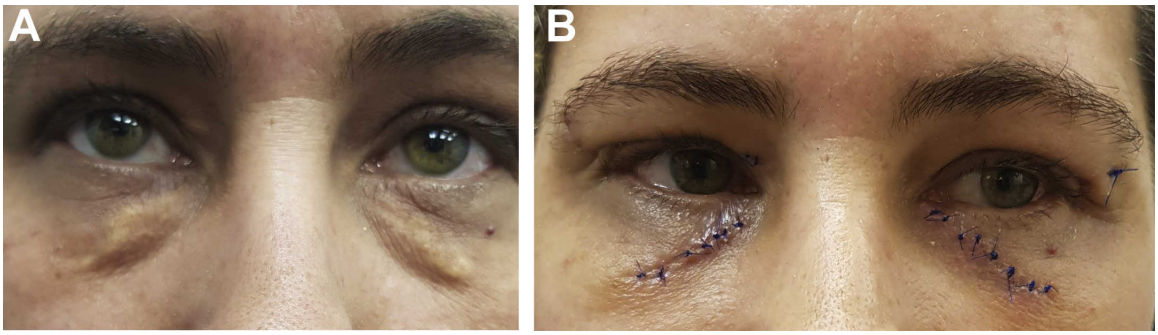

FIG. 7 Photo of post laser treatment photo of lesions involving the medial sides of the lower eyelids. The tissue is scarred, it involves the medial canthus, and with no clear margin between the lesion and the skin. The lesion maximal width is 7 mm. (*A*) The operation included undermining of the skin was used, canthopexy with polypropylene suture and direct closure.(*B*).

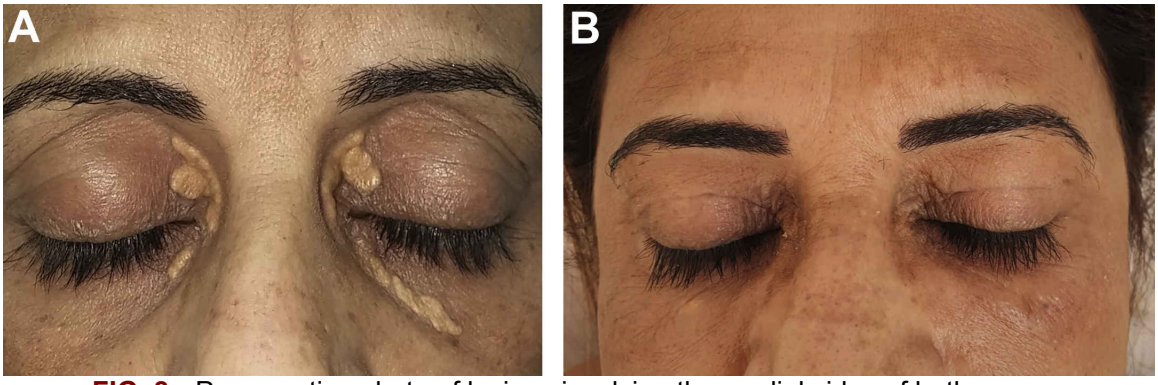

FIG. 8 Preoperative photo of lesions involving the medial sides of both upper and lower eyelids. (*A*) The lesions are extensive, with width of more than 5 mm, and it involved the medial canthus. The operation included undermining of the skin was used, and local skin flaps. (*B*) Postoperative photo at 12 months after surgical excision.

Lesion extending to temporal lower lid

If the lesions extend beyond the middle nasal and toward the temporal lower lid, even when there is redundant skin, traction forces may cause tension resulting in ectropion. So, it is advisable to perform canthopexy. We use a double-armed 5 to 0 Prolene suture on a spatulated needle that is passed 5 mm superolaterally to the lateral canthus, through the skin 5 mm, then passed through the periosteum, the lateral canthus, and back 5 mm superolaterally to the lateral canthus. The edges are tightened in the superolateral skin, and it can be removed after 7 days.

Extensive lower lid lesions

Whenever the height of the XP is more than 5 mm, it usually is too large for a primary closure, and local flaps of free skin grafts can be used [3].

If cases with extensive or multiple islands of lesions, the surgery can include lower lid blepharoplasty. In such cases, the lesions should first be excised, and then local rotational flaps should be used to close the defects. Eventually, if excess skin and muscle still persist, it can be excised with a subciliary incision. However, this can lead to prolonged edema between the 2 incisions.

In some cases of very extensive lower lid XP, an upper eyelid blepharoplasty can be performed simultaneously and the upper eyelid skin can be used as free skin grafts [3]. Possible disadvantages can be misalignment of the color of the graft and graft rejection (unlikely in eyelid skin). However, the upper lid skin graft is a favorable graft for lower lid.

Nasal bridge

Sometimes XPs extend to the nasal bridge or as a separate island lesion. The nasal skin is thicker than the eyelid skin, and for some patients these lesions are less prominent and do not pose an aesthetic problem. The surgeon should discuss the issue with the patient, and, if necessary, it is possible to enlarge the flap or the graft to cover the XP in the nasal area.

Giant xanthelasmas

This term is used to indicate the XP extensively involving all 4 eyelids. The lesions are too large for skin and flaps. They are uncommon, yet are more difficult to treat and have a high recurrence rate (80%). Even if these young and middle-aged patients adhere to a strict low-lipid diet and the oral use of statins, the lesions tend to extend and occupy the eyelids' surface. These lesions, because of their extension, require a well-thought-out therapeutic approach. Corradino and colleagues [52] presented their experience with ultrapulsed laser CO_2 treatment. The treatment is completed in approximately 6 to 8 weeks; wound healing is slow and occurs by secondary intention. The aesthetic result is satisfactory, and no functional alterations or pathologic scarring in the eyelids treated occurred [52]. An alternative to CO_2 laser in these cases is staged excision in a serial staged approach [53].

Clinics care points

- Surgical excision has been the traditional method for treating XP. It achieve complete excision and minimize recurrence
- Considering the advantages and disadvantages of each method, it seems that for the most of XP cases surgical treatment is a worthy solution.
- Nonsurgical treatment is suitable for lesions that are limited to the superficial dermis, lesion height of less than 5 mm, and lesion onset of less than 1 year.
- Other lesions including deeper lesions extending to the inner dermis or musculature, lesion height of more than 5 mm or long-standing lesions should be excised surgically.
- Simple excision with or without blepharoplasty can be conducted in lesions on upper eyelids only, or lesions that extend to medial canthal area.
- In advanced cases, like medial side of both upper and lower eyelids and diffuse lesions that involve medial and lateral of both upper and lower eyelids, local flaps and skin grafts can be carried out.

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Refractive Error Changes Associated with Eyelid Weight Placement

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Keywords

Lagophthalmos; Exposure keratopathy; Eyelid loading; Eyelid weight; Corneal astigmatism; Refractive error; Facial palsy; Gold weight

Key points

- Induction of corneal astigmatism is a possible complication of upper eyelid loading for treatment of lagophthalmos, which can lead to reduced visual acuity and decreased patient satisfaction.
- The most common surgical approach is the use of a gold weight with a pretarsal technique, which may have higher rates of corneal astigmatism compared with newer approaches and platinum implant options.
- A combined high tarsal and levator fixation surgical technique using a standard gold weight does not appear to induce corneal astigmatism.
- Platinum chains have been reported to be as effective as gold implants in reducing lagophthalmos and have fewer complications, including lower risk of corneal astigmatism.
- There are few studies evaluating the refractive error changes associated with upper eyelid weight loading. Future studies should evaluate rates and objective measurements of corneal astigmatism in their complications.

Introduction

Lagophthalmos, commonly due to facial nerve (cranial nerve VII) paralysis, is the inability to fully close the eyelids. Bell palsy is the most common cause of facial nerve paralysis and occurs in 30 in 100,000 individuals each year [1]. Without proper eyelid closure, the cornea does not receive adequate lubrication and is susceptible to exposure keratopathy in the form of dry eye syndrome, corneal ulcers, and perforations that potentially can lead to blindness. As such, it is important to prioritize ocular preservation in the management of lagophthalmos. Facial paralysis also can impose numerous psychosocial effects on a patient and have negative consequences on quality of life [2]. Treatment with upper eyelid gold weights has been shown to significantly improve quality of life for patients with lagophthalmos, particularly in terms of mental health [3]. The use of platinum chain implants also has been associated with improved quality of life due to the reduction in use of eye ointment and nocturnal devices, which can have functional limitations on day-to-day life [4].

Conservative treatment options include topical ophthalmic ointments, lubricating eye drops, soft contact lenses, eyelid taping, scleral shells, and temporary tarsorrhaphy [4]. Other temporary measures include external eyelid weight placement, hyaluronic acid gel, and botulinum toxin A injection [5]. For patients with lagophthalmos, however, who are unlikely to recover with time or spontaneously, or who are unable to perform these frequent measures, it may be more appropriate to seek out a longer-term solution.

Eyelid weight placement is a well-established surgical intervention for the management of lagophthalmos, and newer surgical techniques and options for weight loading have evolved over time. Eyelid loading for facial paralysis was introduced by Sheehan [6] in 1950 using tantalum wire and mesh. The first reported use of gold plate insertion was by Illig [7] in 1958, before being popularized by Jobe [8] in 1974. Over the past 50 years, gold weight implants have become a standard approach to gravity-assisted eyelid loading due to high density, malleability, and reduction in scarring [9]. More recently, platinum chain implants and platinum segments have been introduced as weight implant options with fewer complications compared with gold implants due to improved biocompatibility and volume reduction [10,11]. Upper eyelid loading generally is a well-tolerated procedure. The most common complications

of upper eyelid loading include infection, allergy (Fig. 1), extrusion of the implant (Fig. 2), migration, poor cosmesis, and induction of corneal astigmatism [12].

The goal of surgical management for lagophthalmos is to optimize functional and cosmetic outcomes while minimizing the risk for complications. Although this procedure has been successful in treating lagophthalmos, a risk exists of additional ocular complications with reduction in visual function. There are few studies assessing the refractive error changes or induced ptosis associated with eyelid weight loading. This review aims to focus on the available literature regarding refractive error changes associated with eyelid weight loading and options for minimizing this complication.

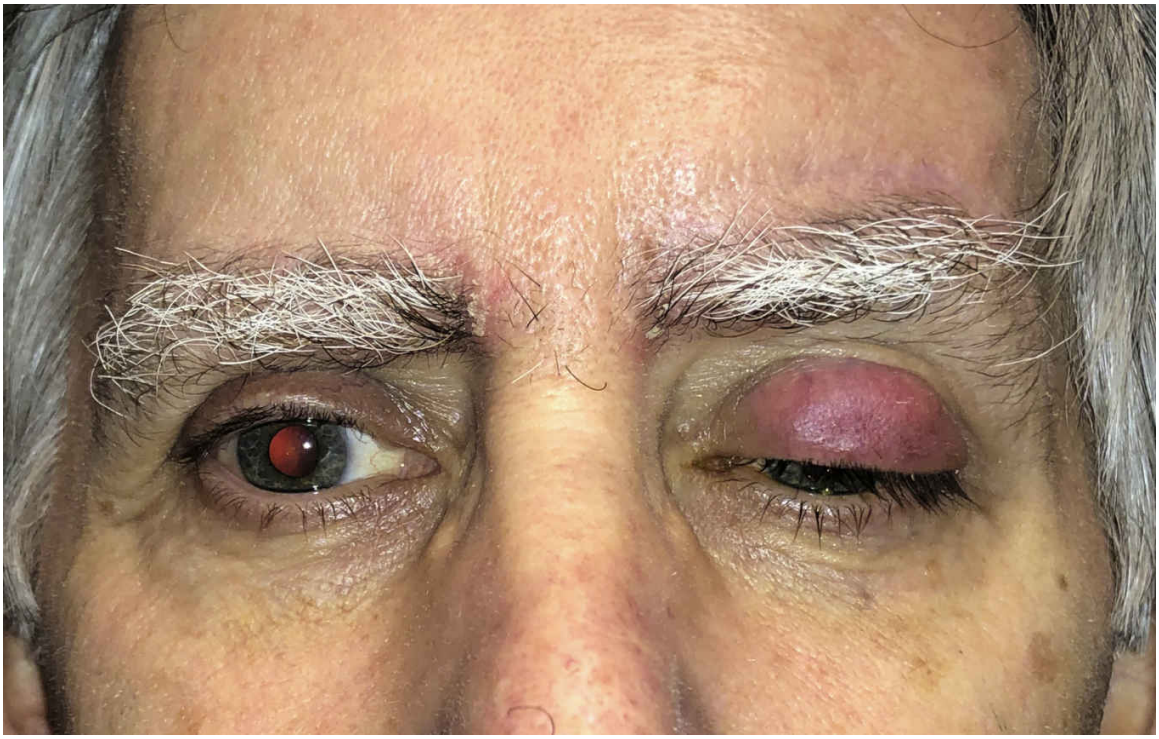

FIG. 1 Erythema and edema from a gold allergy as well as secondary ptosis and lumpy visibility of the implant—left upper eyelid.

Significance

Efficacy of upper eyelid weight placement

Upper eyelid loading is an established procedure for treatment of paralytic lagophthalmos, with resolution of lagophthalmos and complete eyelid closure in up to 84.5% of patients receiving rigid gold implants [13]. Gold weight implants also have been used effectively in the treatment of thyroid-related upper eyelid retraction in terms of cosmetic appearance and improvement of eyelid retraction [14]. Advantages of upper eyelid loading include eyelid closure while preserving the visual field, reversibility, and ability to combine the procedure with other surgical eyelid corrections, making it an appropriate treatment option for both reversible and irreversible causes of facial nerve paralysis [15].

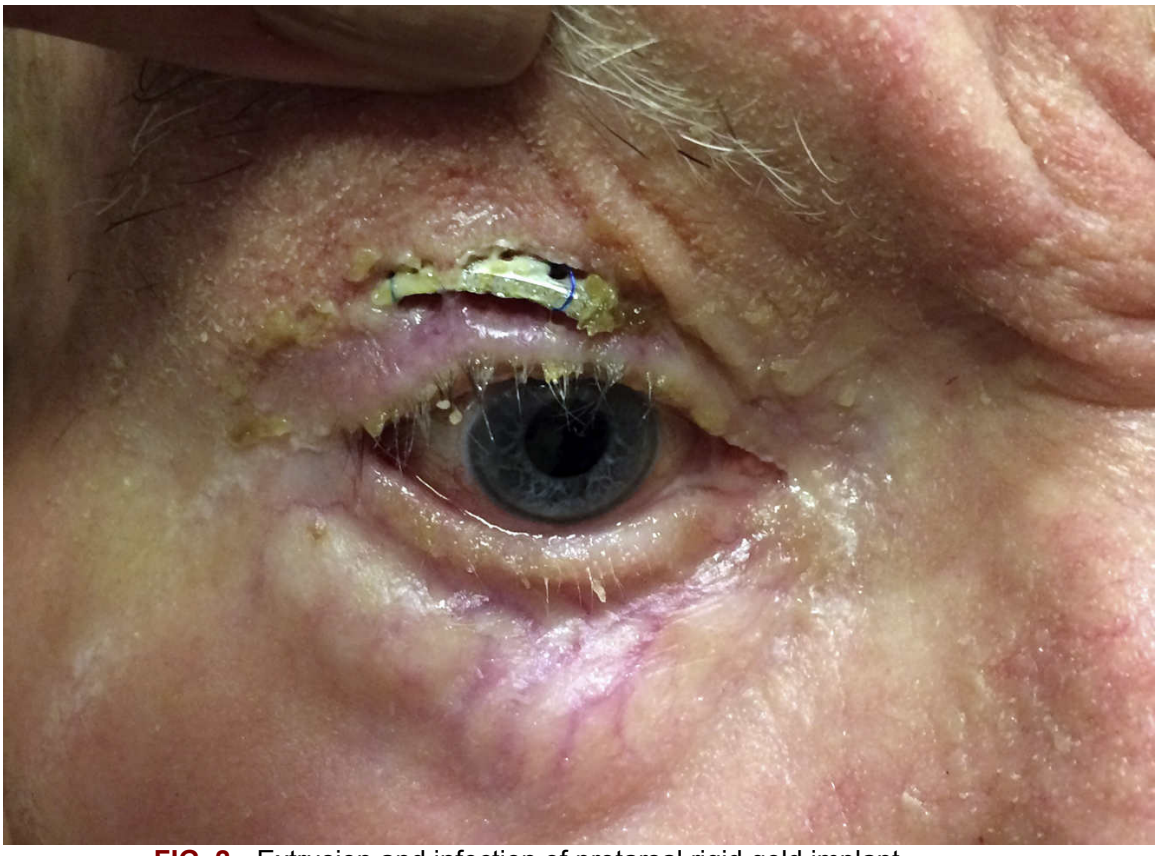

FIG. 2 Extrusion and infection of pretarsal rigid gold implant.

Causes of lagophthalmos

The most common causes of lagophthalmos leading to the need for surgical eyelid weight implantation include facial nerve paralysis from Bell palsy or an acoustic neuroma, incomplete blink lagophthalmos, and nocturnal lagophthalmos. Other causes are summarized in Table 1.

Operative technique

Pretarsal implant placement (Fig. 3; see Fig. 5) is the most common technique used by practicing physicians due to its simplicity, effectiveness, and reversibility in the management of lagophthalmos [16]. Many investigators, however, have proposed alternative surgical approaches to minimize potential side effects. Specifically, a combined pretarsal and direct levator aponeurosis fixation technique (Figs. 4 and 5) has been demonstrated to be effective in preventing induced corneal astigmatism [12]. These surgical approaches are summarized in Table 2 and Fig. 5.

Complications of upper eyelid loading

Common complications of upper eyelid loading are summarized in Table 3 and Fig. 6.

Refractive error changes

Corneal astigmatism is a known possible postoperative complication of upper eyelid loading with a rigid gold plate with an incidence of 11.5% [13]. Corneal astigmatism can lead to changes in visual acuity, which has been shown to negatively affect patient satisfaction following gold weight implant for facial paralysis [19]. Due to the importance of both functional and aesthetic outcomes of this procedure, it is important to assess the potential for visual changes for a patient postoperatively. Few studies exist addressing the refractive error changes that may occur as a result of upper eyelid loading. Changes associated with rigid gold plate implants before transitioning to discussion regarding platinum chains and platinum segments are discussed.

Table 1 Potential etiologies of lagophthalmos

Congenital	Idiopathic	Toxic
• **Coloboma of eyelid** • **Goldenhar syndrome** • **Ichthyosis** • **Moebius syndrome**	• Amyloidosis • Bell palsy • Giant cell arteritis • Guillain-Barré syndrome • Multiple sclerosis • Myasthenia gravis • Sarcoidosis	• Alcohol excess • Arsenic • Carbon monoxide • Diphtheria • Tetanus • Thalidomide

Cicatricial	Infectious	Traumatic
• **Chemical burns** • **Laser ablative resurfacing** • **Ocular cicatricial pemphigoid** • **Solar elastosis** • **Stevens-Johnson syndrome** • **Trauma**	• Bacterial • Fungal • Viral	• Birth trauma • Facial injuries • Skull fractures

Iatrogenic	Metabolic	Tumors
• **Laser resurfacing** • **Surgery** • **Postsurgical** • **Upper blepharoplasty**	• Diabetes mellitus • Hyperthyroidism • Vitamin A deficiency	• Acoustic neuroma • Facial nerve tumor • Parotid tumors

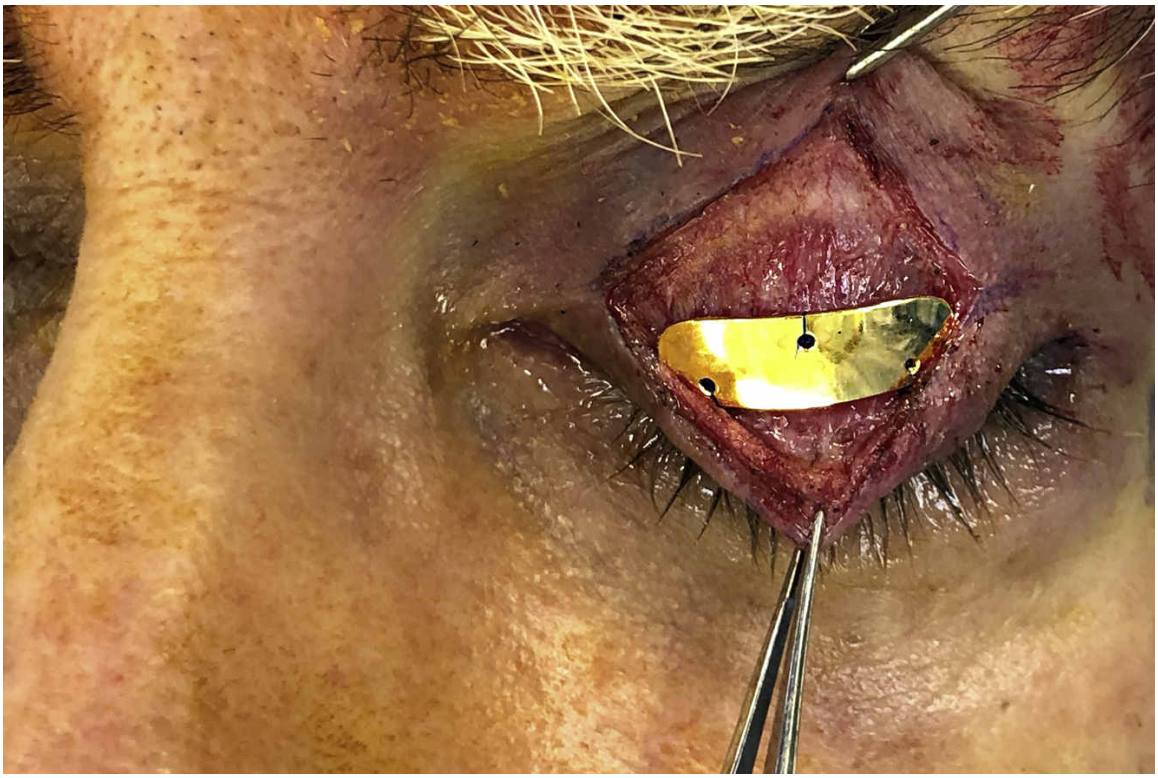

FIG. 3 Pretarsal implant placement with rigid gold implant.

Gold weight implant

Corneal astigmatism has been reported previously as a complication of gold implants and can be associated with the increased eyelid pressure from the weighted implant as well as the curvature of the implant. A questionnaire on patient perspectives of ocular symptoms from facial paralysis by Sönmez and colleagues [20] found that visual acuity had the lowest subjective score following gold weight implantation, indicating the importance of emphasizing the preservation of visual function for postoperative patient satisfaction.

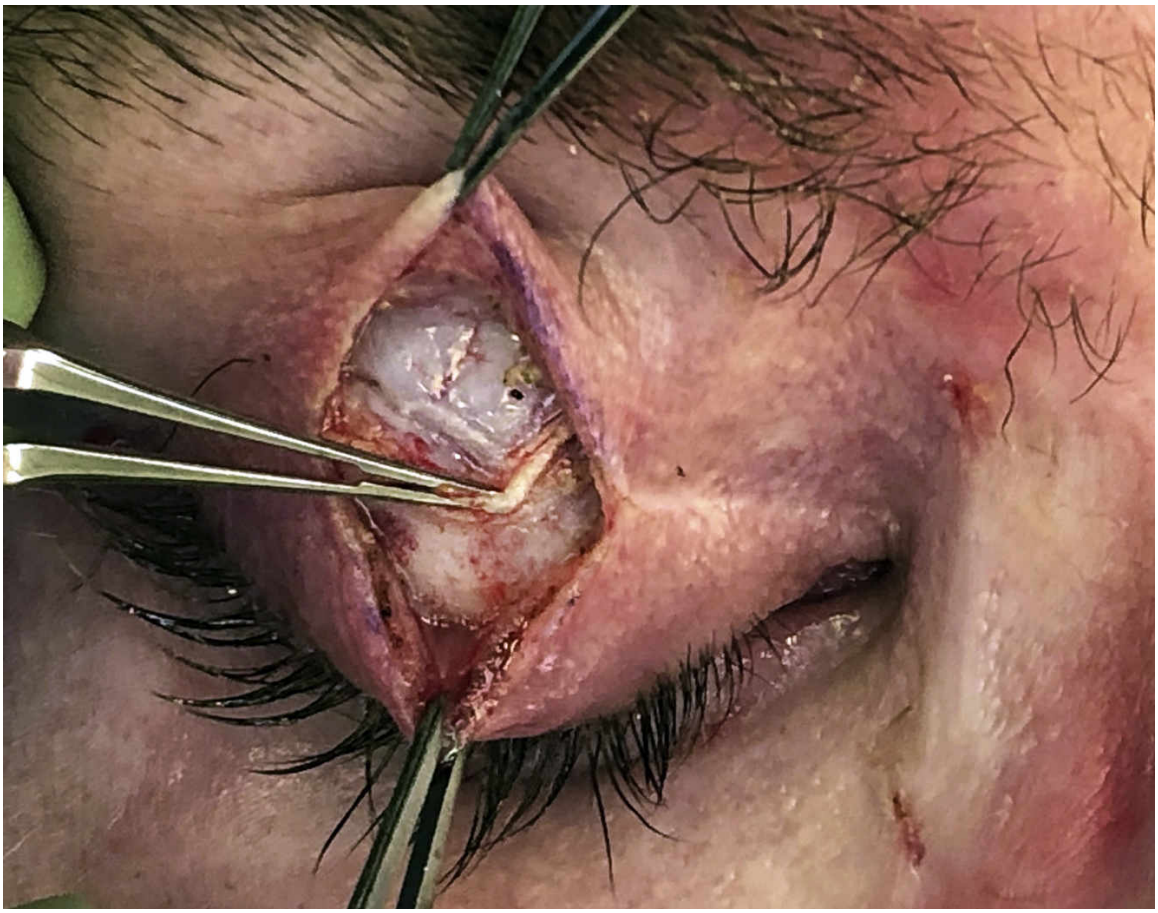

FIG. 4 Combined pretarsal and direct levator aponeurosis (indicated by forceps) fixation technique.

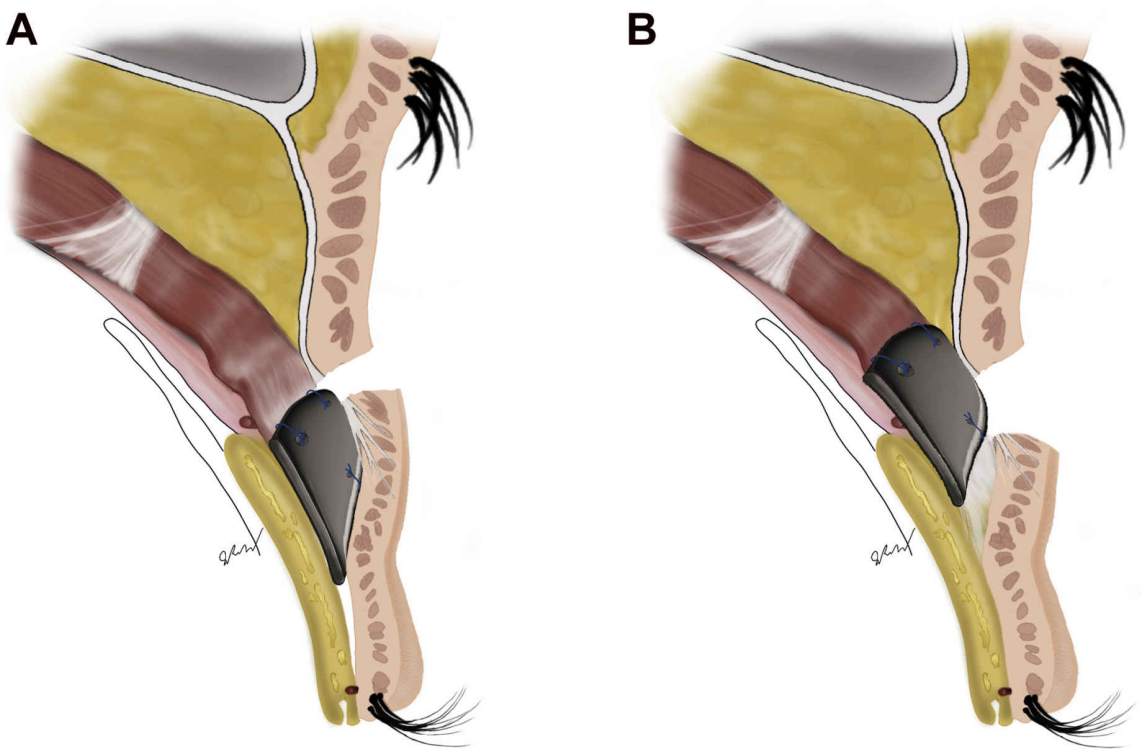

FIG. 5 Pretarsal (*A*) versus the higher pretarsal-levator aponeurosis fixation (*B*) placement.
(Illustration by Cat N. Burkat, MD, FACS.)

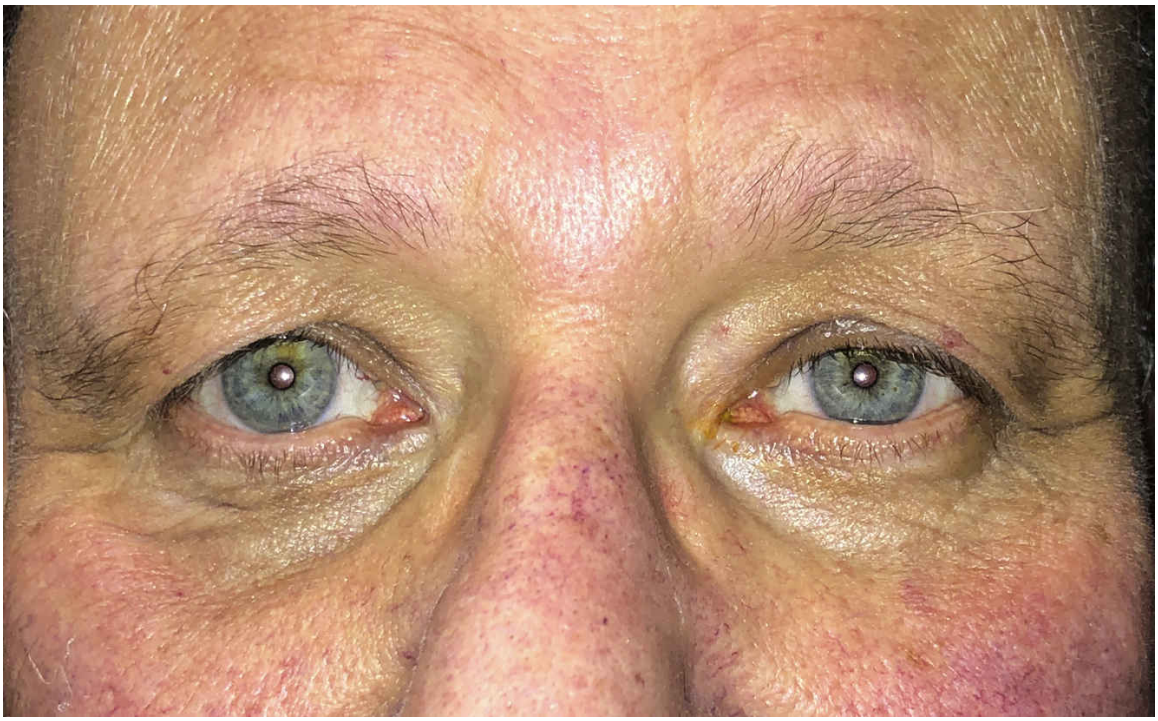

FIG. 6 Induced left ptosis from implant.

Table 2 Advantages and disadvantages to various surgical approaches for upper eyelid loading

Surgical approach	Advantages	Disadvantages
Pretarsal fixation (see Figs. 3 and 5)	• Simple procedure • Minimal dissection to remove weight	• Visible eyelid lump • Visible implant • Extrusion • Migration • Iatrogenic ptosis • **Corneal astigmatism**
Retrograde approach	• Preserves levator aponeurosis, reduces risk of ptosis	• Risk of implant extrusion • Conspicuous scar
Modified retrograde	• Lower risk of extrusion and visual field disruption	• Technically more difficult
Combined pretarsal and direct levator fixation	• Lower risk of migration and extrusion • **No alteration in corneal astigmatism** • Lower implant weight required for eyelid closure	• Iatrogenic ptosis upon removal • Not for patients whose paralyzed eyelid may recover
Intraorbital fixation	• Improved aesthetic outcome • Lower risk of extrusion	• May worsen nocturnal lagophthalmos • **Corneal astigmatism**
Septal fixation	• Improved aesthetic outcome • Lower risk of iatrogenic ptosis upon removal	• Heavier average weight needed for complete eyelid closure
Postseptal fixation [17]	• Reduced implant visibility, implant exposure, and entropion	• Risk of incomplete closure and need for revision

Data from Refs. [17,18]

Table 3 Reported complications of upper eyelid loading

Complication	Frequency	Management
Migration [13]	13.4%	• Topical antibiotics • Removal or repositioning of implant; nonabsorbable fixation sutures
Corneal astigmatism [13]	11.5%	• Removal of implant • Platinum weight > gold weight • Combined pretarsus and levator aponeurosis fixation technique • Cylinder lens
Infection [13]	7.0%	• Antibiotics • Drainage of abscess or implant removal if needed
Extrusion [13] (see Fig. 2)	6.8%	• Topical antibiotics • Removal or repositioning of implant; nonabsorbable fixation sutures • Switch to alternative material if needed
Bulging [13] (see Fig. 1)	6.4%	• Implant exchange with thinner profile weight • Higher placement of implant
Allergy (see Fig. 1)	—	• Removal of implant • Switch to alternative material • Treat with steroids
Poor cosmesis	—	• Implant exchange with thinner profile weight • Levator repair if ptosis • Higher placement of implant if visible
Ptosis (see Fig. 6)	—	• Implant exchange with lighter weight • Levator repair if needed

Data from Refs. [13,18]

A prospective, cohort study of 18 patients by Mavrikakis and colleagues [21] reported corneal topography changes resulting in a significantly increased with-the-rule corneal astigmatism by 1.4 diopters (D) ±2.0 D from a mean of 0.3 D to 1.7 D following pretarsal placement of a gold weight for facial nerve palsy (P = .034). In patients who had recovery of facial nerve function and elected to have the gold weight removed (n = 9), there appears to have been a reversal of the with-the-rule corneal astigmatism with a reduction by 1.2 D ± 2.1 D from a mean of 2.2 D to 1.0 D following removal (P = .136). This indicates that although upper eyelid loading can induce corneal changes, it appears to be reversible. Additionally, there appears to be a greater effect on the vertical axis of the orbit than the horizontal axis.

In 2004, Caesar and colleagues [22] introduced a combined high pretarsal and levator fixation technique for upper eyelid loading with a gold weight implant. The investigators placed an additional suture from the levator aponeurosis to the implant and reported reduced implant migration and extrusion with this modification. They also noted that a lighter implant weight was required for closure, which improved the aesthetic appearance.

Saleh and colleagues [12] evaluated the astigmatic effect of this technique and found that this technique did not appear to cause a significant change in corneal astigmatism postoperatively based on automated refraction readings, automated refraction axis, keratometry readings, or keratometry axis. This is in contrast to previous studies with pretarsal gold weight implantations, which have been associated with induction of significant with-the-rule corneal astigmatism. They hypothesized that the high positioning of the implant superior to the cornea allowed for evasion of direct contact with the globe while the eye is open, thus reducing corneal warpage.

Key points

- Gold weight standard implants, with pretarsal fixation, have been associated with induced with-the-rule corneal astigmatism that appears to be reversible.
- Using a combined high pretarsal and levator fixation technique with a gold weight may reduce the risk of iatrogenic corneal astigmatism.

Platinum implant

Platinum chain eyelid loading should be considered a first-line treatment of paralytic lagophthalmos due to its superior qualities and outcomes [4]. The transition to utilizing platinum chains, however, has been slow, likely partially due to the higher cost of platinum chains, familiarity with gold weights, and the limited information on long-term outcomes [12]. Platinum chains have several potential advantages over gold weight implants:

- Higher density resulting in a thinner implant

- Flexible shape leading to improved cosmesis in terms of eyelid contour
- Superior biocompatibility reducing the risk for gold allergy [23]

Platinum chains have been shown to have better long-term outcomes compared with gold weights with reduced incidence of weight prominence, implant migration, and need for revision surgery. In an evaluation of late outcomes of upper eyelid loading with gold weights versus platinum chains, Saleh and colleagues [12] found that gold weights were twice as likely to require long-term revision surgery compared with platinum chains. The chain configuration also may have the advantage of minimizing the risk of inducing corneal astigmatism, regardless of surgical approach.

Schrom and colleagues [24] compared the outcomes of 50 pretarsal-implanted rigid gold implants to 46 flexible platinum chains in patients with peripheral facial paralysis and lagophthalmos. The investigators found that both groups were successful in reducing lagophthalmos and keratopathy and improving visual acuity. The use of platinum chains reduced the postoperative occurrence of corneal astigmatism from 24% with gold implants to 6.5% with platinum chains. This study showed that by changing to a flexible implant while retaining the traditional pretarsal-fixation approach, the rate of corneal astigmatism postoperatively could be reduced.

The same group performed a meta-analysis on 212 implantations using flexible platinum chains for lagophthalmos and found a statistically significant lower postoperative complication rate concerning astigmatism, bulging, and postoperative infections with the platinum chain group [25]. The overall complication rate was 45.1% with the use of gold implants and 12.8% with use of the platinum chain. The investigators argue for the effectiveness of platinum chain eyelid loading over gold weight implants in treatment of lagophthalmos.

Silver and colleagues [26] performed a large series from 2004 to 2009 on 100 patients who received a thin-profile, single rigid piece, platinum eyelid implant via a pretarsal surgical approach. There was a 5.9% complication rate, including 3 extrusions, 2 capsule formations, and just 1 case of corneal astigmatism.

Mavrikakis and colleagues [21] demonstrated that pretarsal gold weights led to a statistically significant change in corneal topography and with-the-rule corneal astigmatism. In a follow-up study, the same group

evaluated the corneal topography of 15 patients who underwent upper eyelid platinum chain implantation with pretarsal fixation technique for facial nerve palsy. They found no significant change in corneal astigmatism, contrary to their findings for gold weight implantation. Although this study is small, it aligns with the studies, discussed previously, highlighting the relationship between platinum chain implants and reduction in induction of corneal astigmatism postoperatively.

Key points

- Platinum weights should be considered first line for upper eyelid loading due to a thinner profile and minimal allergic potential.
- Platinum chains appear to reduce the rate of corneal astigmatism following pretarsal upper eyelid loading compared with gold weight implants.
- Platinum chain implantation with a pretarsal fixation technique was not associated with corneal topographic changes or induction of corneal astigmatism.

Platinum segment implant

In 2015, Malhotra and colleagues [11] designed and introduced a new platinum segment chain in the United Kingdom. Platinum segments are composed of individual segments that can be sutured together individually and allow for long-term postoperative adjustability (Fig. 7). Individual segments come in 0.4 g and 0.2 g options and can be combined to assemble the desired weight. In their single-center, single-surgeon, prospective study, they evaluated the outcomes of 18 eyelids of 17 patients undergoing upper eyelid loading for lagophthalmos. The investigators used a high tarsal surgical technique with levator recession. Primary outcome measures included improved lagophthalmos on blink ($P<.0001$) and improved gentle and forced closure ($P = .0004$). Although the study did not evaluate for corneal astigmatism postoperatively, they observed a mean improvement of 0.05 in best corrected logarithm of the minimum angle of resolution (logMAR) visual acuity at 3 months (not statistically significant).

In particular, the study found that individual platinum segments were valuable in cases of patients who had a preexisting gold weight or

platinum chain and needed additional weight added, avoiding the need for an implant exchange.

Additionally, the individually sutured together segments allow for a better profile on the eyelid due to multiple pivot points.

Platinum segments were approved by the Food and Drug Administration for the treatment of lagophthalmos in 2017. Malhotra and colleagues published a 5-year series from 2013 to 2018 reporting the outcomes of 122 upper eyelids of 117 patients that received platinum segment chains for upper eyelid loading [27]. They utilized a supratarsal approach with levator aponeurosis recession. After long-term evaluation, the investigators were able to validate their results from their preliminary study. Platinum segments were found to have favorable outcomes in treatment of lagophthalmos on blink, gentle, and forced closures (P<.001). Added benefits of platinum segments included

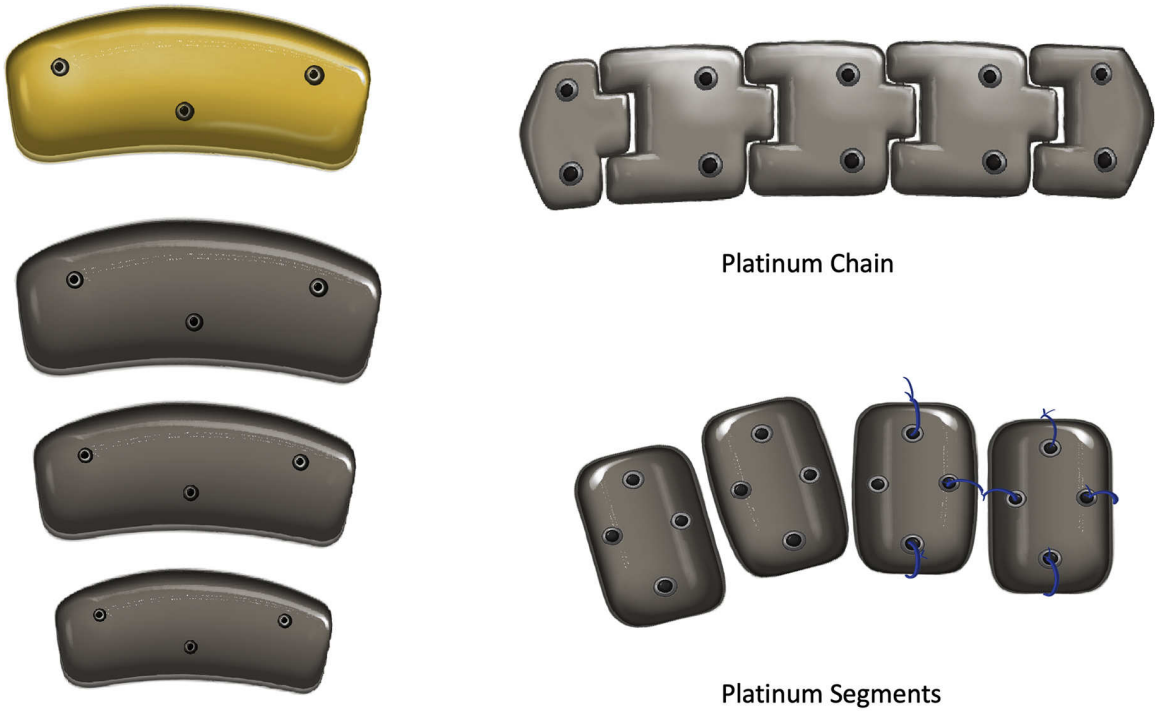

FIG. 7 Schematic illustration of the standard rigid eyelid weights, chain implants, and individual platinum segments.
(Illustration by Cat N. Burkat, MD, FACS.)

- Postoperative adjustability, particularly to add weight and adjust contour
- Reduced health care costs from avoiding implant exchange surgery
- Avoidance of allergic reactions seen with gold

The study had a 5.7% complication rate that required intervention, including 5 cases requiring surgical intervention for migration or infection. The follow-up study did not evaluate for corneal astigmatism as a postoperative complication but did not find a statistically significant change in visual acuity at the 3-month or final follow-up. Further and expanded evaluation of the effect of platinum segment chains is needed to determine whether this new option provides the benefit of avoiding induction of corneal astigmatism.

Key points

- Platinum segment chains are a newer option for upper eyelid loading that appears to offer the added benefits of postoperative adjustability and eyelid contouring.
- The effect of platinum segment chains on refractive error is inconclusive at this time.

Relevance and future avenues

Upper eyelid loading has been used as the surgical treatment of lagophthalmos for approximately 70 years. Since it first was introduced, the procedure itself has undergone numerous adaptations and revisions to best optimize the functional and aesthetic results for patients. Corneal astigmatism is a recognized potential complication that can lead to reduced visual acuity and, therefore, reduced patient satisfaction postoperatively [19]. For patients who are seeking a surgical procedure for the treatment of an ophthalmologic concern, it may be suboptimal to choose a treatment option that could lead to an additional visual concern. Patients should be fully educated on their treatment options, as well as potential complications—including the less commonly discussed risk for refractive error changes. Clinicians should engage in shared decision-making to determine the best course of action for patients based on their clinical considerations and preferences.

Despite advances in implant materials and surgical techniques, the most commonly used procedure continues to be pretarsal placement with a gold weight implant. Platinum implants, whether the thinner single-piece rigid implants or the chains, have been shown superior in numerous avenues, including reduced risk of induction of corneal astigmatism, better cosmetic outcomes, and improved biocompatibility, limiting the risk for allergic reactions. Platinum implants has had limited traction and use in clinical practice, however. This brings up the following questions and areas for exploration:

1. What are the barriers to transitioning to platinum implants as the standard protocol for upper eyelid loading for lagophthalmos?
2. How can the additional cost of platinum as a standard implant be balanced with the added benefits?
3. What are current treatment and surgical preferences from a provider standpoint?
4. What is left to be investigated?

Transition to platinum

The transition to adopting platinum chain implants as the standard implant has been slow. Siah and colleagues [28] hypothesize that the transition has been restricted primarily by the higher initial cost of

platinum chain implants compared with gold weight implants. In addition, they propose that the few data available to clinicians surrounding long-term outcomes of gold weight implants in terms of the high rate of aesthetic concerns and need for revision surgery may be contributing to the slower transition as well. This secondarily creates an insurance barrier for the more costly platinum options if gold implants appear to be largely successful and still used widely. Because immediate outcomes of upper eyelid loading largely are successful, both clinicians and insurers may not be as aware of how common long-term potential complications that can affect patient satisfaction can be. Finally, greater familiarity with the use of gold weight implants over platinum chains may influence clinicians to continue practicing what they know to be a simple and effective procedure. Providing more education and objective data on the subtleties between these 2 different metals and their long-term outcomes and offering platinum chain or segment samples to surgeons to test could be avenues for encouraging the transition to platinum chains.

Cost of platinum versus gold

The initial cost of utilizing flexible platinum chain implants is higher than traditional rigid gold weight implants and may be an upfront barrier to transitioning to a platinum standard. Most patients need 0.8-g, 1.0-g, or 1.2-g weight to achieve proper closure of the upper eyelid [16]. There have been other studies reporting average weights ranging from 0.8 g up to 2.2 g, with an average weight of 1.6 g [29]. Depending on the weight needed, the cost of the implant may vary and range from $270 to $400 for rigid gold implants, $420 to $550 for rigid platinum implants, and $600 to $900 for flexible platinum chain implants.

Two main options exist for rigid gold eyelid weights: the MedDev Contour eyelid implant and the MedDev ThinProfile eyelid implant (MedDev, Sunnyvale, CA). ThinProfile weights are 40% thinner than the Contour line, offering better cosmesis and tapering to the natural eyelid, albeit at a higher price, which, therefore, may be a barrier for insurance coverage. The same rigid implant options are available in platinum (Contour and ThinProfile). Some insurances may require demonstration of failure, or poor tolerance or allergy, to a gold implant prior to using platinum. The thinner weights measure 0.6 mm in thickness compared with 1.0 mm for standard gold and platinum implants.

The flexible platinum eyelid chain was introduced by Berhaus and Schrom and continues to become more widely utilized (spiggle-theis.com/en/products/eyelid-implants). As of the end of 2020, a 0.4-g platinum segment cost approximately $200, so a commonly used 1.2-g platinum segment chain (comprised of 3 segments) would cost $570 to $600. In comparison, a thin-profile, 1.2-g platinum single piece rigid implant costs $500 to $550 on average, with a platinum chain costing up to 50% more.

More recently, the introduction of the Malhotra platinum segment implant allows for individual segment chains to be sutured together, thereby offering postoperative adjustability. This offers an advantage if additional weight needs to be implanted and allows for the addition of a segment, without the need for an explant surgery. This also could be useful to refine eyelid contour should a small segment be needed medially or laterally. The investigators propose that this new platinum segment option may offer more affordability compared with standard platinum chains [11]. The product is sold by Altomed in the United Kingdom (Altomed.com/product-category/implants/lidimplants/platinumlidimplants, Altomed, Boldon, UK).

Future avenues

As discussed previously, future studies should evaluate the use of the various eyelid weights, in particular the platinum chain and segments, with objective data that study the effects of weight loading on postoperative corneal topography and corneal astigmatism. Because many studies have been limited by small numbers of patients and varying fixation techniques, larger prospective studies would be beneficial.

Summary

Paralytic lagophthalmos can result from many etiologies and can have far-reaching effects on the day-to-day lives of patients who may suffer from dry eye syndrome, corneal ulcers, and the need to use lubricating eye drops frequently throughout the day. Without proper treatment, the exposure of the cornea can lead to blindness, a feared and severe complication. Fortunately, there are effective treatment options available to reduce lagophthalmos and help patients preserve their ocular function.

Upper eyelid loading with weight implants has been an established, effective surgical treatment option for those patients who fail more conservative treatment options. Although this procedure is not new, the initial pretarsal surgical approach has undergone many alterations and transitions in order to optimize functional and cosmetic outcomes for patients, while minimizing the risk of potential known complications. Common complications include migration, extrusion, allergy, bulging, poor cosmesis, and iatrogenic corneal astigmatism. This article focuses on discussing the refractive error changes associated with upper eyelid weight loading, which often is under-reported and under-recognized.

Refractive error changes in the form of iatrogenic induction of corneal astigmatism is a potential complication of upper eyelid weight loading, with an incidence of 11.5% [13]. In turn, this can lead to reduced visual acuity and reduced patient satisfaction. Although iatrogenic corneal astigmatism is a recognized entity, few studies exist that report on rates and objective measurements of corneal astigmatism in their complications. This article discusses the available studies in the literature that have focused on different surgical approaches and on materials that appear to have an effect on the frequency of corneal astigmatism as a complication of upper eyelid loading.

Currently, the most common surgical approach is the use of a gold weight with a pretarsal technique, which may have higher rates of corneal astigmatism compared with newer approaches and platinum implant options. A combined high tarsal and levator fixation surgical technique using a standard gold weight does not appear to induce corneal astigmatism. Platinum chains have been reported to be as effective as gold implants in reducing lagophthalmos and have fewer complications, including lower risk of corneal astigmatism. These 2 modifications to the classic pretarsal gold weight approach appear to be the optimal choices available for reducing the risk of iatrogenic corneal astigmatism. In

addition, new options, such as the platinum segment chain, now are available, and further studies are needed to investigate how this compares with current approaches and develops over time.

Although platinum has been shown to have superior outcomes in comparison to gold implants, the transition to utilizing platinum as the default choice in clinical practice has been limited. This most likely is due to the higher cost of platinum and few data reporting on the long-term outcomes of gold weight implants, which suggest higher rates of aesthetic complications and the need for revision surgery. Additional measures should be taken to help encourage the transition to platinum as the standard of care to help optimize patient outcomes and reduce the need for revision surgery.

From the authors' assessment of the literature, few studies incorporate the evaluation of refractive error changes and corneal astigmatism as a reported complication in association with upper eyelid weight loading for lagophthalmos. In addition, the studies that do exist are limited by small trials. Because refractive error changes can have such an important implication on patient satisfaction and quality of life, the authors believe that rates and objective measurements of corneal astigmatism are important measures that should be included in future studies. Further evaluation is needed to determine the optimal approach of surgical management for lagophthalmos that creates a balance between functional and aesthetic outcomes for the patient and minimizes complications of upper eyelid loading, including the risk for iatrogenic refractive error changes.

Clinics care points

- Patients should be aware of the approximately 11.5% risk of refractive error changes from iatrogenic corneal astigmatism following upper eyelid weight loading.
- Platinum weights are preferable because they have demonstrated a decreased risk of allergy, extrusion, and postoperative refraction changes (particularly with platinum chains).
- Placing the weight higher on the levator aponeurosis and tarsal plate also may decrease postoperative complications.

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Refractive Change after Upper Eyelid Surgery

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Keywords

Refractive change; Refractive error; Astigmatism; Blepharoplasty; Ptosis repair; Corneal topography; Keratometry; Eyelid surgery

Key points

- Eyelid malposition can affect corneal topography and thus refractive error.
- Upper eyelid surgery to correct ptosis and dermatochalasis can alter corneal topography, leading to postoperative long-term visual changes.
- Patients undergoing upper eyelid surgery should be counseled of the potential for visual changes after surgery.

Introduction

Upper eyelid ptosis and dermatochalasis are associated with impairment of vision and can be cosmetic concerns for patients as well.

Ptosis can be divided into 2 distinct categories: congenital and acquired. Congenital ptosis often is related to insufficient development of the levator muscle. Patients with congenital ptosis often require early correction with ptosis repair surgery to prevent amblyopia if the ptosis is severe enough to interfere with the visual axis. Acquired ptosis is most often aponeurotic, or involutional, in nature. Neurogenic, myogenic, and mechanical forms of acquired ptosis can occur, but generally are less common.

Ptosis repair surgeries, such as external levator repair and conjunctivomullerectomy, as well as blepharoplasty surgery to correct dermatochalasis, are medically indicated when they cause a significant decline in peripheral vision (Figs. 1 and 2). Although the significant portion of visual impairment from eyelid ptosis and dermatochalasis results from physical obstruction of the visual axis, more recent literature has demonstrated that upper eyelid pathologic conditions can induce corneal changes, which also can contribute to a change in vision in many patients.

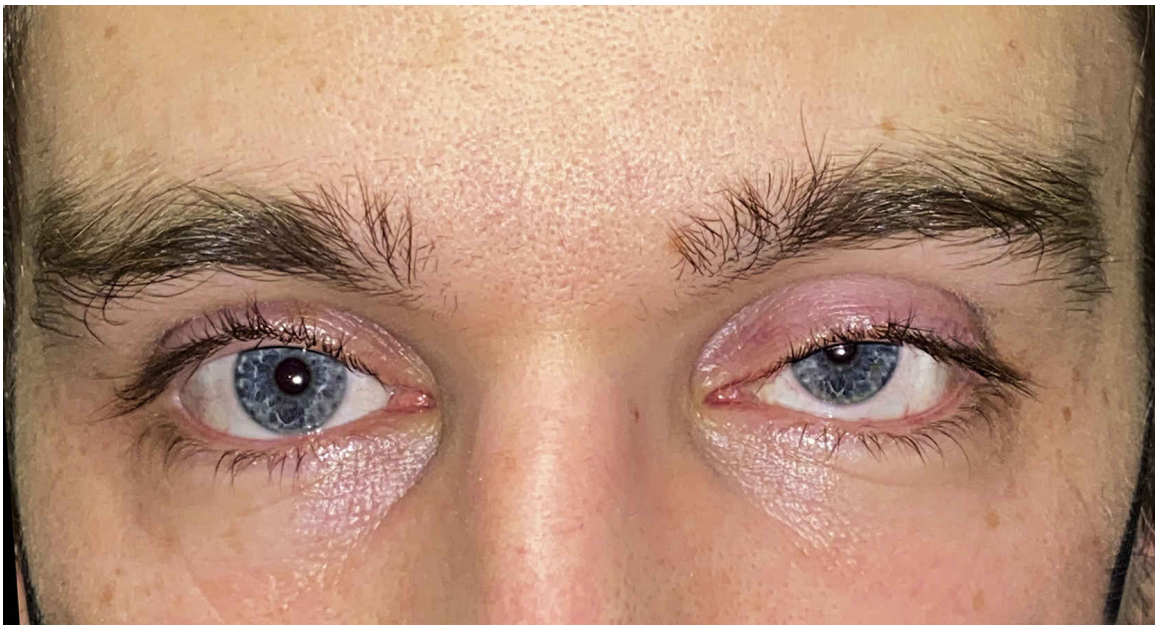

FIG. 1 Patient with upper eyelid ptosis of the left eye.

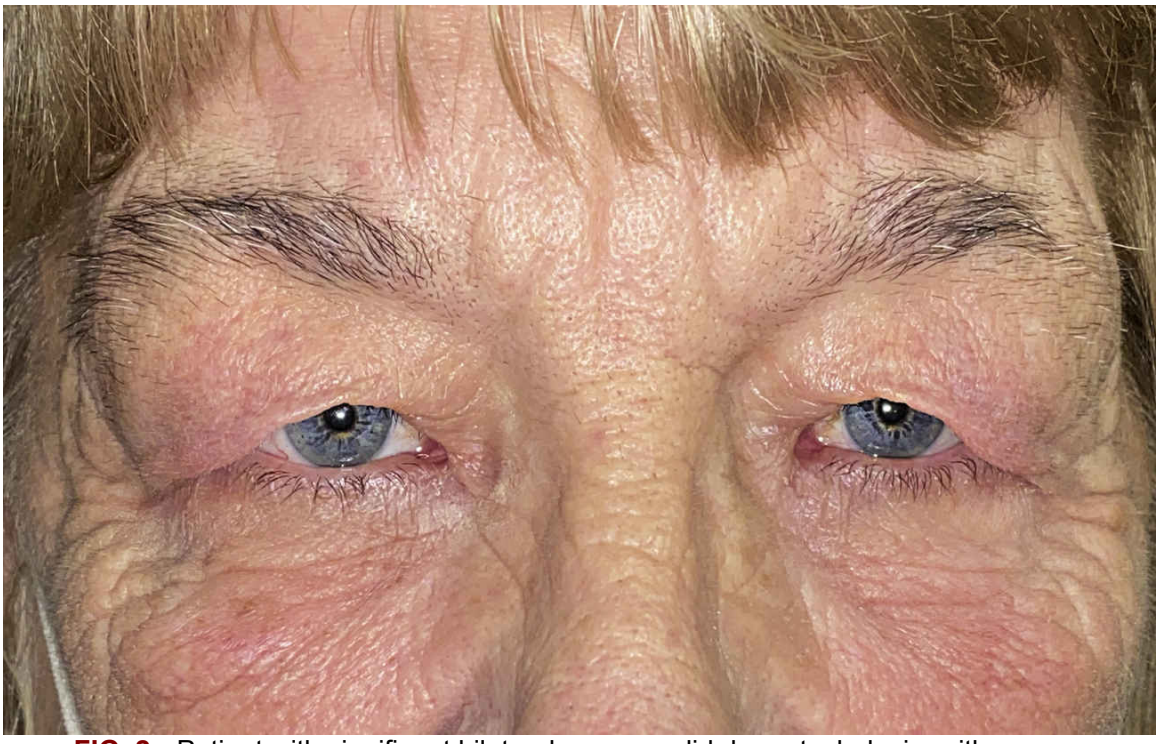

FIG. 2 Patient with significant bilateral upper eyelid dermatochalasis, with skin hooding over the eyelid margins.

Ptosis repair and blepharoplasty surgeries are the most common surgeries of the upper eyelid. Therefore it is critical for surgeons to understand the underlying pathophysiology of refractive changes caused by eyelid malposition, and to minimize the postoperative refractive changes various surgical interventions may induce.

Preoperative changes

Prior studies have demonstrated that eyelids can influence the shape of the cornea [1]. In particular, eyelid malposition and redundant upper eyelid skin have been noted to cause peripheral flatting of the cornea. This peripheral flattening can induce steepening of the central cornea in the 90° meridian [2,3] (Fig. 3). This finding of a change in corneal topography also has been demonstrated in studies looking at the effect of eyelid masses such as hemangiomas and chalazia, as well as implants such as gold/platinum weights [4].

Addressing any preexisting eyelid pathologic condition, therefore, is necessary before refractive surgeries to optimize visual outcomes [5]. Preoperative evaluation should include, at minimum, careful eyelid evaluation, cataract lens calculations, refractive error, and visual acuity to help decrease and prevent unexpected refractive changes.

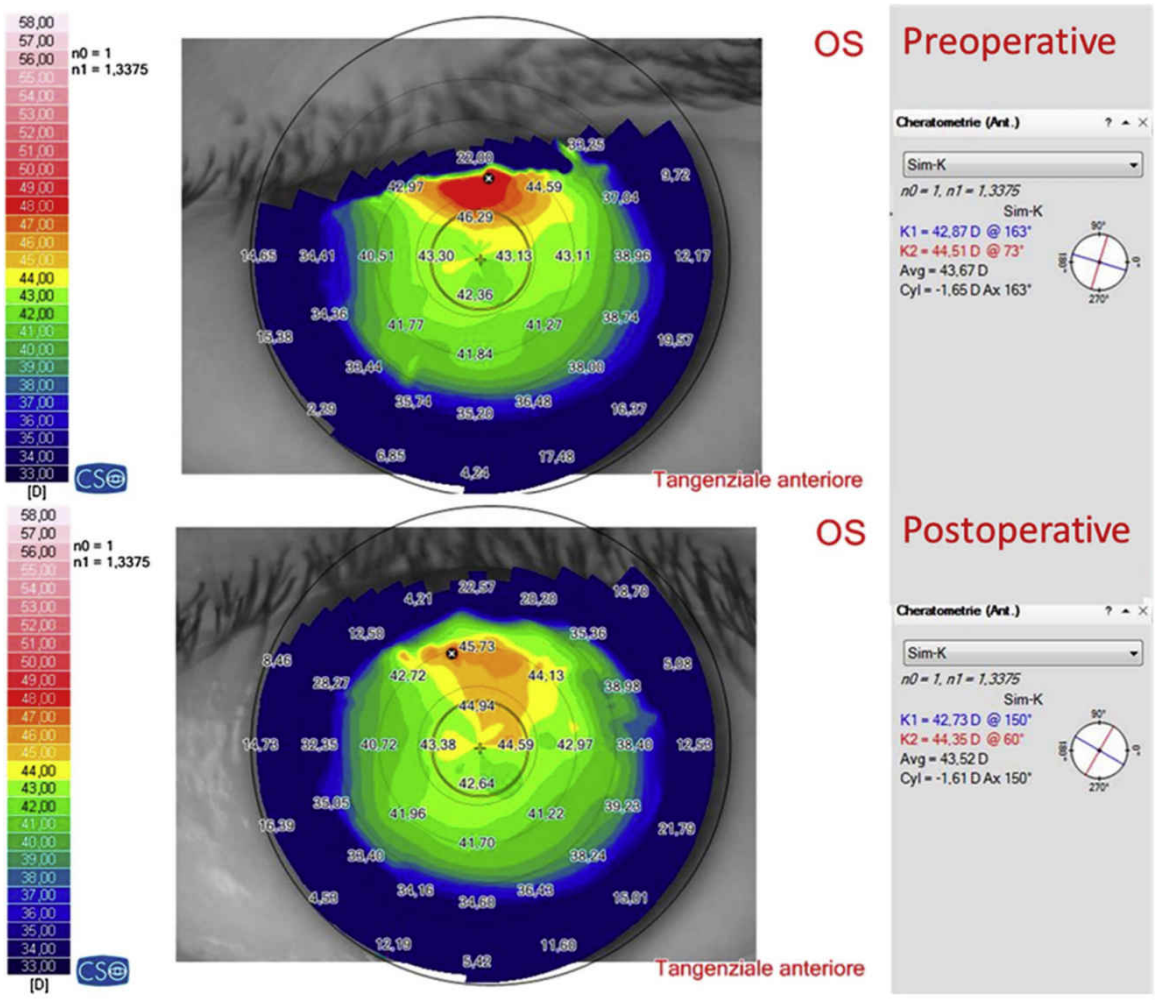

FIG. 3 Corneal topography of a patient with eyelid ptosis before and after ptosis repair. There is increased corneal steepening centrally before surgery (top corneal topography), which is flattened following surgery, as demonstrated on the bottom topography.
(*From* Savino G, Battendieri R, Riso M, Traina S, Poscia A, D'Amico G, Caporossi A. Corneal Topographic Changes After Eyelid Ptosis Surgery. Cornea. 2016 Apr;35(4):501-5; with permission.)

Postoperative changes

The literature has long demonstrated a qualitative change in vision following upper eyelid surgery, with the most common cause typically attributed to dry eyes. However, several studies have demonstrated changes in keratometry and corneal topography, which may also help explain this often underrecognized visual change.

Upper eyelid surgery, including ptosis repair and blepharoplasty, change the upper eyelid position and the upper eyelid contour. This change in eyelid position on the peripheral cornea and the tension applied by the upper eyelid change the force vectors and dynamics of the upper eyelid. A study conducted by Brown and colleagues demonstrated a change in corneal astigmatism of approximately 0.68 and 0.61 D, at 1 and 3 months postoperatively, in patients who underwent ptosis repair surgery. In contrast, a change in corneal astigmatism of 0.49 and 0.57 D was measured at 1 and 3 months postoperatively in patients who underwent blepharoplasty, using standard keratometry and corneal video keratography [6].

Zinkernagel and colleagues [7] also showed a statistical change in corneal astigmatism using computed corneal topography. The study further demonstrated a statistically significant difference between different types of surgery:

- Patients undergoing skin-only blepharoplasty were found to have the lowest incidence of postsurgical corneal topography change, with only 12% of patients affected with a mean dioptric change of 0.25 D.
- Blepharoplasty with medial fat pad reduction and blepharoplasty with reduction of the entire fat pad were associated with a mean dioptric change of 0.30 D in 37% and 50% of patients, respectively.
- Patients who underwent ptosis repair surgery were at the highest risk for refractive change with 62% of patients noting a median dioptric change of 0.30 D.
- No statistically significant change in astigmatism axis was found in this study in any of the aforementioned groups.

Limited studies exist looking at long-term outcomes following upper eyelid surgery. One retrospective qualitative study explored postoperative outcomes 1 year following surgery. Of the 106 patients recruited to the

study, 6 patients, or 5.7%, noted a subjective visual change 1 year following surgery. Of those patients, 3 patients noted worse vision not related to dry eye, 2 patients had improved vision, and 1 patient had a subjective inability to wear contact lenses [8]. Some studies have shown that refractive error changes after upper eyelid surgery can be long lasting. Measurable corneal astigmatism changes have been observed up to 3 months postoperatively after ptosis surgery or blepharoplasty [6]. In another study looking at corneal astigmatism after ptosis surgery, 72% of patients had astigmatism changes at 6 weeks postoperatively, and 20% continued to have such changes lasting up to a year [9].

Although there may be significant change in the power of corneal astigmatism as seen on corneal topography, it remains unclear if the degree of change is significant in the long term to cause permanent visual change long after surgery. These changes, in general, are thought to be secondary to the force applied by the eyelid on the cornea, and the subsequent reshaping once the eyelid is elevated and the pressure relieved on the cornea. As edema improves in the postoperative period, there also can be reasonable expectation of change in corneal topography. In addition, as skin continues to relax through postoperative healing and aging, the upper eyelid dynamics on the corneal surface may continue to change, although this remains a theoretic phenomenon.

Clinical relevance

Postoperative visual changes following uncomplicated upper eyelid surgery are not uncommon [10]. The most common causes in the early postoperative period are visually significant eyelid skin edema and dry eye, which typically resolve within 5 days to 3 weeks [8]. However, studies have demonstrated that persistent visual change can result due to changes in corneal topography following surgery.

Thus adequate counseling of patients undergoing either functional or cosmetic upper eyelid surgery is crucial [10]. For patients who are phakic and plan to undergo both cataract and upper eyelid surgery in close timing to each other, it is important to recognize that intraocular lens calculations may be affected by eyelid surgery. For optimal refractive outcome, electing to have upper eyelid surgery before cataract surgery may be a consideration. Patients who are pseudophakic and undergoing upper eyelid surgery may require refraction following surgery; this may be of particular importance in patients who are pseudophakic with a multifocal or a toric intraocular lens who have tried to minimize their postcataract refractive error. Such patients should be counseled that eyelid surgery may cause a small, but potentially significant, change in the quality of their vision. Therefore, adequate preoperative counseling of patients regarding this underrecognized occurrence can help allay shock and distress postoperatively and provide reassurance that in most instances the visual change will resolve without permanent sequelae within a few months.

Clinics care points

- The most common visual changes after routine upper eyelid surgery include dry eye and eyelid edema, which tend to resolve within 5 days to 3 weeks.
- Longer-lasting refractive errors can be attributed to changes in corneal astigmatism caused by a change in the pressure applied by the upper eyelid on the cornea; obtaining a corneal topography can better assess such changes.
- Patients undergoing upper eyelid surgery should be advised that approximately 50% of patients experience temporary refractive changes after surgery, and 20% can have residual effects up to a year.
- As more than 70% of patients can demonstrate astigmatic changes at 6 weeks after eyelid surgery, new glasses should be deferred until a delayed postoperative refraction can demonstrate stability.
- Careful preoperative evaluation including eyelid evaluation should be considered before refractive or cataract surgeries to minimize postoperative variations/errors in the desired postoperative refraction.

Acknowledgments

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Canalicular Stenosis Secondary to Chemotherapeutic Agents

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Keywords

Lacrimal drainage system; Canalicular stenosis; Nasolacrimal obstruction; Chemotherapeutic; Epiphora; Tearing; Docetaxel; 5-Fluorouracil

Key points

- Chemotherapeutic drugs have been shown to cause canalicular stenosis.
- Common hypotheses include drug-related inflammation, fibrosis, scarring, and eventually stenosis of the lacrimal system.
- Canalicular stenosis can lead to epiphora, which affects vision and vision-related quality of life.
- The standard treatment of canalicular stenosis is silicone tube intubation, with a potential Jones bypass tube placement or surgical intervention with dacryocystorhinostomy if the abnormality is severe.
- Being cognizant of chemotherapy-related canalicular stenosis and diagnosing it early can facilitate early intervention, prevent long-term scarring, reduce the need for invasive procedures, and minimize potentially poor outcomes.

Introduction

The lacrimal system of the eye is responsible for the production and drainage of tears that lubricate the ocular surface. It is lined by a highly proliferative mucous membrane, and the balance between the production and drainage determines whether an eye is well lubricated, dry, or has excessive tearing, also known as epiphora (Fig. 1). Epiphora can be a result of excessive tear production or reduced tear drainage (lacrimal outflow). Drainage insufficiency is primarily due to an anatomic abnormality, including a partial or complete blockage along the lacrimal drainage system, or eyelid malposition [1].

Tears drain through the puncta on each eyelid, through the upper and lower canaliculi, into the common canaliculus and lacrimal sac, and finally exit through the nasolacrimal duct. Canalicular stenosis can be a congenital abnormality or due to eyelid inflammatory syndromes (postherpetic, viral), trauma, punctal plugs, and canaliculoliths or acquired through exposure to certain medications. Several chemotherapeutic drugs have been shown to cause epiphora [1–14]. Medications that are known to cause canalicular stenosis include

- Chemotherapeutic agents, such as docetaxel, 5-fluorouracil (5-FU), and mitomycin-C (MMC)[1–7]
- Glaucoma medications, such as pilocarpine, timolol, and dorzolamide [15,16]

Chemotherapeutic agents known to cause canalicular stenosis

5-Fluorouracil

5-FU blocks the function of thymidylate synthetase leading to the inhibition of DNA synthesis. It is commonly used in the treatment of gastrointestinal, breast, genitourinary tract, and skin cancers [12,13]. Some of the side effects caused by 5-FU include anorexia, nausea, dermatitis, thrombocytopenia, and ocular side effects such as conjunctivitis, cicatricial ectropion, circumorbital edema, and dacryostenosis, which was first described in 1987 [13,14]. 5-FU is systemically absorbed and secreted into the tears. It is hypothesized that the secretion of F-5U into tears and its subsequent passage through the lacrimal drainage system causes canalicular stenosis. The mechanism for this is theorized to be secondary to chronic inflammation and acute inflammatory edema, leading to punctal and canalicular scarring and possible long-term stenosis if severe or untreated [12].

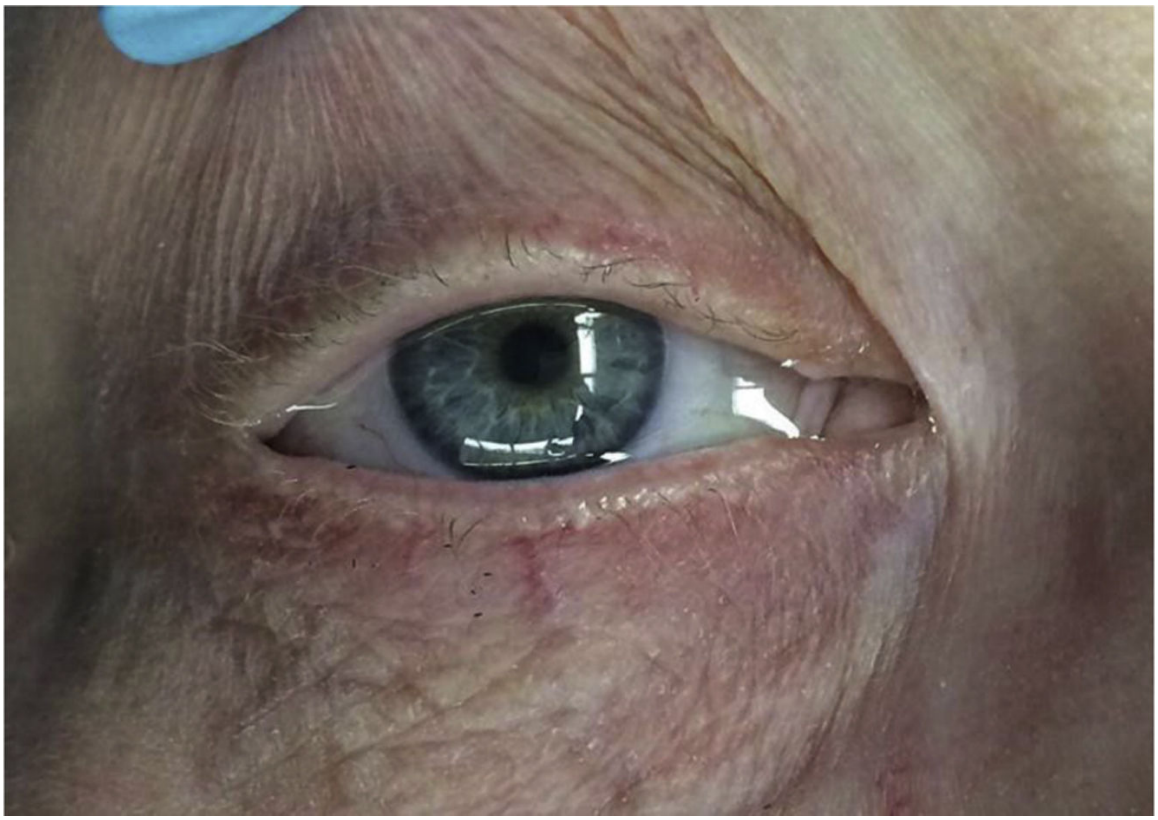

FIG. 1 Evaluation of the eye revealing an elevated tear meniscus. (*From* Enghelberg M., Burkat C.N. Canalicular Obstructions and Management. In: Cohen A., Burkat C, eds. Oculofacial, Orbital, and Lacrimal Surgery. Springer, Cham; 2019.)

Mitomycin-C

MMC is a chemotherapeutic antibiotic that cross-links DNA base pairs adenine and guanine, inhibiting the synthesis of DNA. It has been used to treat several ocular conditions, including conjunctival corneal intraepithelial neoplasia [17], primary acquired melanoma [18], as well as glaucoma [19] and pterygium surgeries [3]. Punctal-canalicular stenosis secondary to MMC was first described in 2003 in a case report of a 62-year-old woman who was treated with MMC for corneal epithelial dysplasia [20]. Canalicular stenosis was attributed to the inflammatory reaction caused by MMC, which likely led to fibrosis and stenosis of the punctal-canalicular system [20]. An additional theory suggests that MMC can cause nonspecific inflammation, leading to epithelial sloughing and subepithelial fibrosis, eventually resulting in canalicular stenosis [3].

Docetaxel

Docetaxel (trade names: Taxotere, Docecad) is a cell-specific cytotoxic agent used in the treatment of breast and lung cancer and interferes with the process of mitosis by binding to microtubules and preventing cell division. Some well-documented side effects of the drug include neutropenic fevers, anemia, thrombocytopenia, myalgia, anorexia, and peripheral neuropathy [21].

One of the ocular side effects of docetaxel is epiphora, which was first described in 2001 in patients who were being treated with weekly infusions, for typically 10 or more cycles [22]. It was noted that even when docetaxel was discontinued after several months, the epiphora did not completely resolve in some patients. Subsequent studies since then demonstrated as high as 60% of patients on docetaxel have symptoms of epiphora [23]. It is hypothesized that docetaxel is secreted in the tears and induces fibrosis of the mucous-lined lacrimal drainage system, causing punctal and canalicular stenosis [22]. Alternatively, the canalicular stenosis could be an overall systemic side effect of the drug, as it has been known to cause fibrosis in other areas of the body [22,23]. Esmaeli and colleagues also noted that 77% of patients undergoing weekly docetaxel reported epiphora, compared with 11% who had infusions every 3 weeks [24]. The milder degree of stenosis in the latter group may also further suggest that docetaxel be administered every 3 weeks, rather than weekly, to minimize canalicular complications. If weekly infusions are required, then early referral from the treating oncologist and silicone intubation should be performed once epiphora begins.

In summary, the leading hypotheses for the mechanism of canalicular stenosis secondary to chemotherapeutic agents involve inflammation, fibrosis, and eventually stenosis of the canalicular system.

Significance of epiphora secondary to canalicular abnormality

An optimal tear film, approximately 3 μm, plays a key role in the optics of the eye [25]. Just as dry eye syndrome can have a significant impact on visual quality of life (QOL) [26,27], epiphora has also been shown to affect QOL [28], although it remains an underrecognized problem. One of the reasons epiphora is underrecognized is likely due to the fact that it does not often cause a decline in visual acuity on routine testing.

The Monk score is a subjective scale from 0 to 4 that gathers information about the severity of epiphora [29]. The Glasgow Benefit Inventory (GBI) questionnaire, developed by Robinson and colleagues, has been validated to assess patient outcomes after oculoplastic procedures [30,31]. The Lac-Q is another questionnaire specifically to assess the social impact and lacrimal symptoms in patients with nasolacrimal duct obstruction [32].

Shin and colleagues found that outdoor activities were the most affected by epiphora, likely due to reflex tearing from external stimuli such as wind when outdoors, which can add to the already existing epiphora [28]. Activities such as reading can be routinely affected due to an increase in the tear meniscus when looking down, making it difficult to have a clear view. In addition, epiphora can cause blurry vision, difficulty with daytime and nighttime driving, sore eyelid skin and dermatitis from the constant wiping of tears, and can be embarrassing for patients, as it can seem that they are tearful or crying [33]. Studies have shown that patients with epiphora experience activity limitations and visual disability similar to those patients who are awaiting cataract surgery on their second eye [28,34,35]; this emphasizes the need to recognize epiphora and treat the underlying cause to improve outcomes as well as QOL.

Management of canalicular stenosis

The management of epiphora involves evaluation of the tear film on the ocular surface, the tear meniscus, and evaluating fluorescein dye disappearance [1]. Dilation and irrigation of the lacrimal system occurs early in the process of evaluating canalicular stenosis and obstruction (Fig. 2). Careful attention to these main aspects when performing diagnostic probing is critical to guiding the surgical approach (Fig. 3):

- Presence and degree of punctal stenosis
- Severity of stenosis of the canaliculus (often graded 1+ mild to 4+ severe/complete)
- Focal area versus diffuse stenosis
- Distance of stenosis/obstruction from punctum (severe obstruction in the proximal 5 mm often warrants conjunctivodacryocystorhinostomy [CDCR] surgery)

With topical medications, the upper lacrimal system tends to be more affected than the lower lacrimal system, as it is closer to the conjunctiva and fornix [36]. Canalicular stenosis, when diagnosed early, can be managed with silicone tube intubation (either monocanalicular or bicanalicular) (Fig. 4), but if the obstruction is severe or complete by probing on examination, then a permanent glass pyrex (Jones) tube placement may be required (Fig. 5). Sometimes severe stenosis or obstruction in the canaliculi may require a surgical correction with dacryocystorhinostomy (DCR), and if more proximal obstruction, then CDCR or canaliculodacryocystorhinostomy are used to treat nasolacrimal duct obstruction [1]. Focal distal canalicular obstruction, in some cases, can be managed with trephination or excision of scar along with silicone tube placement [1].

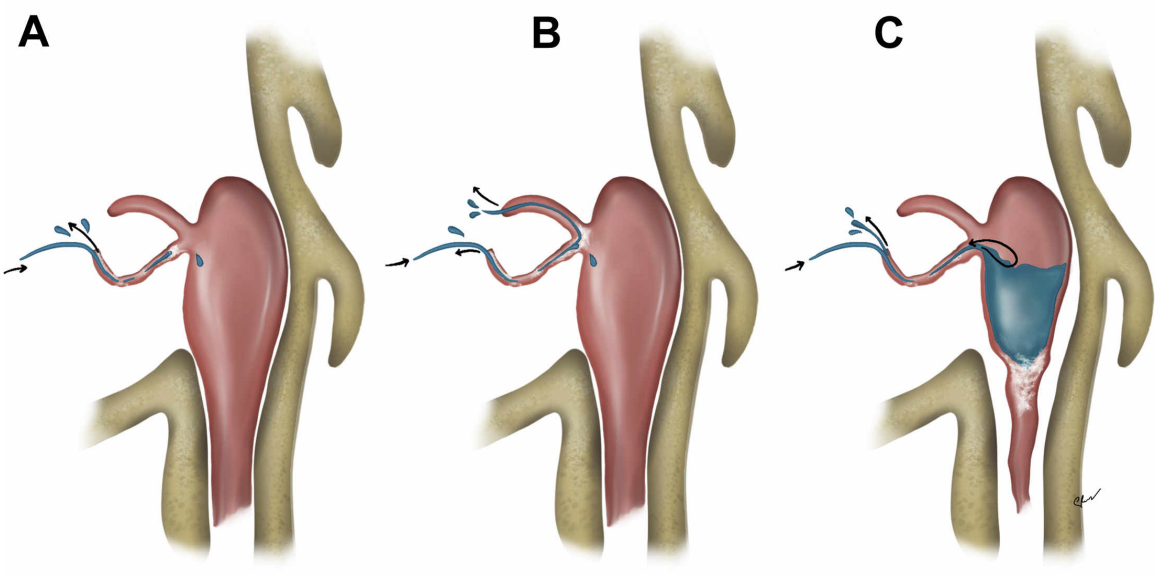

FIG. 2 Lacrimal system irrigation findings: inferior punctal stenosis and focal areas of canalicular stenosis result in reflux from the same punctum (*A*); irrigation demonstrates diminished drainage and partial reflux from the same and opposite canaliculus if common canalicular stenosis is present (*B*); partial reflux from the upper canaliculus may indicate nasolacrimal sac and duct obstruction (*C*).

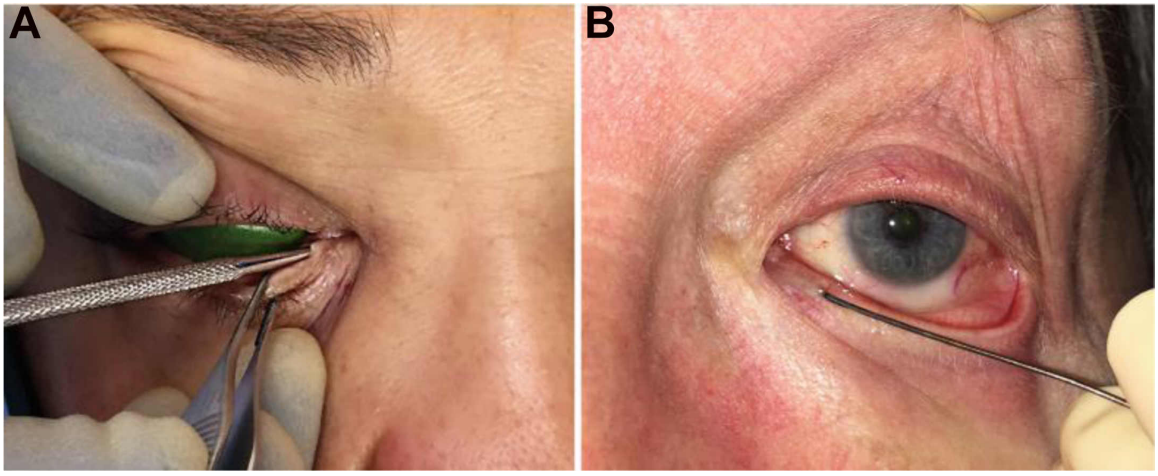

FIG. 3 Dilation of inferior punctum with a punctal dilator (*A*); Bowman probe being passed through the punctum to evaluate patency of the punctum and canaliculus (*B*).
(*From* Enghelberg M., Burkat C.N. Canalicular Obstructions and Management. In: Cohen A., Burkat C, eds. Oculofacial, Orbital, and Lacrimal Surgery. Springer, Cham; 2019.)

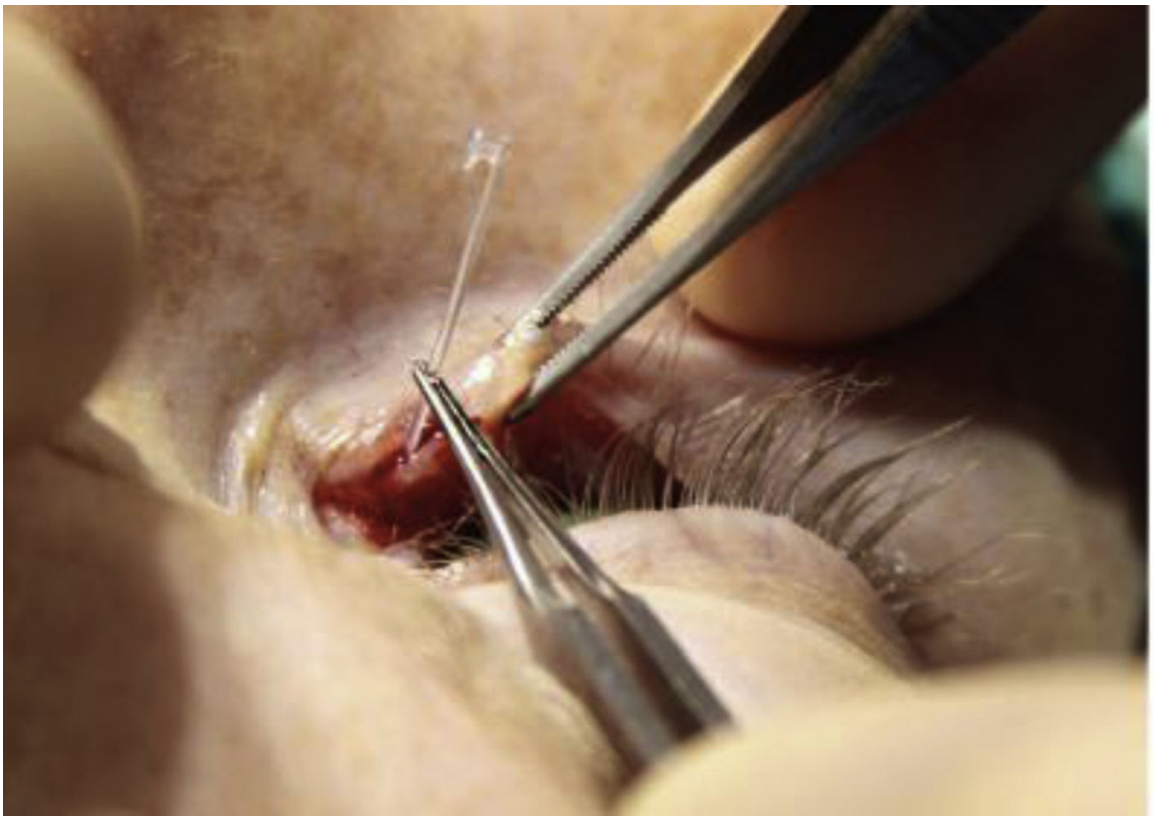

FIG. 4 A monocanalicular silicone stent being placed in the inferior canaliculus after canaliculotomy.
(*From* Enghelberg M., Burkat C.N. (2019) Canalicular Obstructions and Management. In: Cohen A., Burkat C. (eds) Oculofacial, Orbital, and Lacrimal Surgery. Springer, Cham; 2019.)

Using the GBI, Monk, and Lac-Q questionnaires, studies have shown that patient satisfaction and QOL were improved after DCR for nasolacrimal duct blockage and epiphora [29,32,33]. For patients who are affected with canalicular stenosis but do not wish to undergo surgery or have characteristics and comorbidities that make surgery risky, treatment with botulinum toxin can be offered [37,38]. Botulinum toxin can be injected into the main and accessory lacrimal glands, blocking the presynaptic release of acetylcholine, leading to a decrease in tear production and secretion. Preferably, the lateral eyelid is everted, and the palpebral lobe in the superolateral fornix is injected; this avoids the anterior approach injection that may result in iatrogenic ptosis before levator muscle chemodenervation. A few studies have shown that 63% to 71% of patients with epiphora have significant improvement in their symptoms with 2.5 to 5 units of botulinum toxin [37,38].

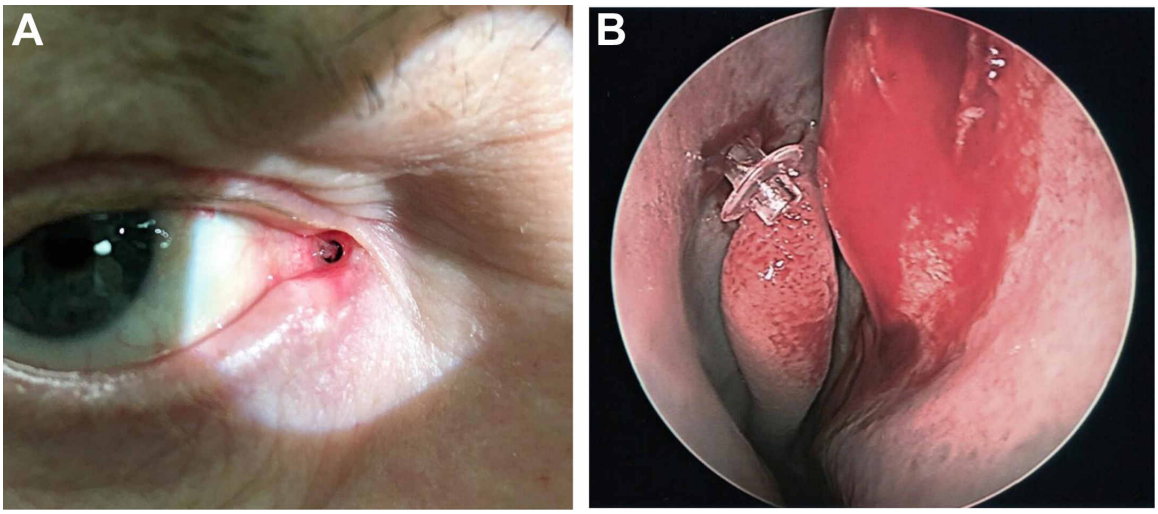

FIG. 5 Exterior view of a permanent pyrex Jones tube in the medial canthus (*A*); interior view of the Jones tube in place in the middle meatus (*B*). (*From* Enghelberg M., Burkat C.N. (2019) Canalicular Obstructions and Management. In: Cohen A., Burkat C, eds. Oculofacial, Orbital, and Lacrimal Surgery. Springer, Cham; 2019.)

Understanding the risks of canalicular stenosis secondary to chemotherapeutic agents is essential, as early diagnosis can aid in reducing the risk of permanent scarring or damage to the lacrimal drainage system; this is critical as long-standing damage and fibrosis could lead to the need for more invasive procedures or surgeries and potentially poor outcomes. Therefore, close communication with oncologists can help increase their awareness of this concern and assist in early referral for management.

With 5-FU, epiphora was observed in as high as 50% of patients who were taking the medication [39]. Further, higher doses and longer durations of the medication were noted to have obvious canalicular fibrosis [2]; this emphasizes the need for early recognition and intervention. Interestingly, one study showed resolution of symptoms with discontinuation of therapy [40]. Such resolution may suggest reversibility of the underlying process. One hypothesis is that 5-FU could cause inflammation of the canalicular system, without long-term fibrosis; hence, discontinuation of the drug helps with resolution of epiphora [39].

Ten to fourteen percent of patients who were taking topical MMC 4 times a day for various durations (but for at least 7 consecutive days) were noted to have punctal stenosis [41]. In patients who were on MMC 4 times a day for 2 weeks, the incidence of punctal or canalicular stenosis at 1 month was noted to be 64% [3]. Although it is thought that MMC causes

canalicular stenosis through an inflammatory process leading to fibrosis, it should be noted that MMC is commonly used after ocular surgeries, such as pterygium excision, for its antifibrotic properties [41,42].

As mentioned previously, studies have shown that the duration and dosage of docetaxel affects the risk of canalicular stenosis. Compared with patients who received docetaxel once every 3 weeks for a short period of time, those who received it once every week or once every 3 weeks, but for a longer duration, were at a higher risk of acquiring canalicular stenosis [22,23,43,44]. Patients on weekly docetaxel were more likely to have canalicular stenosis compared with those on triweekly docetaxel [23,45]. Thirty-nine percent of patients on triweekly docetaxel had epiphora, and none of them had evidence of canalicular stenosis, whereas 69% of patients in the weekly docetaxel group experienced epiphora, and one-third of them were noted to have moderate-to-severe canalicular stenosis [23]. With docetaxel, it was noted that once the canaliculi were severely narrowed, the process was typically irreversible and required surgical intervention, such as a CDCR with placement of permanent pyrex glass (Jones) tubes to treat the obstruction and reestablish lacrimal outflow [43]. These surgeries can improve, but may not completely eliminate, tearing for the patient, and may also subject the patient to potential lifelong complications with the pyrex tube. Therefore, the clinician's goal is to reduce the need for surgery by being aware of this side effect of docetaxel, recognizing epiphora and canalicular stenosis early, and recommending bicanalicular silicone stent intubation to prevent permanent canalicular closure [43].

Summary

Several chemotherapeutic agents have been noted to cause punctal and canalicular disruption in the form of inflammation, fibrosis, or a combination of both, leading to epiphora. This disruption is an underrecognized issue, and efforts to improve screening and early recognition need to be established. Unfortunately, by the time patients are referred to the appropriate surgeon, they may have been suffering from canalicular stenosis for many years. Therefore, all patients with tearing symptoms should be routinely asked if they are currently being, or have previously been, treated with systemic chemotherapy. Some patients may benefit from prophylactic silicone tube intubation while they are undergoing treatment with chemotherapeutic agents, especially if they need to be on higher doses or require the drug for longer durations [46]. Delays in recognition could lead to advanced abnormalities, requiring more invasive interventions and potentially worse outcomes. Although a baseline evaluation by an ophthalmologist before starting these medications may not be necessary, a routine follow-up should be recommended to aid in the early recognition and diagnosis of canalicular stenosis, as well as timely interventions.

Clinics care points

- When evaluating patients with symptoms of epiphora, inquire about current or past use of chemotherapeutic agents, including MMC, 5-FU, and docetaxel.
- When examining patients exposed to the aforementioned chemotherapeutic agents, carefully examine the lacrimal system, specifically the caliber of the puncta and canaliculi, along with dilation and irrigation to assess stenosis and/or obstruction.
- Once symptoms of epiphora manifest, early consideration of silicone tube intubation can reduce the risk of permanent scarring and obstruction, as well as improve vision-related QOL.
- The silicone tubes (stents) should generally be left in place for the duration of chemotherapy.
- In cases of severe canalicular stenosis, surgical intervention with a dacryocystorhinostomy or CDCR may be necessary.
- Temporary relief of epiphora may be achieved by focal injection of the lacrimal glands with botulinum toxin.

Acknowledgments

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Uveitis

OUTLINE

Optical Coherence Tomography Angiography in White Dot Syndromes

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Optical coherence tomography angiography; OCTA; White dot syndromes

Key points

- OCTA is a useful clinical tool for diagnosing and monitoring patients with white dot syndromes.
- Specific findings are discussed for birdshot chorioretinopathy (BSCR), multiple evanescent white dot syndrome (MEWDS), punctate inner choroiditis (PIC), multifocal choroiditis (MFC), serpiginous choroiditis (SC), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and acute zonal occult outer retinopathy (AZOOR).
- Each disease covered includes clinical presentation, examination findings, and descriptions of standard multimodal imaging and optical coherence tomographic angiography (OCTA) findings.

Introduction

The white dot syndromes (WDS) are a group of uncommon posterior uveitides characterized by inflammation within outer retina, retinal pigment epithelium (RPE), choroid, or a combination of these structures [1]. WDS appear as yellow-white lesions within the fundus. Patients may present with blurred vision, photopsias, visual field defects, or visual acuity change that can range from mild to severe impairment [1,2]. The WDS have distinct features but share certain characteristics and often present a diagnostic and therapeutic challenge for clinicians. Hypothesized causes include autoimmunity or genetic predisposition, followed by an inciting environmental event like a viral infection or vaccination [2]. The WDS may present in one or both eyes, and when bilateral, there may be asymmetry. The age of onset generally is greater than 50 years, but can range from the second to the sixth decade of life. Anterior chamber and vitreous inflammation is uncommon but can be seen in certain WDS. Various imaging techniques are used for the diagnosis and monitoring of WDS, including spectral domain optical coherence tomography (SD-OCT or OCT), fluorescein angiography (FA), fundus autofluorescence (FAF), indocyanine green angiography (ICGA), and electroretinography [1].

FA and ICGA are the current gold-standard vascular imaging techniques that provide 2-dimensional visualization of blood flow in the retinal and choroidal vessels, respectively, and can help in the diagnosis of WDS. These techniques are useful for detecting patterns of vascular pathology evidenced by dye pooling or staining [3]. Optical coherence tomography angiography (OCTA) is a newer imaging technology that allows for 3-dimensional visualization of choroidal and retinal structures and concurrent evaluation of vascular flow, thereby evaluating normal function as well as pathologic conditions. OCTA has been used clinically for myriad conditions, including age-related macular degeneration, diabetic retinopathy, artery and vein occlusions, and glaucoma [3]. In WDS in particular, OCTA has been useful in confirming findings seen with other imaging modalities and providing more insight into the pathogenesis and features that distinguish the WDS from each other. In this article, we will discuss the OCTA findings described in certain WDS including birdshot chorioretinopathy (BSCR), multiple evanescent white dot syndrome (MEWDS), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous chorioretinopathy (SC), and

punctate inner choroiditis (PIC) and comment on the implications for diagnosis and management of these conditions.

Overview

OCTA is an expansion from the imaging processes of OCT that allows visualization of flow through different segmented areas of ocular tissue [4]. The basis of OCTA relies on the reflectance of a light source off the surface of moving blood cells, eliminating the need for dyes [5]; this allows for noninvasive visualization of the retinal and choroidal microvasculature [2,3].

OCT technology, developed in 1999, is an imaging modality that creates cross-sectional representations of tissue from various consecutive scans at varying depths. Initially, OCT images were gathered through time domain (TD) detection, but later advancements in imaging have led to Fourier domain (FD) detection, which includes both spectral domain (SD) and swept source (SS) types, that allows for faster detection [5,6]. These methods rely on simultaneous analysis of tissue reflectance, rather than relying on time-intensive sequential imaging [7]. The basis of OCTA is to repeatedly scan a region and then examine the resultant images for changes. Stationary tissue structures will show little change, whereas moving structures, namely, the flow of blood through vessels, can show changes from one image to the next [4]. Different wavelengths are used to generate these representations of flow. Shorter wavelengths (SD-OCT of near 800 nm) penetrate less and cause more scatter from media opacities, and longer wavelengths (SS-OCT of near 1050 nm) have higher penetrance through deeper tissue, but lower axial resolution [4,8]. As the images produced are 3-dimensional, it is possible to localize and delineate structures and pathologies. En face images can be scrolled through like a cube scan, from the internal limiting membrane (ILM) to the choroid, to view particular layers of interest. Scans are produced in 6 seconds, versus 10 to 30 minutes for the FA and ICGA [5]. OCTA has the potential to generate images with higher contrast and resolution of the microvasculature than conventional FA. Overall, OCTA is less expensive to perform, faster, less invasive, and produces higher resolution images than either FA or ICGA. As of 2017, 2 OCTA devices have been approved by the US Food and Drug Administration: AngioVue (Optovue, Inc, Fremont, CA, USA) and AngioPlex (Zeiss, Carl Zeiss Meditec AG, Jena, Germany).

Limitations of OCTA are mostly due to the speed at which OCT B-scans can be obtained. The use of FD-OCT systems decreases this constraint, as imaging speeds are higher than TD-OCT systems [2,9]. Areas of slow blood flow such as microaneurysms, leaks, or fibrotic choroidal

neovascular membranes (CNVMs) fall below the minimum threshold of detection. Increased time between scans not only decreases the movement threshold but also increases background artifacts. Image artifacts can be caused by nonerythrocyte motion, such as patient movement. In addition, structures that block light can obscure deeper tissues, including larger vessels, hemorrhage, and blinks [3]. Field of view ranges from 2 × 2 mm to 12 × 12 mm, although resolution decreases as the field of view widens. Thus, large pathologic conditions may not be completely contained within a single scan or imaged at sufficient resolution for detailed evaluation [3].

Cross-sectional and en face visualizations of the posterior circulation

Optovue AngioVue system technology is based on the AngioVue Imaging System (Optovue, Inc, Freemont, CA, USA), using the split-spectrum amplitude-decorrelation angiography algorithm. Amplitude decorrelation assesses the difference in amplitudes over time between 2 different OCT B-scans over the same area to calculate motion [4]. The split-spectrum amplitude-decorrelation technique divides an acquired image into an exponentially greater number of B-scans, thereby significantly amplifying the decorrelation analysis. This averaged technique reduces background noise and improves visualization of the retinal and choroidal vasculatures [5]. AngioVue provides a default angiographic display scheme that defines en face angiographic slabs relative to a simplified set of reference planes (Fig. 1). The current software can reliably segment the acquired angiographic slabs using these reference planes. These planes include the ILM, outer boundary of the inner plexiform layer (IPL), and the "RPE reference," which is the best fit surface under the RPE and approximates the Bruch membrane position. The 4 default en face display slab definitions are as follows:

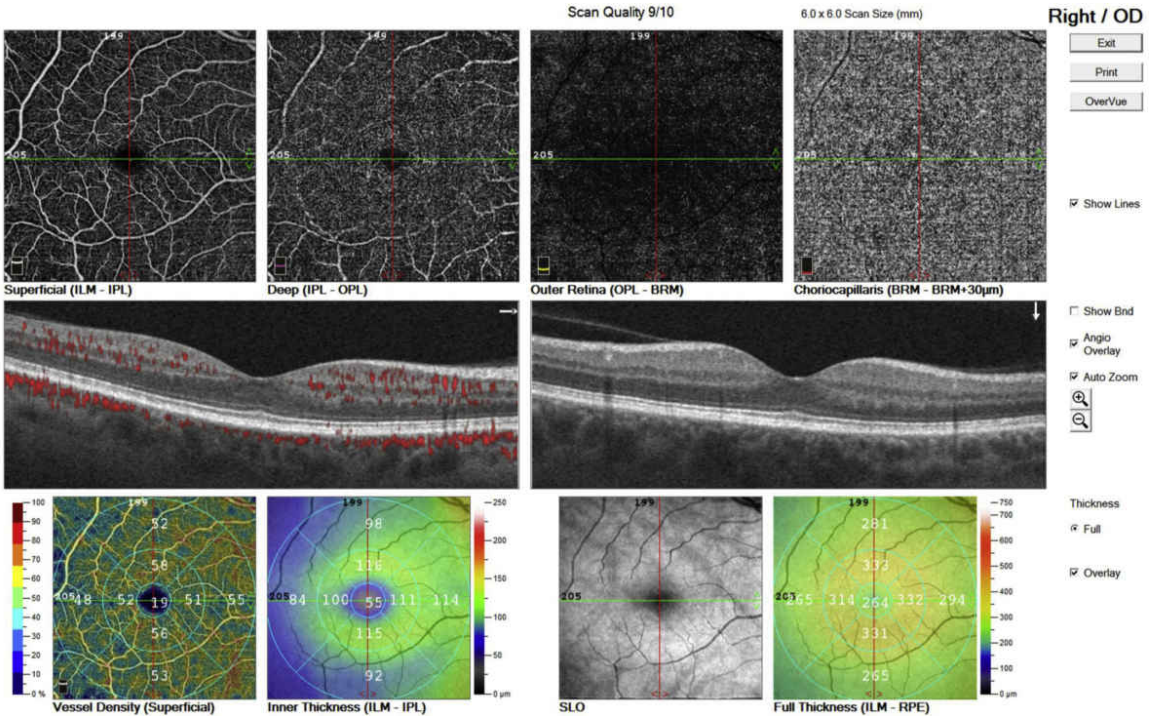

FIG. 1 Default angiographic display scheme, depicting findings in a patient without retinal pathologic condition. This 6 × 6-mm scan shows the 4 default slab images of the superficial, deep, and outer retina, as well as the choriocapillaris. Also included are OCT individual line scans, one including angio overlay, as well as analyses of vessel density and retinal thickness.

1. Superficial retinal capillary plexus (SCP): 3 µm below the ILM to 15 µm below the IPL
2. Deep retinal capillary plexus (DCP): 15 to 70 µm below the IPL
3. Outer retina: 70 µm below the IPL to 30 µm below the RPE reference
4. Choriocapillaris: 30 to 60 µm below the RPE reference. [2].

In the following sections we describe the individual WDS and OCTA findings in each.

Birdshot chorioretinopathy

BSCR is a bilateral chronic disease with a strong association to HLA-A29. The name is derived from the characteristic deep yellow-white lesions most often surrounding and nasal to the optic disc in a shotgun-spray distribution. It is observed that 84% of patients present after age 40 years, with a mean age of 53 years [10]. Patients often present with decreased vision, floaters, nyctalopia, and photopsias [11]. Cystoid macular edema (CME) is common, present in 84% of patients in one study, as is cataract formation and visual field defects; less common is subretinal neovascularization [10].

On FA, the lesions may show no angiographic abnormality or may have early blockage and late staining. Retinal venule leakage often is seen, as well as hyperfluorescence of the optic disc [11]. ICGA shows characteristic hypocyanescent, well-circumscribed lesions often more numerous than seen on clinical examination [12]. FAF often shows hypoautofluorescent lesions correlating well with those seen in ICGA.

OCTA performed using a prototype Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) has been evaluated in patients with BSCR, with one study analyzing 64 affected eyes. Capillary loops were the most common findings, with 60% of eyes showing loops in the SCP and 76% showing loops in the DCP. Telangiectatic vessels were seen in the SCP in 44% of eyes, and the DCP in 66% of eyes. Increased intercapillary spaces with decreased blood flow and partially nonperfused areas also were seen (Fig. 2). The microvascular macular changes may explain or contribute to the frequent finding of CME in patients with BSCR [13]. A separate study used AngioVue OCTA software to evaluate the choriocapillaris (CC) of patients with macular birdshot lesions finding corresponding disruption of the RPE and distinct flow voids in the CC at each lesion, thought to be either atrophy of the CC or flow below the detectable threshold of OCTA [14].

Multiple evanescent white dot syndrome

MEWDS is an acute, unilateral inflammatory disease of the outer retina, primarily involving the ellipsoid zone (EZ) and outer nuclear layer [15], with extension to the inner retinal layers and choroid [16]. MEWDS primarily occurs in healthy, young adult women, often after a viral illness, although it may develop at any age and in any gender [15–17]. Presenting symptoms include blurred vision, photopsia, dyschromatopsia, and temporal vision loss or scotomas [15–17]. On fundoscopy, patients have poorly demarcated yellow-white lesions at the RPE or outer retina and foveal granularity [15,16]. FA shows hyperfluorescent lesions in the midretina in a wreathlike configuration. ICGA shows hypocyanescent lesions, often in greater numbers than FA [15,16]. OCT reveals accumulation of hyperreflective material on the RPE and outer nuclear layer with disruption to the EZ [15–17]. FAF shows hyperautofluorescence of active lesions that fades in later stages with speckled hypoautofluorescence often remaining in the macula [15]. The pathogenesis of MEWDS is debated. MEWDS was formerly considered a chorioretinitis owing to evidence of choroidal hypoperfusion or nonperfusion on ICGA. OCTA confirms decreased blood flow to the CC and deep capillary plexus [12,17]. However, these areas of hypoperfusion do not correlate with ICGA lesions, suggesting they are a consequence of primary RPE dysfunction rather than choroidal inflammation [16]; this corroborates previous reports of photoreceptor dysfunction seen on electrophysiology [16]. Thus, multimodal imaging findings, including OCTA, suggest that damage to the RPE underlies the pathogenesis of MEWDS, rather than primary choroid dysfunction. MEWDS generally is self-limiting. OCTA may play a useful role in observing disease progression, as flow densities in the deep capillary plexus and CC should increase as the lesions resolve. OCTA also has been used to monitor regression of CNVMs, a rare complication of MEWDS [16].

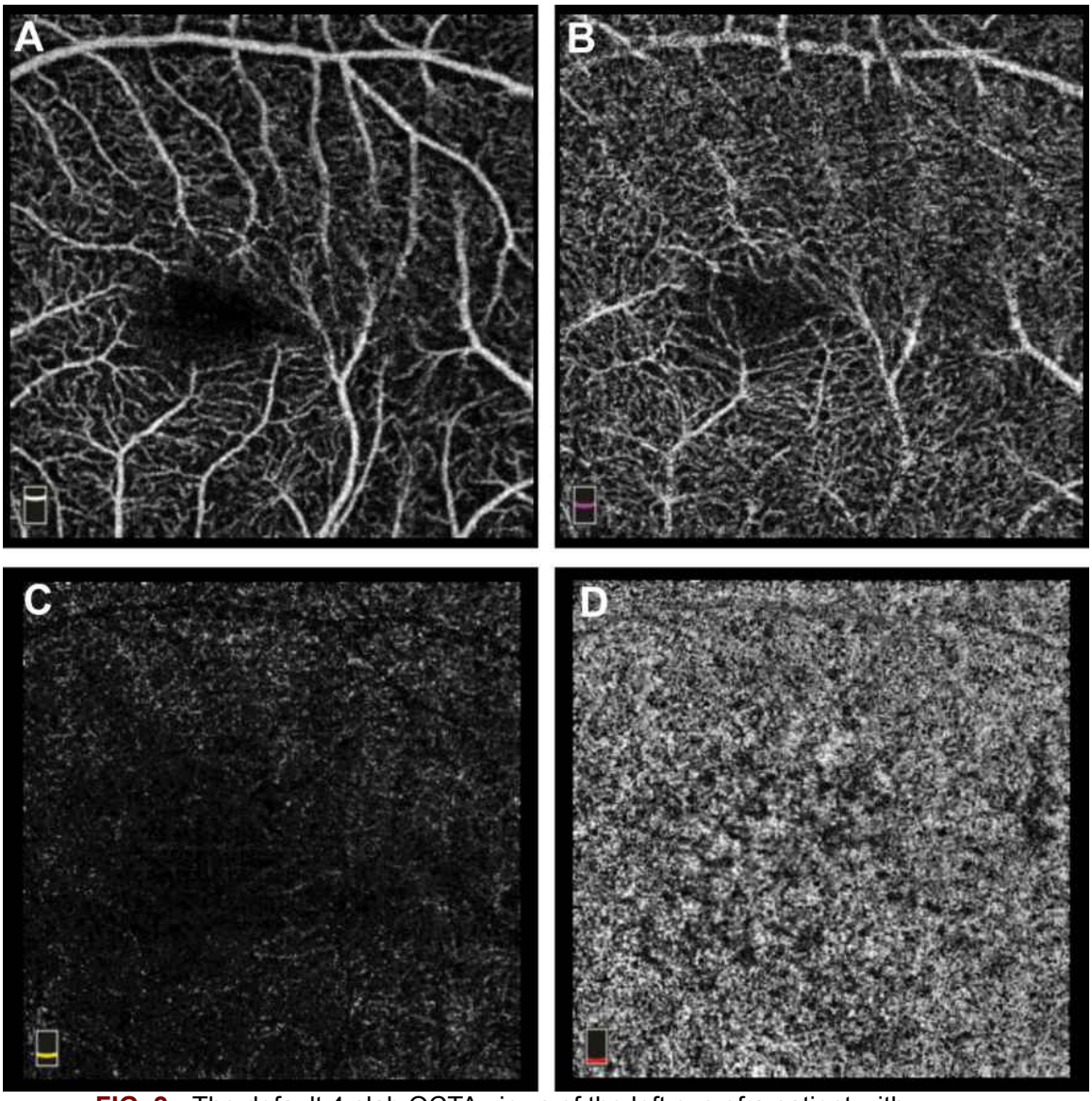

FIG. 2 The default 4-slab OCTA views of the left eye of a patient with BSCR. Superficial (*A*) and deep (*B*) capillary plexus both show dilated capillaries and increased intercapillary space. The outer retinal slab (*C*) has no characteristic changes. The choriocapillaris slab (*D*) shows areas of stippled hypoperfusion, although there are no characteristic areas of hypoperfusion correlating with birdshot lesions.

Punctate inner choroiditis

PIC has some degree of overlap with multifocal choroiditis (MFC) with panuveitis and subretinal fibrosis and uveitis syndrome, although it is considered to be a distinct entity. PIC primarily affects young myopic women, who may present with scotomas, blurred central vision, photopsias, floaters, photophobia, and metamorphopsia [18]. Fundus findings consist of small yellow-white lesions of the outer retina and choroid within the posterior pole, occasionally with neurosensory detachment of the retina at the lesion, and no vitritis. CNVM is a common complication and may develop early or later in the disease course [19].

Active lesions are hyperfluorescent on early frames of FA and show late staining. Inactive old lesions typically show window defects [19]. If CNVM develops, it will present as early hyperfluorescence with leakage on later frames of FA, but this can be difficult to distinguish in some cases from the staining of active lesions. ICGA shows hypocyanescent lesions that may be more numerous than those seen on clinical examination or FA [20]. FAF shows a hyperautofluorescent halo surrounding active lesions, with hypoautofluorescent inactive lesions [21]. OCT typically shows subretinal hyperreflective inflammatory material, but may also have photoreceptor loss or findings typical of CNVM. In addition, focal choroidal excavation has been described in a subset of patients with PIC [22].

OCTA has been found useful in distinguishing active inflammatory lesions from the secondary complication of CNVM, a distinction that historically has been difficult to tease out with only FA. OCTA has been used to visualize blood flow in CNVMs of patients with PIC lesions who had inconclusive findings on FA [23]. Review of the literature shows no published studies discussing characteristic findings of OCTA in lesions without choroidal neovascularization.

Serpiginous choroiditis

SC is a rare form of posterior uveitis presenting in young to middle-aged adults, often bilateral, and most often asymptomatic until the fovea becomes affected, resulting in blurred central vision, although scotomas may be noted earlier. Characteristic fundus lesions involve the outer retina and choroid, are gray to yellow, and often start near the nerve with extension centrifugally, sometimes in a serpentine manner giving the disease its name. Other presentations can include a macular lesion that enlarges toward the nerve, or multiple lesions that eventually coalesce, often called ampiginous, because of its similarities to APMPPE. A defining characteristic of SC is progressive growth of lesions, often with intervening periods of quiescence [24].

FA during the active phase of disease shows hypofluorescent lesions in early phases, with hyperfluorescent late leakage and staining of active borders of the lesion. During inactive disease, FA can show hypofluorescent lesions with some staining of the borders [24]. ICGA is more sensitive than FA for SC and can help stage disease activity. All stages of disease show hypocyanescence early, reflecting either loss or low perfusion of the CC and active stages of disease showing leakage on ICGA [25]. FAF has been established as a reliable way to follow disease activity of SC, with active portions of lesions showing hyperautofluorescence and inactive lesions demonstrating hypoautofluorescence [26]. OCT imaging of active lesions shows hyperreflective areas involving the RPE and outer retina including the EZ and external limiting membrane, with little to no distortion of the inner retina. With healing the hyperreflectivity diminishes, and inactive lesions typically have disorganization of the outer retina and RPE with indistinguishable layers [26].

OCTA has been used to evaluate macular lesions in patients with SC. In an evaluation of 3 patients with OCTA using a Zeiss PLEX Elite 9000 SS-OCT (Carl Zeiss Meditec AG), flow voids in the CC slab were noted that correlated well in area and shape to those seen in ICGA, and the outer nuclear layer slab was found to have a slightly smaller flow void (Fig. 3). FAF lesions of the RPE were found to be similar in size to the CC slab. Patients with active flare as demonstrated on FAF and FA were noted to have new or enlarged flow voids on the CC slab of the OCTA images. Some of the flow voids were seen to resolve after initiation of immunomodulatory therapy. Pakzad-Vaezi and colleagues [27] discussed the possibility that OCTA is likely a more sensitive evaluation of the CC,

thought to be the primary site of disease in SC, and that FAF assessing the RPE may only reflect later disruption of secondary sites of inflammation.

Acute posterior multifocal placoid pigment epitheliopathy

APMPPE is an uncommon inflammatory chorioretinopathy with an estimated incidence of 0.15 cases per 100,000 persons [28]. APMPPE is usually bilateral, affects women and men equally, has a tendency to occur between the second to fourth decades of life, and can have associated systemic conditions. The most common complaint is blurred vision with central or paracentral scotomas, photopsias, and metamorphopsias, which may be associated with a flulike prodrome and headaches. Dilated fundus examination reveals creamy yellow or grey-white placoid lesions at the level of the RPE in the posterior pole. Cases often are self-limited, and visual symptoms resolve by 4 to 8 weeks. Patients can develop cerebral vasculitis, which is life threatening. Systemic steroids have been used to hasten visual recovery, especially in cases with macular involvement or with suspected cerebral vasculitis [29]. On FA, the active lesions show early hypofluorescence followed by late irregular hyperfluorescent staining. On ICGA, active placoid lesions manifest as early and late hypocyanescence. The placoid lesions generally appear hypoautofluorescent on FAF and may have active edges that are hyperautoflourescent. OCT during active disease demonstrates lesions with hyperreflectivity from the outer plexiform layer to the RPE and disruption of the EZ. With disease resolution, the hyperreflectivity of outer layers disappears, the EZ re-emerges, although focal photoreceptor and RPE atrophy can occur [30,31]. OCTA findings for APMPPE using the OptoVue AngioVue were described in 5 patients, during the acute and healing phases [32]. OCTA revealed CC flow abnormalities underlying acute and healed APMPPE lesions. In acute lesions, significant loss of CC flow occurred, whereas healed lesions showed distinct small vascular flow channels with intervening no-flow zones, distinct from surrounding unaffected zones of the CC. The dense low-flow areas seen on OCTA during the acute phase correspond to the hypocyanescent areas on ICGA. These findings support the theory of a choroidal vasculitis leading to partial occlusion of the CC with secondary ischemia of the overlying RPE and outer retina versus the traditional theory of the primary insult of inflammation at the level of the RPE and outer retina [32]. Another study evaluated 10 eyes of 5 patients with APMPPE with OCTA from acute to healing phases and compared it with other multimodal imaging

techniques [33]. Their findings also suggested a primary insult at the level of the CC, and the authors proposed 4 phases of APMPPE lesions: choroidal, in which lesions could only be detected by OCTA, ICGA, and early FA but not by OCT or FAF; chorioretinal, in which lesions could be detected by all imaging modalities; transitional with changes on OCTA and OCT; and resolution, with changes on OCT but with normalized CC vascular pattern on OCTA [33].

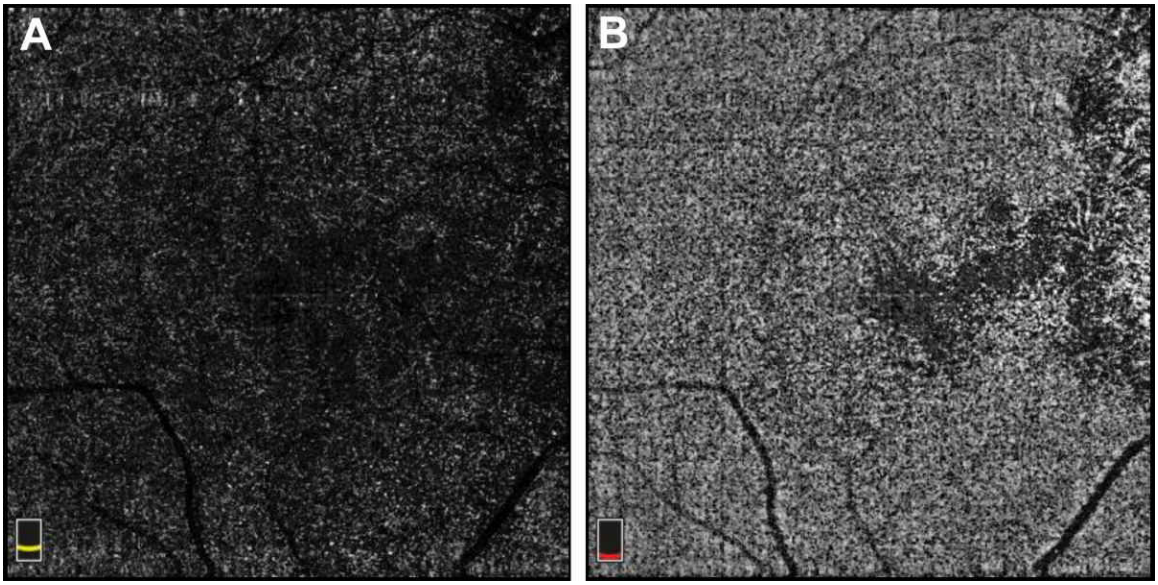

FIG. 3 OCTA slab images of the outer retina (*A*) and choriocapillaris (*B*) of the right eye of a patient with serpiginous choroiditis showing the characteristic flow void in the area of the active and prior inflammation more prominent in the choriocapillaris. The remaining slabs showed normal morphology in this patient.

Acute zonal occult outer retinopathy

The original description of acute zonal occult outer retinopathy (AZOOR) by Gass [34] in 1992 included 13 patients who presented with photopsias, central vision changes, a normal fundus examination initially with subsequent geographic areas of atrophy, and pigmentary degeneration. With the advent of multimodal imaging, AZOOR has been redefined and should be considered in young female patients, presenting with photopsia in a localized area of the visual field along with an abnormal visual field test [35]. OCT, FAF, FA, and ICGA can demonstrate abnormalities at the level of the photoreceptors/EZ followed by involvement of the RPE and choroid. Typical trizonal patterns can be seen on OCT, FAF imaging, and ICGA. Most striking are the trizonal patterns seen on FAF with zone 1 showing normal autofluorescence in the area outside of a delineating line, zone 2 with speckled hyperautofluorescence seen within the AZOOR lesion, and zone 3 corresponding to the hypoautofluorescence due to the development of choroidal atrophy. The disease may be unilateral or bilateral, and progressive diffuse retinal degeneration may occur. OCTA and OCT reveal 3 zones as well, with healthy photoreceptors and chorioretinal vasculature on OCT in zone 1; zone 2 with photoreceptor irregularities but normal-appearing RPE and choroid on OCT without any apparent changes in the CC on OCTA, and zone 3 with markedly reduced areas of choroidal flow on OCTA [20].

Multifocal choroiditis

MFC is an idiopathic inflammatory disorder affecting the choroid, retina, and vitreous. MFC presents asymmetrically, most often in young women with myopia, with symptoms of floaters, photopsias, enlargement of the physiologic blind spot, and decreased vision. Fundus examination reveals multiple old, atrophic lesions that appear as punched-out, white-yellow dots in a peripapillary, midperipheral, and anterior equatorial distribution. Active lesions appear creamy yellow and opaque with indistinct borders that become more defined over time.

MFC is often grouped together with PIC; however, each disease has distinct phenotypic characteristics. MFC is characterized by chorioretinal lesions found not only within the posterior pole but also in the periphery, evidence of anterior chamber and vitreous inflammation, larger size of chorioretinal lesions, and less propensity toward CNVM formation compared with PIC. A recent study of 343 eyes of 185 patients with clinical diagnoses of MFC and PIC found that PIC was characterized by the presence of smaller, posterior pole lesions without associated intraocular inflammation. PIC also was associated with a significantly higher proportion of eyes with myopia and a higher degree of myopic refractive error than MFC [36].

FA in MFC shows early hypofluorescence with late staining of acute active lesions, whereas atrophic scars reveal transmission defects. Early hyperfluorescence and late leakage can be seen in the presence of macular edema and CNVM. ICGA can reveal multiple hypocyanescent lesions that are more numerous than those apparent on clinical examination or FA. FAF reveals hyperautofluorescence of active lesions and punctate hypoautofluorescent spots in areas of chorioretinal atrophy [37]. OCT may show hyperreflective drusen-like material beneath the RPE at the site of active lesions. OCTA studies have been performed on patients with MFC and PIC grouped together [38] and has been found useful in distinguishing active inflammatory lesions from the secondary complication of CNVM, as discussed in the PIC section. In lesions with both active inflammation and CNVM, OCTA has been found useful in the diagnosis of CNVM and also in monitoring the effect of anti-vascular endothelial growth factor treatment by serial imaging of regression of the CNVM [39].

Relevance and future avenues

WDS are a collection of orphan diseases that have a variety of presentations and clinical and imaging findings, and prognosis ranges from full recovery without treatment to permanent sequelae or frequent recurrence. These syndromes have been categorized based on phenotypic presentation; however, overlap exists with some of the diseases, and they are often thought to be on a continuum. Some disease processes may change over time to become more consistent with different diagnoses, such as APMPPE to relentless placoid chorioretinitis. Although widely accepted clinical criteria are established for each of these diseases, the clinical picture does not always neatly fit into one diagnosis. The expanding diagnostic strategies for patients with these conditions, namely, multimodal imaging, including OCTA, can help to reach a diagnosis, determine prognosis, monitor for complications, and determine treatment plans.

OCTA is especially advantageous because it provides a noninvasive method of evaluating fundus lesions. The relative speed of evaluation compared with traditional methods of intravenous angiography over the course of 10 to 20 minutes, as well as the elimination of need for contrast media with its accompanying risks, makes OCTA an examination that can be repeated at each visit and used to determine progression or resolution, potentially earlier than gold-standard dye-dependent imaging techniques.

Vision-threatening complications of WDS, namely, choroidal neovascularization, occur with different frequency among the different diagnoses. CNVMs are often detected only after visual symptoms develop, either from hemorrhage or leakage. The ability to regularly evaluate capillary blood flow through fundus lesions may allow for earlier detection of CNVM and prevention of vision loss in a greater number of patients.

As described by Pakzad-Vaezi and colleagues [27], OCTA in patients with SC shows expansion of CC flow voids during flare of disease and was able to detect changes not seen on FAF. For diseases such as SC, it is advantageous to have imaging dedicated for evaluating the CC, the likely primary site of inflammation, instead of the RPE through FAF, which is likely damaged as a sequelae of underlying inflammation. As OCTA becomes more widespread in use, larger studies on specific disease processes may help determine how to best use this new technology to

make earlier clinical decisions, such as local injection therapy or commencement or modification of immunosuppressive therapies.

Artificial intelligence and computerized evaluation of fundus imaging currently is being studied and has been implemented in more common retinal diseases including diabetic retinopathy and age-related macular degeneration, as well as glaucoma. As technology is developed and advanced, applications may develop that will assist in the diagnosis and management of less common diseases such as the WDS. Specific areas that may be of interest will be in the early detection of CNVM and determination of geographic areas of involvement for inflammatory lesions to determine progression.

Summary

WDS are a group of heterogeneous diseases with areas of overlap. A wide range of prognoses and complications exist. At present, well-established diagnostic criteria exist for each disease, which include well-described findings on physical examination, OCT, FA, ICGA, and FAF. Current published literature regarding use of OCTA in patients with WDS has established trends in specific findings. In the near future, increasing clinical use of OCTA will allow for further description and understanding of the disease processes and can significantly impact the timing of clinical decision making.

Clinics care points

- OCTA is a relatively new technology with most detailed descriptions in the literature focusing on clinical use in detecting CNVM in AMD. OCTA has been less extensively studied in WDS.
- Current use of OCTA in WDS has clinical value more easily applied in diseases with higher rate of CNVM, including PIC and serpiginous choroiditis.
- When looking for changes on OCTA, imaging artifact is often present and prevents the use of OCTA as a singular test, however it is a helpful tool as a part of multimodal imaging.

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