Issue 4

CUTTING EDGE

Glaucoma

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Springer Healthcare Education

SUN PHARMA

SOME HEIGHTS ARE THRILLING

BUT AN ELEVATED IOP IS NOT

In Glaucoma, 40% of treated patients required two or more medications to achieve a 20% reduction from baseline IOP by year 5[1]

In Primary Open Angle Glaucoma & Ocular Hypertension

℞ BRIMOLOL

Brimonidine Tartrate 0.15% + Timolol Maleate 0.5%

For Combined Power, Greater Benefits...

36% (8.3 mmHg) additional IOP reduction from latanoprost treated baseline[1]

At 12 weeks, fixed-dose combination provided 8.3 mmHg IOP reduction from latanoprost baseline at peak effect (~2 mmHg more than adjunctive timolol)[1]

IOP - Intra Ocular Pressure | 1. Clinical Ophthalmology 2011:5 945-953
In this study, at baseline on latanoprost, patients with IOP ≥21 mmHg in at least one eye were randomized to twice-daily fixed brimonidine tartrate 0.2%/timolol maleate 0.5% combination (n = 102) or timolol 0.5% (n = 102), each adjunctive to latanoprost for 12 weeks. | IOP was measured at 8 am and 10 am at baseline, week 6, and week 12. | In a 12 months randomized, multicenter study, brimonidine-Purite 0.15% and 0.2% provided intraocular pressure lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. (J Glaucoma. 2002 Apr;11(2):119-26.)

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Step by step procedure for online viewing:

1. Go to http://collections.medengine.com/ophthalmology/cutting-edge-glaucoma/ or scan QR code.
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4. The PDF file can be downloaded too for offline reading.

WHAT'S NEW

Minimally Invasive Glaucoma Surgery: Where We Are, and What the Future Holds

Fareed Rifai[1], Crystal P. Le[1], Lauren Lim[1], Ze Zhang[1]

Abstract

Purpose of Review: Minimally invasive glaucoma surgery, or MIGS, has revolutionized the glaucoma surgical space in the past 15 years. The high safety profile and moderate efficacy of MIGS has enabled earlier surgical intervention for glaucoma, providing safe and sight-saving care sooner. This review aims to examine the latest evidence on available devices and techniques.
Recent Findings: Trabecular outflow remains a mainstay for MIGS targets, with distal outflow enhancement and alternative drainage pathways showing efficacy. Comparisons of various MIGS devices and techniques are emerging, which will enable glaucoma surgeons to better design individualized care for their patients. While no single MIGS has emerged as significantly superior to others; some MIGS may be better suited for some types of glaucoma, however.
Summary: Minimally invasive glaucoma surgeries provide safe and effective alternatives to traditional filtering glaucoma surgeries in many patients. The high safety profile of MIGS enable earlier surgical interventions, which can improve visual outcome and patients' quality of life. There is an abundance of evidence showing the efficacy and safety of various MIGS, with innovations continuing to advance the surgical treatment of glaucoma.

Keywords: MIGS, Microinvasive glaucoma surgery, Minimally invasive glaucoma surgery, Trabecular microbypass, Goniotomy, Canaloplasty, Trabeculotomy

Introduction

Glaucoma is a progressive optic neuropathy that can result in permanent vision loss. It affects over 60 million people (3.5% of population) worldwide and is estimated to increase to 111.8 million by year 2040 [1].

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It is the leading cause of irreversible blindness in the world [2]. Risk factors for glaucoma include elevated intraocular pressure (IOP) [3-6], African ancestry [5], positive family [5], older age [3, 5] and thin central corneal thickness. [5] IOP is currently the only modifiable risk factor for glaucoma to reduce the risk of progression [7].

Treatment for glaucoma include topical medications, laser, and surgery. Usually, if medical and laser therapy is unable to adequately lower IOP to reach target levels, surgery is often required.

Traditional glaucoma surgeries include trabeculectomy and glaucoma drainage device implantation. While effective, these filtering procedures require extensive post-operative follow-up and prolonged recovery. They are also prone to episcleral fibrosis and subsequent failure. Filtering surgeries are associated with serious risk of early and late complications including bleb

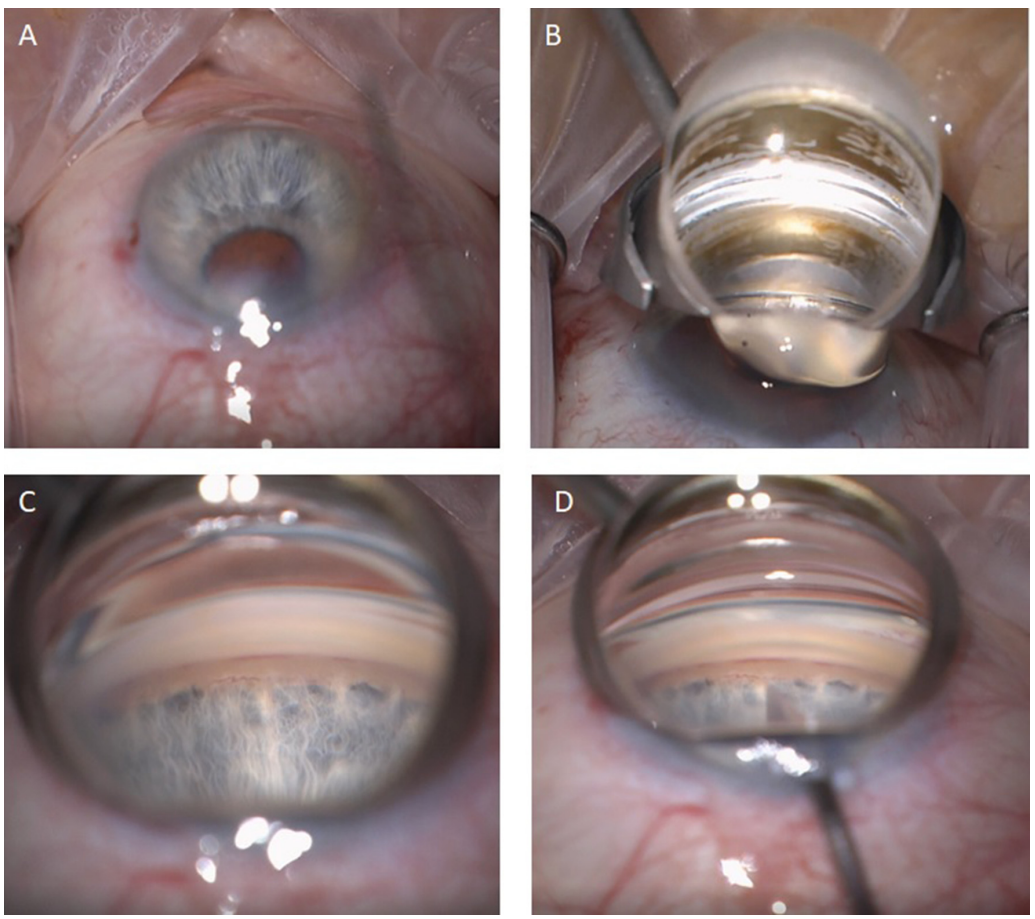

Fig. 1: Common surgical approach for Ab interno surgery. **A** Patient's head is rotated 30° away from the surgeon and OVD is used to inflate the anterior chamber. **B** Gonioprism applied to the cornea to ensure proper view. **C** Adequate illumination and magnification to view angle structures is critical to successful MIGS. **D** Insertion of device/implant through temporal clear corneal incision under gonioscopic guidance.

leak, bleb-related infections, and device extrusion. In the Tube versus trabeculectomy study, average IOP decreased by 10.7 mmHg in the tube group and 13 mmHg in the trabeculectomy group. However, 34% of tube group and 36% of trabeculectomy group developed late complications including vision threatening complications such as hypotony, choroidal effusions, maculopathy, and erosion [8].

Thus, there is a need to create effective but safer glaucoma surgeries. Since the early 2000s, the surgical field of glaucoma has been revolutionized by the world of minimally, or microinvasive, glaucoma surgery (MIGS). MIGS is generally defined by five key components: high safety profile with rapid recovery, minimal disruption of normal anatomy, ab interno approach, efficacy in lowering IOP, and ease of use for surgeons [9•].

These procedures work by either augmenting traditional aqueous outflow through trabecular meshwork (TM) and Schlemm's canal (SC), or creating regulated outflow into the suprachoroidal and subconjunctival space. Many of the procedures are likely not sufficient for patients with advanced disease as they do not provide the very low IOP targets required.

The surgical approach for majority of MIGS is similar. An ab interno approach under direct gonioscopic guidance is always used. Implantation or insertion occurs through a small clear corneal incision. The patient's head is turned 30–45° away and the microscope rotated 30° toward the surgeon. Viscoelastic is used to fill the anterior chamber and can be used to deepen the nasal angle to facilitate the view (Fig. 1).

This review aims to summarize the latest update on MIGS available and their clinical efficacy data.

Trabecular Meshwork-Based MIGS

The juxtacanalicular TM represents the site of greatest outflow resistance prior to aqueous humor entering SC. Devices and surgical procedures have been designed to bypass this source of resistance.

Trabecular Bypass Devices (Fig. 2)

iStent and iStent Inject

The iStent (G1-IS) is a L-shaped heparin-coated, titanium micro-bypass device (Glaukos, San Clemente, CA) that was FDA approved in 2012 to use in combination with cataract surgery (Table 1). It is easiest to insert with a 15° approach toward the sclera while advancing until the retention arches are within SC before deployment (Fig. 3). Blood reflux is often observed indicating correct positioning. Most common adverse events include obstruction or malposition of the iStent and temporary post-operative hyphema. No hypotony, endothelial cell loss or increased inflammation were reported.

The first generation iStent has been largely replaced by the second-generation device of the same material: the iStent inject (G2-M-IS), which was developed to improve ease of implantation.

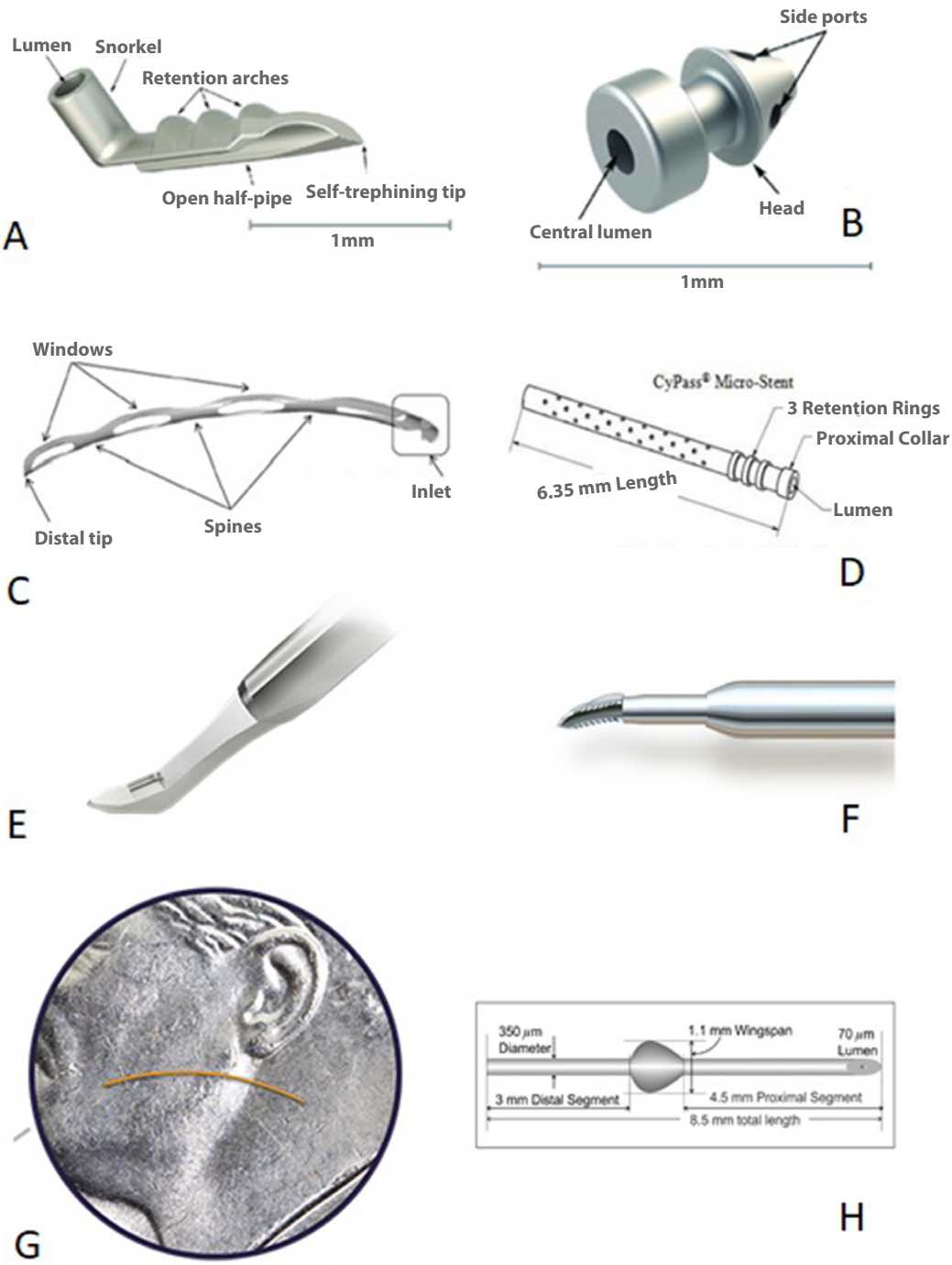

Fig. 2: MIGS Devices. A iStent G1 (Glaukos Corporation, San Clemente, CA, USA). B iStent inject (Glaukos Corporation, San Clemente, CA, USA). C Hydrus (Ivantis, Irvine, CA, USA). D CyPass (Alcon, Fort Worth, Texas, USA). E Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA, USA). F TrabEx (MST, Redmond, Washington, USA). G Xen gel stent (Allergan, Dublin, Ireland). H Preserflo Microshunt (Santen, Miami, FL, US).

Table 1: Implantable MIGS devices.

Implant Device	iStent	iStent inject	Hydrus	CyPass	Istent Supra	Miniject	Xen	PreserFlow Microshunt
Mechanism of action	Trabecular bypass	Trabecular bypass	Trabecular bypass	Suprachoroidal flow	Suprachoroidal flow	Suprachoroidal flow	Subconjuncti-val outflow	Subconjuncti-val outflow
Size/dimensions	0.3 mm×1 mm	360 um×230 um with 80 um outlet	8 mm	6.35 mm with 510 um outer diameter	4 mm with 0.16–0.17 mm lumen	5 mm oblong design	6 mm with 45 um lumen	8.5 mm with 70 um lumen
Material	Heparin-coated non-ferromagnetic titanium	Heparin-coated non-ferromag-netic titanium	Nickel-titanium alloy (nitinol)	Polyamide	Polyethersul-fone and titanium	porous silicone STAR® material	Collagen-derived porcine gelatin cross-linked with glutaraldehyde	poly(styrene—*block*—isobutylene—*block*—styrene), or SIBS
Manufacturer	Glaukos, Laguna Hills, CA	Glaukos, Laguna Hills, CA	Ivantis, Irvine CA	Alcon, Fort Worth, Tx	Glaukos, Laguna Hills, CA	iStar Medical, Wavre, Belgium	Allergan, Dublin Ireland	Santen, Miami, FL
Indications	Mild to mod-erate open angle glaucoma	Mild to moderate open angle glaucoma	Mild to moderate open angle glaucoma	Currently withdrawn	Investigational	Investigational	Moderate to severe glaucoma Patients with glaucoma not at target	Investigational
Potential adverse events/ risks	Hyphema, malposition of stent	Hyphema, malposition of stent	Hyphema, malposition of stent, PAS	ECD loss, corneal edema, hypotony, myopic shift, choroidal effusion, hyphema			Need for bleb needling, hypotony, extrusion, bleb leak and infection	

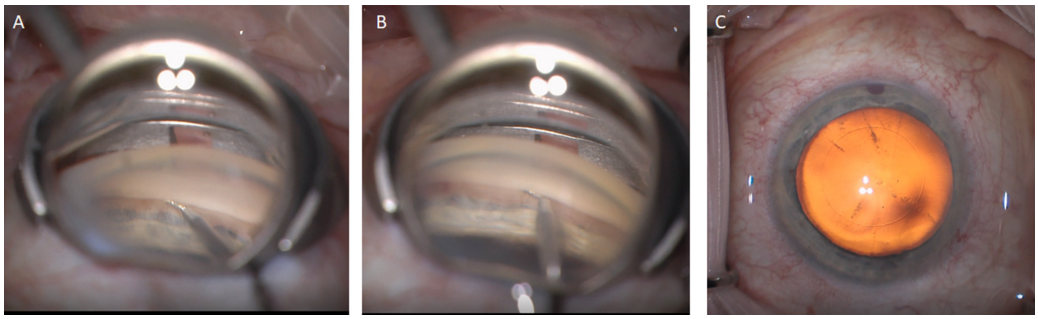

Fig. 3: iStent G1 insertion under gonioscopic view. **A** Angling 15° away from TM for insertion of the G1 iStent. **B** Advancing into Schlemm's canal. **C** Blood reflux from Schlemm's canal after proper iStent implantation.

It is 360 μm long with a 230 μm diameter and four 50 μm side outlets to maximize flow (Fig. 3). It was FDA approved in 2018 as a two-stent system to be inserted in the same ab interno approach. By inserting two stents into the TM directly two to three clock hours apart, a new patent channel into SC is created, increasing outflow to the collector channels. The latest iteration comes in the form of the iStent inject W, featuring a wider flange allowing better visualization. In initial studies, the devices were implanted after phacoemulsification. However, some surgeons prefer insertion beforehand due to a clearer cornea, less hyphema, and ability to insert before any potential complications from cataract surgery. There have not been any large studies demonstrating any difference between order of implantation. Fea *et al.* compared iStent with phacoemulsification to phacoemulsification alone in a prospective randomized clinical trial. At 15 months of follow-up, mean IOP in the iStent group was significantly lower compared to the PE-alone group: 14.8 ± 1.2 mmHg and 15.7 ± 1.1 mmHg [10]. Samuelson *et al.* compared iStent or iStent inject to phacoemulsification alone. At 2 years, 66% of iStent eyes achieved primary outcome (≥ 20% IOP reduction) versus 48% in the control group [11••]. 75.8% of iStent inject eyes versus 61% of phacoemulsification eyes achieved the primary outcome with mean IOP reduction of 7 mmHg vs 5.4 mm Hg, respectively [12]. The iStent Infinite, a three-stent, wide-flange version of the iStent inject, is currently undergoing investigational trial for standalone surgery for moderate to severe glaucoma.

Hydrus

The Hydrus Microstent (Ivantis Inc, Irvine, CA) is an aqueous drainage device introduced in 2011 in Europe, and in 2018 in the U.S (Table 1). The nitinol (nickel-titanium alloy) device is curvilinear, 8 mm in length with a 290-micron lumen, with three windows designed to dilate SC and function as a scaffold, increasing access to the collector channels, as well as an inlet that creates a trabecular bypass.

Hydrus comes preloaded on an injector with a sharp tip used to pierce the TM to enter SC. It is then advanced into SC until the site interlock to allow release from the injector.

In the Horizon study, 546 patients were randomized 2:1 to Hydrus with phacoemulsification alone and followed over 2 years. 77.3% of the Hydrus group had > 20% unmedicated IOP

reduction compared to 57.8% in the phacoemulsification group. 30% or greater reduction in unmedicated IOP at 24 months was found in 53.4% Hydrus vs. 32.1% phacoemulsification eyes [13]. At three-year follow-up, 73% of Hydrus group were medication-free compared to 48% in the phacoemulsification group. A statistically significant reduction in the need for secondary incisional glaucoma surgery was demonstrated in the Hydrus group [14••].

Another prospective randomized controlled trial by Pfeiffer *et al*. also compared Hydrus with phacoemulsification to phacoemulsification alone. 80% of Hydrus eyes versus 46% of phacoemulsification eyes had ≥ 20% reduction IOP at 24 months. Both groups had similar occurrence of adverse effects except for Hydrus group had 12% developing peripheral anterior synechiae [15].

Comparison of iStent Inject and Hydrus

In the COMPARE trial, 152 eyes with primary open angle glaucoma (POAG) on multiple topical medications were randomized 1:1 to either the Hydrus or iStent inject on phakic or pseudophakic patients. At one year, 46.0% of Hydrus vs. 24.0% of iStent eyes were medication-free. Medication-free IOP ≤ 18 was reached in 30.1% Hydrus vs. 9.0% iStent eyes [16•].

A meta-analysis by Otarola *et al*. analyzed the trial by Pfeiffer *et al*. the HORIZON trial, and the COMPARE trial, concluding that there was moderate evidence that the Hydrus would increase the number of patients that would be medication-free and decrease unmedicated IOP of least 2 mmHg compared to phacoemulsification. There was low certainty evidence from only the COMPARE trial that showed the Hydrus was more effective than iStent in reducing medications and decreasing unmedicated IOP [17].

Trabecular Excision or Ablation

Trabectome

Trabectome (NeoMedix, Irvine, CA) was approved by the US FDA in 2004. It is an ab interno electrosurgical device used to ablate up to 180° of TM. The Trabectome tip can be inserted through a small clear corneal incision with minimal heat dissipation to nearby tissues. It uses a bipolar 550 kHz electrode with adjustable power to ablate the TM with minimal thermal transfer to the outer wall of SC. The device contains a footplate that guides the tip and protect adjacent tissues. There is constant irrigation and aspiration that maintains the anterior chamber and removes debris. Trabectome is approved for treatment of open angle glaucoma with uncontrolled IOP regardless of lens status but is often performed in combination with phacoemulsification.

Contraindications to Trabectome are active neovascular glaucoma, active uveitis, elevated EVP, angle dysgenesis, and inadequate view of the angle. Postoperative IOP typically decrease to mid-teens. Younger patients are at risk for worse outcomes [18]. Most common adverse events involve hyphema, incomplete or improper TM ablation, damage to the ciliary body, and PAS formation [19, 20••].

The Trabectome Study Group has published the largest source of data on the Trabectome. In a prospective study on patients with OAG, mean IOP reduction of 11.9 mmHg and medication reduction of 0.8 was observed at 1 year follow-up [20••]. Trabectome appears to lead to greater IOP reduction in pseudoexfoliation glaucoma (PXG) (44%) than POAG (34%) [21].

Phacoemulsification combined with Trabectome has been extensively studied and appears to have additional IOP-lowering effect [21-23]. Francis *et al.* reported IOP reduction of 4.5 mmHg and medication reduction of 1.3 at 12 months [22]. Ting *et al.* showed mean IOP reduction of 4.3 mmHg in POAG and 7.5 mmHg in PXG (Tables 2 and 3) [21].

Kahook Dual Blade (KDB)

The Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA) is a single-use, disposable instrument for performing 3–5 clock hours of Ab interno Goniotomy (Table 2). Its sharp tip, two blades and footplate with a total width of 230 microns are designed to achieve near-complete excision of TM. It is approved for use as standalone or combined with cataract extraction. It is indicated for open angle glaucoma and ocular hypertension, though studies have shown efficacy in eyes with at least 3 clock hours of PAS [24•]. Potential complications include difficulty removing the TM strip, hyphema, Descemet tears, iridodialysis, PAS, and corneal edema. The newest iteration of blade is the KDB GLIDE, designed to allow more precise and smooth excision of the TM with a rounded heel.

The role of KDB goniotomy combined with phacoemulsification have been reported by a number of studies, though long-term data are limited. At 6 months, IOP reduction of up to

Table 2: Non-device-based MIGS procedures.

Procedure	GATT	OMNI	ABiC	Trabectome	KDB	TrabEx
Mechanism	Trabecular aqueous outflow enhancement	Trabecular aqueous outflow enhancement, Viscodilation of Schlemm's canal	Viscodilation of Schlemm's canal	Trabecular aqueous outflow enhancement	Trabecular aqueous outflow enhancement	Trabecular aqueous outflow enhancement
Device or material	Prolene suture or iTrack microcatheter	OMNI surgical system	iTrack microcatheter	Trabectome	KDB	TrabEx
Indications	Open angle glaucoma (primary and secondary), congenital glaucoma, juvenile open angle glaucoma	Open angle glaucoma (primary and secondary)	Open angle glaucoma (primary and secondary)	Open angle glaucoma (primary and secondary), some narrow angle glaucoma with limited PAS	Open angle glaucoma (primary and secondary), some narrow angle glaucomas with limited PAS	Open angle glaucoma (primary and secondary), some narrow angle glaucomas with limited PAS
Potential adverse events/risks	Hyphema, damage to nearby structures	Hyphema, damage to nearby structures	Hyphema, damage to nearby structures	Hyphema, PAS, damage to nearby structures	Hyphema, damage to nearby structures	Hyphema, damage to nearby structures

Table 3: Efficacy studies for various MIGS.

Study/Author	Type of study	Number enrolled at baseline (N)	Length of follow-up	Mean % IOP reduction and % medication reduction from baseline
iStent				
Fea *et al*. [10]	Double blinded RCT	36	16 months	17.3% IOP reduction and 80% medication reduction in the iStent + PE group; 9.2% IOP reduction and 31.6% medication reduction in PE group
Samuelson *et al*. [11••]	Multicenter RCT	240	12 months	8% IOP reduction with 87% medication reduction in istent + PE group; 5.5% IOP reduction and 73% medication reduction in PE group
iStent inject				
Samuelson *et al*. [12]	Prospective multicenter RCT		24 months	iStent inject: 31% IOP reduction in eyes that did not undergo further surgeries PE only: 27% IOP reduction in eyes that did not undergo further surgeries
Hydrus				
Samuelson *et al*. [13]	Multicenter RCT	546	24 months	Hydrus: 29.8% IOP reduction and 82.4% medication reduction; 77.3% achieved > 20% IOP reduction Hydrus + PE: 20.9% IOP reduction 58.8% medication reduction; 57.8% achieved > 20% IOP reduction
Horizon trial Ahmed *et al*. [14••]	Multicenter RCT	556	48 months	Hydrus:6.7% IOP reduction and 76.5% medication reduction PE:6% IOP reduction and 52.9% medication reduction
Pfeiffer *et al*. [15]	Single blinded, RCT	100	24 months	50% IOP reduction in Hydrus + PE group; 28% IOP reduction in PE group
Trabectome				
Jea *et al*. [18]	Retrospective cohort study	417	24 months	Trabectome: 43.5% IOP reduction and 3% increase in medications Trabeculectomy: 61.3% IOP reduction 77% medication reduction
Minkler *et al*. [20••]	Consecutive prospective case series	101	30 months	40.9% IOP reduction
Francis *et al*. [22]	Consecutive prospective case series	304	12 months	22.5% IOP reduction and 45.7 medication reduction
Ting *et al*. [21]	Consecutive prospective case series	517	12 months	44% IOP reduction and 28% medication reduction in PXG, 34% IOP reduction and 21% medication reduction in POAG
Ting *et al*. [21]	Consecutive prospective case series	308	12 months	35% IOP reduction and 38% medication reduction in PXG, 22% IOP reduction and 31% medication reduction in POAG

continued

Table 3: *continued*

Kahook Dual Blade (KDB)				
Dorairaj *et al*. [24•]	Retrospective review	42	12 months	47.2% IOP reduction and 91.7% medication reduction
Greenwood *et al*. [26]	Prospective interventional series	71	6 months	26.4% IOP reduction and 47.8% medication reduction
ElMallah *et al*. [28]	Retrospective review	42	12 months	19.3% IOP reduction and 12.5% medication reduction
Laroche *et al*. [30]	Retrospective review	63	6 months	19.5% IOP reduction and 38.5% medication reduction
Berdahl *et al*. [31]	Retrospective review	53	6 months	29.8–43.8% IOP reduction and 40% medication reduction
Salinas *et al*. [32]	Retrospective review	116	18 months	KDB + PE: 12.7% IOP reduction and 45.8% medication reduction KDB alone: 31.2% IOP reduction and 13.8% medication increase
GATT				
Grover *et al*. [34••]	Prospective consecutive case series	85	12 months	39% IOP reduction and 53% medication reduction in GATT only group; 35% IOP reduction and 48% medication reduction in GATT/PE group
Grover *et al*. [35]	Retrospective review	35	24 months	40% IOP reduction
Grover *et al*. [36]	Retrospective review	14	12 months	45.8% IOP reduction, 67% reduction in medications
OMNI				
Vold *et al*. [37]	Retrospective multicenter review	48	12 months	28.4% IOP reduction in group 1 (baseline IOP > 18 mm Hg) 9.7% IOP reduction in group 2 (baseline IOP ≤ 18 mm Hg) (not statistically significant)
ABiC				
Gallardo *et al*. [40••]	Retrospective consecutive case series	75	12 months	34.8% IOP reduction and 60.7% medication reduction
Gallardo *et al*. [41]	Retrospective paired study	12	12 months	Ab interno: 25.4% IOP reduction and 66.7% medication reduction Ab externo: 25.4% IOP reduction and 75% medication reduction
Ondrejka *et al*. [42]	Retrospective review	106	12 months	Group 1 (IOP ≥ 18 mm Hg): 41% IOP reduction and 90.4% medication reduction Group 2 (IOP < 18 mm Hg), no significant change in IOP and 88.9% medication reduction
Hughes *et al*. [43]	Retrospective consecutive case series	89	18 months	36% IOP reduction and 32% medication reduction
Cypass				

continued

Table 3: *continued*

COMPASS XT: Reiss *et al*. [44]	Randomized controlled trial, safety extension study	282	60 months	CyPass group: 34.3% IOP reduction and Control group: 32.3% IOP reduction
iStent Supra				
Junemann *et al*.	Prospective study	73	18 months	50.4% IOP reduction
Miniject				
Denis *et al*. [48]	Prospective single arm study	25	24 months	40.7% IOP reduction and 50% medication reduction
Xen				
Grover *et al*. [49]	Open-label prospective study	65	12 months	37% IOP reduction and 51% medication reduction
Mansouri *et al*. [50•]	Prospective interventional study	149	12 months	31% IOP reduction and 73.6% medication reduction
Smith *et al*. [51]	Interventional case series	3	24 months	49% IOP reduction in case 1, 48% IOP reduction in case 2, 81% IOP reduction in case 3
Arad *et al*. [52]	Consecutive case series	10	13 months	41% IOP reduction
Tan *et al*. [53]	Retrospective review	50	12 months	IOP reduction: Ab interno: 28.6%; Ab externo: 40.1% Medication reduction: Ab interno: 45.3%; Ab externo: 50.8%
Yuan *et al*. [54]	Retrospective review	69	8 months	IOP reduction: Ab interno: 47.4%; Ab externo: 40.1% Medication reduction: Ab interno: 52.9%; Ab externo: 55.3%
Gallardo *et al*. [55]	Retrospective review		12 months	IOP reduction: Ab interno: 39.3%; Ab externo: 51.1% Medication reduction: Ab interno: 69.9%; Ab externo: 63.2%
Purgert *et al*. [56]	Retrospective review	55	6 months	IOP reduction: Ab interno: 30.1%; Ab externo: 30.4% Medication reduction: Ab interno: 51.7%; Ab externo: 75.9%
Preserflo Microshunt				
Batlle *et al*. [57]	Feasibility study, prospective consecutive case series	23	60 months	46% IOP reduction at 4 years, 48.5% IOP reduction at 5 years; 66.7% reduction in medications at 5 years

26% are observed [25•, 26]. At 12 months, IOP reduction of 12.6% to 47% [27-29] are reported. Reduction of medications of 1–2 is observed at 6 months [25•, 26, 30].

As a standalone procedure, at 6 months, KDB lead to IOP reduction ranging from 22 to 43.8%. Medication reduction occurred by up to 47.8% [30-32]. Eyes with higher baseline IOP experienced greater mean IOP reductions [30].

KDB vs iStent

Studies suggest that KDB is comparable, if not superior to iStent implantation combined with cataract surgery. In a retrospective study of 77 eyes undergoing KDB or iStent in combination with phacoemulsification, there was no significant difference in overall success between iStent and KDB via a multivariable logistic regression accounting for age, sex, race, and baseline IOP. Mean IOP decreased by 1.7 mmHg in the iStent group and by 2.4 mmHg in the KDB group. Mean medication use decreased by 1.3 and 0.6, respectively [27].

In a prospective study comparing PE-KDB with PE-iStent, at 12 months, mean IOP was reduced by 3.1 mmHg in the KDB group and 3.4 mmHg in the iStent group. Mean medications were reduced by 1 in both groups. Primary outcome was attained in 93.7% of patients of KDB eyes and 83.3% of iStent eyes (Table 4) [33].

TrabEx and TrabEx+ (Previously Known as Goniotome and Goniotome I/A)

TrabEx (MST, Redmond, Washington, USA) is a single-use, dual-blade device for the excision of up to 6 clock hours of TM via ab interno goniotomy. This device was formerly known as Goniotome (Neomedix USA). It is a serrated, dual-bladed device designed to completely excise TM without leaving flaps that may occlude collector channels. The TrabEx+ offers the additional feature of irrigation and aspiration ports for improved angle visualization and anterior chamber stabilization, eliminating the need for viscoelastic which can trap regurgitating blood and bubbles. The TrabEx+ is approved for use as a standalone procedure or combined with cataract extraction. Large studies on the efficacy and safety of the TrabEx devices have yet to be published.

Table 4: MIGS efficacy comparison studies.

Study/author	Design of study	Number enrolled	Follow-up	Mean% IOP reduction and %medication reduction from baseline
KDB vs istent: ElMallah *et al.* [29]	Retrospective review	315	12 months	KDB + PE: 27.5% IOP reduction iStent + PE: 13.8% IOP reduction
Hydrus vs iStent: Ahmed *et al.* [16•]	Multicenter RCT	152	12 months	Hydrus: 8.9% IOP reduction Istent: 5.2% IOP reduction
KDB vs iStent: Le *et al.* [27]	Retrospective review	77	12 months	KDB: 12.6% IOP reduction and 36.4% medication reduction iStent: 14.3% IOP reduction and 65% medication reduction
KDB vs Trab/360 or GATT: Hirabayashi *et al.* [38]	Retrospective review	101	6 months	Mean IOP reduction similar between KDB and Trab360/GATT group: 83.6% vs 44.5%/73% ($p = 0.858$) *80% of KDB eyes achieved target IOP ≤ 18 mm HG compared to 59.3% GATT eyes without additional interventions at 6 months

GATT

Gonioscopic-assisted transluminal trabeculotomy (GATT) was developed by Grover *et al*. in 2014 [34••]; it involves a circumferential goniotomy using a prolene suture or a flexible illuminated microcatheter (iTrack 250, Ellex, Australia) (Table 2).

In addition to the temporal clear corneal incision, an oblique paracentesis is created superonasally or inferonasally. The catheter or suture is threaded into the anterior chamber to rest near the nasal angle. A microsurgical blade is used to create a 1–2 mm nasal goniotomy. Using microsurgical graspers, the catheter or suture is introduced into SC and advanced circumferentially for 360°. The distal end of the catheter or suture is then grasped and the proximal end pulled out of the eye to create the 360° goniotomy. GATT can be done with or without and prior to or after phacoemulsification (Fig. 4).

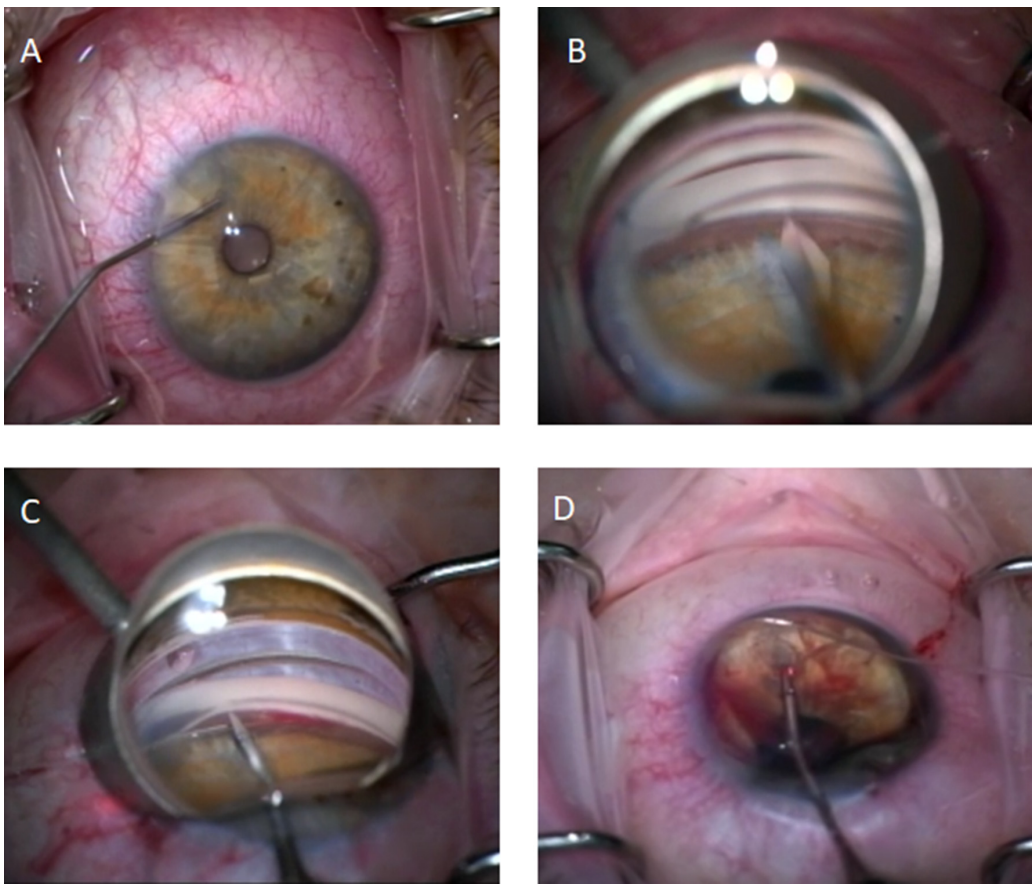

Fig. 4: Steps of GATT and ABiC. **A** Creation of oblique/tangential paracentesis. **B** MVR blade creating 1–2 clock goniotomy nasally. **C** Insertion of microcatheter into SC for 360° (note the red illumination on lower left side of image). **D** Performing the 360 trabeculotomy by removing the catheter. Note: ABiC procedure involves panels **A–C**, with retraction of the catheter while viscoelastic is injected to dilate SC instead of performing the trabeculotomy.

In the original study, GATT showed an IOP reduction of 7.7 mmHg and average decrease in medications of 0.9 at 6 months, and 11.1 mmHg and 1.1 at 12 months in POAG. In secondary OAG, IOP decreased by 17.2 mmHg and medications by 2.2 at 6 months. 9% required repeat glaucoma surgery at 1 year [34••].

GATT can also be used in eyes with history of previous glaucoma surgery, including trabeculectomy, tube shunts, and ECP., where mean IOP decreased by 10.2 mmHg and medications decreased by 1.2 with 60% of patients achieving definition of successful IOP control [35].

The most common complication of GATT is post-operative transient hyphema, seen in 30–50% of patients at the post-op 1 week visit [34••]. Leaving the IOP in the high teens to low 20 s at time of surgery can decrease the risk of hyphema. Contraindications to GATT include persistent use of anticoagulation medications, bleeding disorders, closed angles, and the inability to properly identify the angle anatomy.

GATT is indicated for primary and secondary open angle glaucoma. It has been used in juvenile open angle and congenital glaucoma as well, with reduction of IOP up to 12.5 mmHg and reduction of medications by 1.74 [36].

OMNI

VISCO360 and Trab360 (Sight Sciences, Menlo Park, CA) were designed to perform ab interno trabeculotomy and canaloplasty, respectively (Table 2). They have been combined into the OMNI surgical system, designed to perform up to 360° of trabeculotomy as well as SC viscodilation. It was FDA approved in 2017.

The OMNI is introduced through the main corneal incision, advanced across the anterior chamber toward the nasal angle, and a small goniotomy is created with the cannula tip. The cannula is then inserted into the goniotomy and the microcatheter advanced into SC 180°. Retraction of the catheter injects a predetermined amount of viscoelastic into SC to provide viscodilation. Advancing the catheter again and withdrawing the device completes the trabeculotomy. This can then be repeated for the other 180° if desired.

The ROMEO study found a mean IOP reduction of 6.2 mmHg and medications reduced by 0.5 in patients with preoperative IOP > 18 mmHg. In patients with preoperative IOP < or equal to 18 mmHg, IOP reduction of 1.5 and medication reduction by 0.7 were observed [37].

There is no clear data indicating a clear relationship between degrees of goniotomy or trabeculotomy performed and IOP reduction. In a small study comparing KDB versus 360 trabeculotomy, IOP and medication requirements were similar between the groups (Table 4) [38]. Aqueous angiography may be helpful in the future to determine the high versus low flow regions and allow targeted outflow treatment. This has been demonstrated by a two-dye perfusion system ex vivo [39].

Schlemm Canal Dilation

Traditional canaloplasty is a bleb-less, ab externo procedure that uses a sclerostomy and microcatheter to enter, circumnavigate, and viscodilate SC, ending with a tensioning suture that leads

to decreased aqueous outflow resistance and IOP lowering. Gallardo introduced a modified technique, ab interno canaloplasty (ABiC) through a clear corneal incision using a microcatheter that allows viscodilation of SC [40••]. This is designed to target the distal outflow system beyond the TM (Fig. 4).

A single-center retrospective review of 75 eyes compared ABiC alone vs. ABiC with phacoemulsification. At 12 months, there was a 32.8% reduction in IOP in standalone ABiC and 31.7% IOP reduction in ABiC. There was a 60% reduction in medication usage, and 40% were medication-free. No significant differences in IOP or medication reduction were observed at 12 months. At 24 months, the data demonstrated consistent IOP lowering of 6.5 mmHg. In a study comparing ab externo vs. ab interno canaloplasty, there was no significant difference in IOP lowering or medication reduction at 12 months [40••, 41].

The initial ABiC study was performed with the iTrack microcatheter (Ellex iScience, Fremont, CA), and required grasping the catheter with micro forceps to insert it into the canal 360°. Ondrekja and Körber studied ABiC using the OMNI system in mild to moderate glaucoma patients, divided into two groups based on baseline IOP. At 12 months, mean IOP reduction was 10 mmHg in group 1 (baseline IOP ≥ 18) and 1.3 mmHg group 2 (baseline IOP < 18). 86% of all eyes were medication-free [42]. Higher pre-op IOP was found to be correlated with increased IOP-lowering effect [43].

Suprachoroidal Drainage Devices

The suprachoroidal space is a physiologic route for aqueous humor outflow. Because traditional subconjunctival targeted surgeries may be complicated by a lifetime risk of endophthalmitis, poor cosmesis, and variable would healing response, the suprachoroidal pathway has been investigated as an alternative treatment for glaucoma.

Cypass

The CyPass Micro-Stent (Alcon, Fort Worth, TX) is a polyamide fenestrated tube 6.35 mm in length, designed to create a controlled outflow pathway between the anterior chamber and the supraciliary space (Table 1). It is inserted on a small guidewire. It was FDA approved for use with cataract surgery in 2016. The COMPASS trial evaluated its effectiveness and safety in eyes randomized to phacoemulsification with or without CyPass. The five-year data demonstrated that 46% of eyes in the CyPass group had ≥ 20% unmedicated IOP reduction at 60 months versus 32.1% of control eyes [44].

On August 29, 2018, Alcon announced a voluntary market withdrawal of the CyPass following analysis of post-surgical data from the post-approval safety study. At 5-years, CyPass-implanted eyes had a statistically significant endothelial cell density (ECD) loss of − 20.4% compared with − 10.1% of control eyes. There was no statistically significant difference in baseline cellular morphology. Nine adverse events may have been related to ECD loss, including three with transient focal corneal edema and four that required trimming of the device due to protrusion [45]. Data suggests a correlation between the distance the CyPass device extends into the anterior chamber,

determined by the number of retention rings visible, and the rate of ECD loss. Of the patients with ECD data at both 2 and 5 year follow-up, mean ECD loss over this 3-year period was 3.1% when 0 rings were visible, 8.4% with 1 ring visible, 21% with 2 rings visible, and 31.4% with 3 rings visible. At this time the FDA recommends monitoring all patients whom have had CyPass-implanted undergo periodic ECD monitoring using specular microscopy until stabilization of ECD loss [45]. Clinical findings associated with ECD loss were uncommon (3.3% of implanted eyes), suggesting that ECD may be a subclinical sequela [45, 46]. In the future, if returned to the market, the CyPass may be useful for advanced open angle glaucoma cases.

Other Suprachoroidal Devices

Several other devices currently undergoing clinical trials are also aimed at increasing outflow through the suprachoroidal space (Table 1). The iStent Supra (Glaukos Corporation, San Clemente, CA) is a 4 mm polyethersulfone and titanium stent with a 165-μm heparin-coated lumen. Preliminary results showed IOP reduction of 11.6 mmHg from baseline at 12 months, and 12.5 mmHg by 18 months with no major adverse events [47].

The Miniject (iStar Medical, Wavre, Belgium) is another investigational supraciliary device and is made from proprietary biocompatible silicon material containing a geometric porous microstructure to promote tissue integration with reduced fibrosis. The STAR-I trial evaluated Miniject implantation as a standalone procedure in mild to moderate glaucoma. At 24 months, the device demonstrated a mean IOP reduction of 40.7% and 48% of patients were medication-free. No serious adverse events were reported [48].

Subconjunctival Devices

Subconjunctival filtration creates a new, non-physiologic pathway for aqueous humor outflow and is used in traditional glaucoma filtering procedures such as trabeculectomy and glaucoma drainage devices. New devices targeting the subconjunctival pathway have been developed with aim to decrease complications rates of traditional filtration surgeries.

Xen

The Xen-45 Gel Stent (Allergan, Irvine, California) is a hydrophilic, gelatin stent approved by the FDA in 2016. It is 6 mm long with a 45um lumen and is composed of porcine gelatin cross-linked with glutaraldehyde (Table 1). Outflow is designed to follow Poiseuille's law of laminar flow and minimizes risk of hypotony. It is designed for ab interno insertion through a small clear corneal incision. It is preloaded on a 27-gauge needle that is inserted into the superonasal angle, into the subconjunctival space. The needle is advanced until it emerges from the sclera 3 mm from the limbus, and the injector button is then advanced to deploy the stent. Ideally, the stent tip sits above tenon's capsule and a 1 mm tip remains in the anterior chamber. The stent should move freely under the conjunctiva, and sometimes blunt instrumentation or a needle may be used to

straighten the stent. Mitomycin C is applied to increase the rate of success of aqueous outflow due to the formation of a bleb.

The pivotal FDA study enrolled 65 patients with refractory glaucoma for Xen implantation with mitomycin C. At 12 months, 75.4% of patients had ≥ 20% IOP lowering from baseline with the same or fewer medications. Mean IOP reduction was 9.1 mmHg (37%) and mean medication reduction was 1.8 (51%). Adverse events included needling, non-persistent loss of best corrected visual acuity, and transient hypotony. During the 12-month follow-up period, 32.3% required needling [49]. Examination of Xen alone versus Xen combined with phacoemusification suggests standalone Xen leads to greater IOP reduction than combination surgery: 40% reduction in standalone group versus 22.9% in combination group [50•]. The use of Xen has also been evaluated in pediatric glaucoma with promising results [51, 52].

One of the major challenges for a beginner Xen surgeon is to ensure the tip of the Xen sits above Tenon's layer and not within. There is emerging evidence for Ab externo implantation of the gel stent with and without conjunctival dissection suggesting comparable safety and effectiveness [53-56]. In a study comparing ab interno and ab externo placement, there was no statistically significant difference in mean IOP reduction, medication reduction, secondary glaucoma surgeries or adverse events at 12 months [53]. Further research involving prospective randomized trials are indicated to further evaluate the safety and efficacy of each approach.

PreserFlo Microshunt

The PreserFlo MicroShunt (Santen Inc., Miami, FL) is an 8.5 mm device made of a biocompatible polystyrene material with a 70 μm lumen. It is designed to be implanted ab externo under open conjunctival dissection with mitomycin C. At the time of this review, the MicroShunt is not yet FDA approved. The pivotal study enrolled 23 POAG patients. At 5 years follow-up, mean IOP was reduced by 46%. Mean number of medications was reduced by 1.6. 61.1% of patients were medication-free. The most common adverse events included corneal edema, transient hypotony, bleb-related complications, and device-iris touch. Two patients required reoperation due to bleb failures. There were no reports of chronic hypotony or endophthalmitis. There were no signs of apparent degradation after 5 years [57].

Conclusion

Many MIGSs have emerged in the past 15 years, and we will likely continue to see novel surgical techniques and devices in the future. Moderate efficacy and high safety have been demonstrated by many previous studies, and new data will continue to help us better understand how to design minimally invasive glaucoma surgical treatment for our patients to provide sight-saving care.

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Declarations

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MIGS in Special Cases

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Bullet Points

In this chapter, we will discuss the following:

- The coincident problem of glaucoma and age-related cataract.
- Common microinvasive glaucoma surgery (MIGS) devices.
- The effects of cataract surgery alone on lowering intraocular pressure.
- The effect of phacoemulsification and MIGS on endothelial cell density.
- Efficacy of combined cataract extraction with filtering surgery compared with standalone filtering surgery.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide, and significantly increases in prevalence with age across all ethnic groups [1-3] With a rapidly aging population, the prevalence of glaucoma is expected to increase by 50% from 2020 to 2040 [2]. The current prevalence of glaucoma is 3.5% in people between 40 and 80 years of age [4], while the prevalence of cataracts varies from 3.9% in people aged 55–64 years of age to 92.6% in people ≥ 80 years of age [5]. Given these trends and the association of these conditions together, ophthalmologists will likely face the coincident problem of treating age-related cataract and glaucoma within the same patient and potentially the combined surgical treatment of these conditions together. In treating glaucoma and preventing progression of the disease, lowering intraocular pressure (IOP) is a mainstay of therapy, whether that is accomplished medically or surgically. Effective IOP control can slow glaucoma progression and reduce further visual field loss [6, 7].

A recent major development in glaucoma surgery is a new class of devices called microinvasive glaucoma surgery (MIGS) [8]. MIGS is a group of surgical procedures that are conjunctival sparing, minimally traumatic, and increase aqueous humor outflow by directly accessing Schlemm's canal, or by redirecting fluid from the anterior chamber to the suprachoroidal or subconjunctival space [9]. A meta-analysis showed that MIGS was effective in lowering both IOP and medication burden, with a good safety profile [10]. Given their ab interno approach, MIGS can easily be combined with cataract surgery by utilizing the same clear corneal incision that would be created for phacoemulsification.

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In this chapter, we will present the utility of three common MIGS devices in the cataract population, discuss the IOP-lowering effects of cataract surgery alone, as well as touch upon the effect of combined phaco-MIGS on endothelial cell density. Lastly, we will review the efficacy data of combining cataract extraction with filtering surgery versus filtering surgery alone. Table 1 at the end of this chapter outlines a brief summary of different MIGS devices available.

iStent

The iStent (Glaukos, San Clemente, CA) is an ab interno trabecular microbypass stent that has been demonstrated to effectively and safely reduce intraocular pressure when implanted alone, or in

Table 1: A comparison of microinvasive glaucoma surgery (MIGS) devices.

MIGS device	Company	Year commercial use began	Pros	Cons	Level of evidence[a]
Schlemm canal					
iStent	Glaukos	2012 – iStent trabecular micro-bypass 2018 – iStent inject 2020 – iStent inject-W	Excellent safety outcomes Versatile and efficient procedure Shorter learning curve Multiple iStents can be injected for additional IOP-lowering effect	Small device may be prone to under- or overimplantation When using multiple, should ideally be placed apart, which can be technically demanding Less efficacy than subconjunctival approaches	Level I (various randomized controlled trials have demonstrated efficacy)
Hydrus	Ivantis	2018	Excellent safety outcomes Potential for greater IOP reduction with single implant Single implant access >3 clock-hours of distal outflow	Larger device may reduce some of the versatility in different eye anatomies Less efficacy than subconjunctival approaches	Level I (various randomized controlled trials have demonstrated efficacy)
Kahook dual blade	New World medical	2015	Nonimplant approach	Higher risk of intraoperative and postoperative hyphema Less efficacy than subconjunctival approaches	Level II (evidence from well-designed trials without randomization)
Subconjunctival					
XEN-45 gel stent	Allergan	2017	Allows for implantation without conjunctival/tenons dissection Demonstrated similar efficacy to trabeculectomy	Risks inherent to bleb-forming procedures, such as blebitis and hypotony-related complications High postoperative needling rates.	Level II (evidence from well-designed trials without randomization)
Preserflo microshunt	Santen	2021	Promising efficacy results in treating primary and refractory glaucoma	Ab externo approach requiring conjunctival/tenons dissection Risks inherent to bleb-forming procedures, such as blebitis and hypotony-related complications Newer device with less evidence available	Level II (evidence from well-designed trials without randomization)

[a]Roughly adapted from the US Preventive Services Task Force (USPSTF) definitions of levels of evidence

combination with phacoemulsification. It is a heparin-coated, nonferromagnetic titanium device first approved by the US Food and Drug Administration (FDA) in June 2012 [11], and has since quickly gained popularity. A study evaluating long-term data of combined cataract surgery with iStent implantation demonstrated a significant IOP decrease of 3.16 ± 3.9 mmHg after 53 months of follow-up, with good safety outcomes and no serious adverse events related to iStent implantation [12]. Various randomized controlled trials (RCTs) ranging from 12 to 24 months of follow-up have all demonstrated a statistically significant reduction in mean IOP and number of pressure-lowering medications when undergoing combined phacoemulsification with iStent implantation compared to phacoemulsification only, with comparable safety profiles [13-16]. Multiple iStents can also be implanted in a single eye at once to allow titration to achieve target pressure [17]. Currently, there are several iterations of the iStent that exist on the market: the original iStent trabecular microbypass stent and the iStent inject, which is slowly being replaced by the iStent inject W.

Hydrus Microstent

The Hydrus Microstent (Ivantis, Irvine CA) is an ab interno Schlemm's canal MIGS device designed to enhance aqueous outflow into Schlemm's canal and into the distal outflow system. It is an 8-mm flexible, nonluminal open structure, made from nitinol (55% nickel, 45% titanium alloy), and first received FDA approval in 2018 for its use in combination with phacoemulsification [18]. Various prospective and retrospective studies have demonstrated the Hydrus to lower IOP ranging from 2.8 mmHg to 9.0 mmHg from a baseline IOP at a follow-up ranging from 12 to 24 months in both standalone cases and when combined with phacoemulsification with a good safety profile [18-22]. A few RCTs have demonstrated similar efficacy and, when compared to similar RCTs performed for the iStent, imply that the Hydrus may result in greater complete success with less medication dependence and a similar safety profile compared to the iStent inject [23-26]. A 2019 review of the Hydrus microstent concluded that it is able to reproducibly lower IOP to the mid-high teens and reduce medication burden. However, long-term efficacy of the Hydrus will be required to further determine its position along the continuum of glaucoma management [18].

Kahook Dual Blade

The Kahook Dual Blade (KDB, New World Medical, Rancho Cucamonga, CA) is a goniotomy blade introduced in 2015 that is designed to achieve almost complete removal of the trabecular meshwork (TM) through a minimally invasive approach, in order to minimize surrounding tissue damage. In contrast to gonioscopy-assisted transluminal trabeculotomy (GATT) and the trabectome, KDB has less residual trabecular meshwork leaflets and is thought to lead to less fibrosis overtime, thereby producing better long-term outcomes [27]. Additionally, it is a single-use disposable surgical instrument with no implant related risks.

Since its introduction, several studies have assessed its effectiveness in intraocular pressure (IOP) reduction, whether alone or in combination with phacoemulsification. Dorairaj *et al.* conducted a prospective multicenter study of 52 eyes that underwent KDB combined with phacoemulsification [28]. At 1 year, they found an IOP reduction of 26.2% ($p < 0.001$). Additionally,

63.5% of patients used at least one fewer IOP-lowering medications. Similarly, Greenwood *et al.* found that 58.3% of patients achieved at least 20% IOP reduction and 61.7% had at least one medication reduction at 6 months [29]. In a retrospective study assessing the efficacy and safety of KDB at 18 months, 93 eyes underwent phaco-KDB and 23 eyes underwent standalone KDB [30]. There was no statistically significant difference in IOP between the two cohorts at 18 months (standalone 14.4 +/− 3.7 vs. combined 16.7 +/− 7.6, $p = 0.5$). In terms of medication use, the combined group had a significantly lower number of drops (1.3 +/− 1.2 vs. 3.3 +/− 1.2, $p < 0.05$). However, this difference also existed at baseline (2.4 +/− 1.2 vs. 2.9 +/− 1.0, $p < 0.05$). A larger retrospective study of 197 eyes also compared outcomes of standalone KDB ($n = 32$) to phaco-KDB ($n = 165$) at 1 year. Surgical success was defined as at least 20% IOP reduction from baseline. This was achieved in 68.8% of eyes in the standalone KDB cohort and in 71.8% in the phaco-KDB cohort (no p-value given). Both groups also showed a significant IOP and medication reduction from baseline.

Cataract Extraction and Effect on Intraocular Pressure

It has been shown that cataract surgery in glaucoma patients can reduce intraocular pressure (IOP). However, the extent of IOP reduction and the value of cataract surgery as a treatment option to lower IOP is dependent on a few different factors. A 2017 systematic review of 32 studies examined IOP change at a final follow-up period of 12 months or longer in eyes with open-angle glaucoma (OAG), chronic angle-closure glaucoma (ACG), and pseudoexfoliation glaucoma (PXG). It revealed that IOP reduction following cataract extraction in ACG resulted in a decrease of 6.4 mmHg (95% CI: 9.4 to 3.4), while for OAG, it resulted in a decrease of 2.7 mmHg (95% CI: 3.7 to 1.7). For PXG, an IOP drop of 5.8 mmHg (95% CI: 9.5 to 2.0) was determined, but it was acknowledged that further research was required to arrive at an adequate conclusion as this was only based on four studies [31]. It concluded that overall, the effect of cataract surgery on IOP reduction is marked in ACG, moderate in PXG, and small in OAG.

Cataract Extraction and Angle Closure Glaucoma

IOP reduction is more significant in eyes with narrow or closed angles compared to eyes with open angles; as a result, cataract surgery is acknowledged as a valuable glaucoma intervention for those with ACG. Cataract surgery in ACG will deepen the anterior chamber and open the angle [32-35]. In particular, the EAGLE study, which randomized both primary angle closure (PAC) and primary angle closure glaucoma (PACG) patients to receive either clear-lens extraction or standard care with laser peripheral iridotomy and topical medications, concluded that clear-lens extraction was more cost effective and showed greater efficacy. More specifically, lens extraction demonstrated an additional mean IOP reduction of 1.18 mmHg lower versus peripheral iridotomy [36]. This purported clear-lens extraction to be a viable first-line treatment option for PAC and PACG patients. In eyes that have had a history of acute angle closure, the IOP reduction is even greater. A study that compared treatment with cataract surgery against peripheral iridotomy in patients after acute angle closure showed that the mean IOP for those who received cataract surgery was 12.6 ± 1.9 mmHg for the cataract surgery group versus 15.0 ± 3.4 mmHg for the

peripheral iridotomy group. Additionally, at 18 months, only 3% of the cataract surgery group developed an IOP rise postoperatively (defined as IOP > 21 mmHg) versus 46.7% in the LPI group [32]. The IOP-lowering effect of phacoemulsification in angle closure cases is likely secondary to reopening of the angle and allowing for outflow via the conventional pathway.

Cataract Extraction and Pseudoexfoliation Glaucoma

Additionally, in eyes with PXG, cataract extraction has also been shown to significantly reduce IOP. One study showed that the mean IOP dropped from 17.45 ± 3.32 mmHg to 12.57 ± 1.58 mmHg in eyes with PXG after cataract surgery [37]. Pseudoexfoliative material accumulates in the trabecular meshwork, thereby reducing aqueous humor outflow, and can subsequently increase intraocular pressure and lead to glaucoma. With the removal of the lens as well as the central anterior capsule, pseudoexfoliative matter and pigment release is thought to be significantly reduced. There is also likely to be a "washout" effect of fibrillar material during the surgery itself [38, 39].

Despite the purported benefits of cataract surgery in PXG, it is important to remember that these eyes are at increased risk of complications due to the higher incidence of zonular weakness. However, with proper preoperative detection and careful examination for donesis, the astute surgeon can plan accordingly in order to maximize good surgical outcome [38].

Cataract Extraction and Open Angle Glaucoma

The relatively modest reduction in IOP after cataract surgery in OAG has resulted in debate on its value as a glaucoma procedure for eyes with open angles and no pseudoexfoliation syndrome [40]. A 2002 meta-analysis found that cataract extraction usually reduced IOP by 2–4 mmHg; however, the evidence was graded as "weak" as there were no randomized clinical trials and no untreated control groups among the studies [41]. Criticism of using cataract surgery as a treatment method for open angle glaucoma arises from the fact that the studies are often retrospective and many use only a single pressure measurement for the preoperative value. Additionally, many of the studies did not include gonioscopy, which lends to the possibility that angle closure cases had been unintentionally included [40].

Although the mechanism for lowered IOP in ACG and PXG is more straightforward, the mechanism for patients with open angles is poorly understood [42]. A few mechanisms have been proposed for how IOP is lowered in open angle glaucoma. It has been suggested that phacoemulsification increases the postoperative aqueous outflow facility, and cultured trabecular meshwork cells have been found to release interleukins and tumor necrosis factors. This could cause increased synthesis of matrix metalloproteinases in the trabecular meshwork [43].

Despite this modest IOP-lowering effect, there are other reasons why one may choose to perform cataract surgery early in glaucomatous patients – especially if they are at high risk of eventually needing glaucoma surgery. It is well known that glaucoma surgery can cause a cataract to mature soon after. Intraocular lens power calculations and astigmatism correction are also less accurate in situations of hypotony following glaucoma surgery and cataract surgery after a filtering bleb can increase risk of infections. Cataract surgery post filtration surgery can also have

deleterious effects on bleb health. As a result, although IOP reduction is modest in eyes with open angle glaucoma, there could be a multitude of reasons why a surgeon would elect to perform cataract surgery early in a glaucomatous patient [40].

Furthering Our Understanding

Clearly, the amount of IOP reduction in patients after cataract surgery varies based on the type of glaucomatous disease, with particular attention to angle anatomy and the existence of pseudoexfoliation syndrome – although it is unclear if there other factors that come into play as well. Increasing evidence has suggested that the magnitude of IOP reduction following cataract extraction has been shown to be positively correlated to the elevation of preoperative IOP. However, it has also been argued that this could be accounted for due to the statistical phenomenon of regression toward the mean [42]. Additionally, a method for predicting the degree of IOP reduction has been proposed based on a ratio of the preoperative IOP and anterior chamber depth (ACD), measured in mm. One study consistently demonstrated that a greater than 4 mmHg reduction in IOP was found in patients with a pressure-to-ACD ratio of more than 7. In these patients who had presumed normal anterior chamber anatomy, the anterior chamber depth was found to decrease on average by 1.10 mm postoperatively [44].

Although current evidence to date suggests that IOP is indeed reduced following cataract surgery, the exact patient-specific factors that determine the magnitude and duration of the IOP-lowering effects require further investigation.

MIGS and Endothelial Cell Density

In 2018, a MIGS device known as the CyPass Micro-Stent (Alcon, Texas, United States) was voluntarily withdrawn from the manufacturer [45], and was later recalled by the US Food and Drug Administration [46]. The CyPass Micro-Stent was a 6.35 mm-long fenestrated device with 3 retention rings and a collar at the proximal tip. It was intended for supraciliary placement. The removal was due to concerns of progressive loss of endothelial cell loss (ECL) caused by CyPass Micro-Stent implantation. The COMPASS XT trial demonstrated that at 60 months, endothelial cell density (ECD) had reduced by 20.4% in the CyPass Micro-Stent group (which had eyes that underwent phacoemulsification and CyPass implantation) and by 10.1% in the control group (which had eyes that underwent phacoemulsification only) [47, 48]. Additionally, the proportion of subjects with >30% ECL, which is what most surgeons consider clinically significant, was 27.2% in the CyPass Micro-Stent group compared to 10.0% in the control group.

It is important to note that the same study identified device position as the only factor in the analysis that correlated with ECL. When two or three retention rings were visible in the anterior chamber angle, the yearly ECL rate was 6.96% versus 1.39% when no rings were visible. Additionally, the angulation of the device within the chamber likely plays a role as well; some patients with two or more visible rings did not see a significant ECL [3]. Although it is possible that

there are other variables that can affect the ECL (such as material, change in aqueous flow, reflux flow, etc.), there is no evidence of this yet. Further, due to the strong correlation with mechanical positioning of the implant in the anterior chamber with deeper implants having similar ECL levels to controls, this is unlikely [49].

The current recommendation in patients who received the CyPass Micro-Stent is screening with a complete slit-lamp examination including gonioscopy to assess the device's position. In case of clinically apparent or functionally significant changes, such as worsening ECD/pachymetry and/or corneal edema, the intervention of choice is proximal end trimming with microforceps and microscissors. Device explantation is currently not recommended as firm attachments often develop to surrounding uveal tissue by the first postoperative month.

Subsequently, increased scrutiny has been applied to MIGS devices and their effect on ECD. By their very nature, these devices are expected to have an excellent safety profile. Thus, we are willing to surgically intervene earlier for a more modest IOP-lowering effect. High-quality long-term data may be lacking, but from experience with tube shunt and trabeculectomy, ECL with traditional filtering surgery does occur and can be significant. ECL rates at 2 years post-trabeculectomy have been reported to be around 10%. One study has shown a 7.8% and 11.8% ECL rate at 2 years postoperatively for 1-site and 2-site phacotrabeculectomies, respectively [50]. With tube shunt surgery (both Ahmed glaucoma valve and Baerveldt glaucoma implant surgery), ECL rates have been reported to range between 8.0% and 18.6% at 2 years [51-54].

There is limited data on the effect of MIGS devices on ECD. A previous study showed that the iStent Inject (Glaukos Corporation, Laguna Hills, California, USA) did not lead to substantial ECL at 1 year compared to phacoemulsification alone [55]. Additionally, by this point, more than 10 year of data is available on the iStent Inject with no known corneal complications reported. The 3-year results of the HORIZON study, assessing the safety and efficacy of the Hydrus microstent, showed that the addition of the microstent induced a 15% ECL versus 11% in the cataract surgery alone group. The proportion of patients who underwent >30% ECL was 14.2% in the microstent group versus 10% in the cataract surgery alone group. None of these differences were statistically significant. These patients are under continued monitoring for ECL. It is likely that ECD reduction is due to the initial surgical procedure itself, with the extra manipulations required for implantation. The presence of the Hydrus device is not thought to adversely threaten corneal health compared to cataract surgery alone. The iStent and the Hydrus microstent likely differ from the CyPass Micro-Stent in that their inlet lie further from the cornea. The CyPass device follows the curvature of the inner sclera and assumes a more vertical orientation; thus, its proximal tip is located closer to the peripheral cornea. If implanted too anteriorly, the collar can even come into contact with the cornea.

There remains little investigation on long-term effects of subconjunctival MIGS devices, such as the Xen Gel Stent (Allergan) and the PreserFlo MicroShunt (Santen), on the health of corneal endothelial cells. The few studies that have investigated this are small in sample size or investigate short-term effects only [56]. One 2-year study investigating the impact of the Xen Gel Stent on ECD concluded the ECL was similar in amount to standalone phacoemulsification [57].

Standalone Filtering Procedures Versus Combined with Phacoemulsification

Combining glaucoma and cataract surgery offers patients the advantage of having a single surgical experience, reducing risks of repeated surgery, and saving costly operating room time. However, some previous studies have demonstrated that standalone filtering surgeries showed better intraocular pressure (IOP) control than combined glaucoma surgery procedures [58-61]. In a retrospective series of 60 eyes, the IOP was significantly lower in the trabeculectomy group than the phaco-trabeculectomy group (11.08 +/− 2.80 mmHg vs. 15.04 +/− 2.40 mmHg, $p < 0.001$) [58]. Similarly, Kleinmann *et al.* found a significantly larger percentage reduction in IOP after trabeculectomy alone than after trabeculectomy combined with phacoemulsification (48.5% vs. 31.5%) ($P = 0.0001$) [59]. Bellucci *et al.* compared 100 trabeculectomies with 200 phaco-trabeculectomies and found that trabeculectomy alone resulted in a larger mean IOP decrease than phaco-trabeculectomy (11.2 mmHg vs. 3.1 mmHg; $P < 0.01$) [60]. In a retrospective cohort study of 40 eyes, Caprioli *et al.* found that mean IOP decreased more in the trabeculectomy alone group than in the combined phaco-trabeculectomy group (10.3 +/− 7.6 mmHg vs. 6.8 +/− 5.5 mmHg) [61]. They also found that a higher proportion of patients achieved the target pressure in the trabeculectomy alone group (88% vs. 72%). At 2 years, surgical success was achieved in 86% in the trabeculectomy group and in 62% in the phaco-trabeculectomy group. A possible hypothesis for the discrepancy in surgical success seen with combined phaco-trabeculectomy may be that perioperative inflammation associated with phacoemulsification produces negative consequences on bleb survival and IOP [59].

In contrast, other studies have found similar IOP-lowering effects with combined surgery and trabeculectomy alone [62, 63]. In a prospective study, Guggenbach *et al.* found no significant differences in mean IOP reduction between the two groups [62]. Similarly, in a retrospective analysis of 42 eyes, the mean IOPs (22.8 mmHg vs. 22.9 mmHg) and number of glaucoma medications (2.12 vs 0.2.26) were similar for phaco-trabeculectomy and standalone trabeculectomy, respectively [63]. No p-values were given for this study. At 4 years, Wachtl *et al.* also found that phaco-trabeculectomy had similar outcomes as trabeculectomy alone in terms of lowering IOP and reducing glaucoma medications [64]. In patients with primary angle closure glaucoma (PACG), there were no significant differences in mean IOP ($p = 0.42$), number of glaucoma medications ($p = 0.85$), or logMAR visual acuity ($p = 0.42$) between the trabeculectomy and phaco-trabeculectomy groups after 12 months [65]. However, it is important to mention that the IOP-lowering effect of phacoemulsification alone in angle closure cases has previously been documented and could well be a confounder in this latter study [32-35].

In a prospective case series of patients with refractory glaucoma, El Wardani *et al.* compared the efficacy and safety of standalone Baerveldt glaucoma implant (BGI) to combined phacoemulsification and BGI implantation [66]. They found a significantly higher failure rate in the combined group at 3 years (37% vs. 15%, $p = 0.02$). Additionally, a greater proportion of patients in the standalone BGI group had significantly lower IOP at 3 years. However, there were no significant differences in glaucoma medications or complications between the two groups. These results

suggest that combined surgery may have negative long-term effects on bleb survival, and that a staged approach of separating phacoemulsification and tube surgery should be considered.

Rai *et al.* conducted a retrospective cohort study to compare the efficacy of phacoemulsification combined with either Ahmed glaucoma valve (AGV) or BGI [67]. A total of 57 eyes underwent phaco-AGV and 47 eyes underwent phaco-BGI. At 2 years, 44% of the phaco-AGV group and 23% of the phaco-BGI group failed ($p = 0.02$). To the best of our knowledge, all other reports on combined phacoemulsification and tube shunt implantation have been noncomparative with small sample sizes [68-70]. As a result, the studies were only powered to show very large differences in failure rates. With these limitations in mind, all noncomparative studies have shown a significant reduction in IOP from baseline in eyes undergoing combined phacoemulsification and AGV or BGI.

A systematic review by Friedman *et al.* concluded that strong evidence of efficacy only exists for better IOP control with combined glaucoma and cataract surgery compared with cataract surgery alone. Otherwise, there seems to be weak evidence when comparing IOP control in combined cataract extraction and trabeculectomy versus trabeculectomy alone, or when looking at the deleterious effects of cataract surgery on pre-existing filtering blebs [71].

Although primarily considered blebless procedures, MIGS devices have begun to enter traditional filtering surgery territory with the advent of subconjunctival MIGS, such as the Preserflo MicroShunt (Santen) and the XEN Gel Stent (Allergan), while presumably retaining some of the increased safety profile known to MIGS. It has previously been demonstrated that trabecular bypass MIGS combined with cataract surgery lowers IOP and hypotensive medication used compared to cataract surgery alone [24, 23, 72, 73]. However, it is not yet clear whether subconjunctival MIGS combined with cataract surgery presents the same synergistic effect.

Several studies have compared the effectiveness of standalone XEN to combined XEN and phacoemulsification [74]. In a retrospective series comparing 200 cases of standalone XEN to 39 cases of phaco-XEN, Hengerer *et al.* found no significant differences between the two groups in terms of mean IOP at 1 year (standalone 14.3 +/− 4.2 mmHg vs. combined 13.9 +/− 2.5 mmHg) [75]. Similarly, Karimi *et al.* evaluated XEN standalone ($n = 187$) versus combined ($n = 72$) at 12 months [76]. They found no significant difference in outcomes between the two groups, and both cohorts had similar needling and complication rates. In a single center prospective study with 6 months of follow-up, 46.9% of XEN standalone eyes ($n = 81$) and 53.3% of phaco-XEN eyes ($n = 30$) achieved complete success [65]. There were no significant intergroup differences. In a 2-year, prospective, multicenter study, Reitsamer *et al.* compared 120 standalone eyes to 98 combined eyes [77]. The mean changes in IOP from baseline were − 6.4 +/− 5.2 mmHg in standalone and − 5.9 +/− 4.6 mmHg in combined eyes, with no statistically significant differences between the two groups. Additionally, Fea *et al.* compared 298 standalone eyes to 56 combined eyes at 1 year in a prospective, multicenter study [78]. The mean IOP at 1 year was 15.8 mmHg in the combined group and was 15.4 mmHg in the standalone group. There was a significantly lower IOP in the standalone group at the postoperative week 1 visit ($p = 0.04$), but no statistically significant differences at the subsequent follow-up visits. In terms of qualified and complete success, there were no significant differences between the two groups with IOP thresholds of ≤18 and 16 mmHg.

However, with an IOP threshold of ≤14 mmHg, the standalone group achieved a significantly higher success rate (41.6% vs. 22.9%, $p = 0.03$).

The only study to find a significant difference between XEN standalone and phaco-XEN was by Mansouri *et al*. in a prospective, interventional case series that compared the safety and efficacy of XEN standalone ($n = 40$) and combined ($n = 109$) at 1 year [79]. The median percentage IOP reduction was 40% in the XEN standalone group and 22.9% in the phaco-XEN group. Their primary endpoint, a 20% or more decrease from baseline IOP, was achieved in 81.0% of standalone eyes and in 56.1% of combined eyes ($p = 0.04$). However, it is important to note that the XEN standalone group had a higher median preoperative IOP (20 vs. 18 mmHg) and more advanced glaucoma than the XEN combined group. Additionally, more needling procedures were performed in XEN standalone eyes (45% vs. 34%), possibly contributing to a more pronounced IOP reduction.

In a review of previously published studies comparing XEN as a standalone procedure to combined with phacoemulsification, the authors acknowledged the heterogeneity of study design, inclusion and exclusion criteria, and statistical analysis for studies included in their review [74]. The authors themselves also disagree on whether XEN demonstrates better efficacy as a standalone or combined procedure, illustrating the clinical nuance of this question.

Take-Home Messages
• With a global population that is rapidly aging, ophthalmologists are likely going to face an impending burden of coincident age-related cataract and glaucoma patients in their practice.
• The iStent, Hydrus Microstent, and Kahook Dual Blade are some examples of microinvasive glaucoma surgery (MIGS) devices that can be combined with cataract surgery and can lower intraocular pressure (IOP) with minimal trauma to the eye.
• Cataract surgery alone can lower IOP and can be used as a treatment to lower IOP in certain cases; however, the extent to which it is lowered depends on specific patient factors and the type of preexisting glaucomatous disease.
• MIGS devices are expected to have a very high safety profile; as a result, there is ongoing research into how MIGS devices affect endothelial cell density.
• There is evidence that standalone filtering surgeries demonstrate better IOP control than filtering surgeries combined with cataract extraction; however, the extent of this difference and the exact type of filtering surgeries where this is observed may require further investigation.

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CLINICAL VIGNETTE

Intermediary Inflammatory Reaction After Micropulse Cyclophotocoagulation Diode Therapy: A Case Report

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Abstract

Introduction: Of the many types of laser cyclophotocoagulation procedures, micropulse cyclophotocoagulation diode is praised as a noninvasive, safe, and effective procedure with few complications. In this case report, we describe a rare complication that, to the best of our knowledge, has not been previously reported.

Case Report: We report on the case of a 66-year-old African man with a history of end-stage primary open-angle glaucoma. One week after undergoing micropulse cyclophotocoagulation diode therapy in both eyes, he developed severe intermediary inflammation in one eye, associated with decreased visual acuity. The intraocular pressure had significantly decreased after the procedure and was well controlled with intraocular-pressure-lowering medications. Slit lamp examination revealed a moderate anterior chamber inflammation, anterior vitritis, and a large inflammatory membrane attached to the posterior surface of the intraocular implant. A vitrectomy was finally performed in the left eye because of the persistent intermediary inflammation despite the use of high doses of topical and subconjunctival corticosteroids.

Conclusion: Intermediary uveitis is a rare complication after micropulse cyclophotocoagulation diode therapy. To the best of our knowledge, there have been no reports of vitritis after a noncomplicated micropulse cyclophotocoagulation diode in primary open-angle glaucoma.

Keywords: Case report, Ophthalmology, Glaucoma, Micropulse, Vitritis

Introduction

Laser cyclophotocoagulation (CPC) procedures have become a common surgical method used in refractory glaucoma patients to lower intraocular pressure (IOP). The principle is to reduce

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aqueous humor formation by laser-assisted destruction of the ciliary body. Of the many types of CPC procedures, micropulse cyclophotocoagulation diode (MPCPC) has recently gained popularity for its efficacy and safety. In multiple previous studies, micropulse diode laser has been shown to be more selective in targeting damaged tissue and minimizing collateral thermal injury to adjacent tissues [1].

Contrary to classical cyclodiode procedures, such as continuous-wave CPC, MPCPC delivers repetitive, shorter pulses of energy with rest periods, which allows the tissue to cool between laser pulses. It effectively confines the thermal effect to the absorbing tissue, resulting in a reduced risk of postoperative complications [2, 3]. We present the first reported case of intermediary inflammation after MPCPC diode therapy.

Case Presentation

A 66-year-old Congolese man presented to our clinic with a very advanced primary open-angle glaucoma (POAG) that had been rapidly progressing for the past 7 years. The visual field (VF) examination showed an extensive loss, with a more pronounced visual defect in the right eye (RE) Mean Deviation (MD −20.29 dB) than in his left eye (LE) (−17.73 dB). The RE revealed an IOP of 17 mmHg and a best-corrected visual acuity (BCVA) of 0.6. In the LE, we measured an IOP of 13 mmHg and a BCVA of nearly 0.4. His topical treatment consisted of bimatoprost and brimonidine/timolol in both eyes (BE). The VFs are shown in Fig. 1.

Even though the patient did not have a serious past medical history, we discovered a positive familial POAG through his father.

A trabeculectomy with mitomycin (MMC) was performed promptly on his RE to halt the fast progression. Postoperatively, his RE was treated with suturolysis and subconjunctival 5-fluorouracil (5FU) to prevent the scarring of the bleb. One year later, a cataract operation was performed

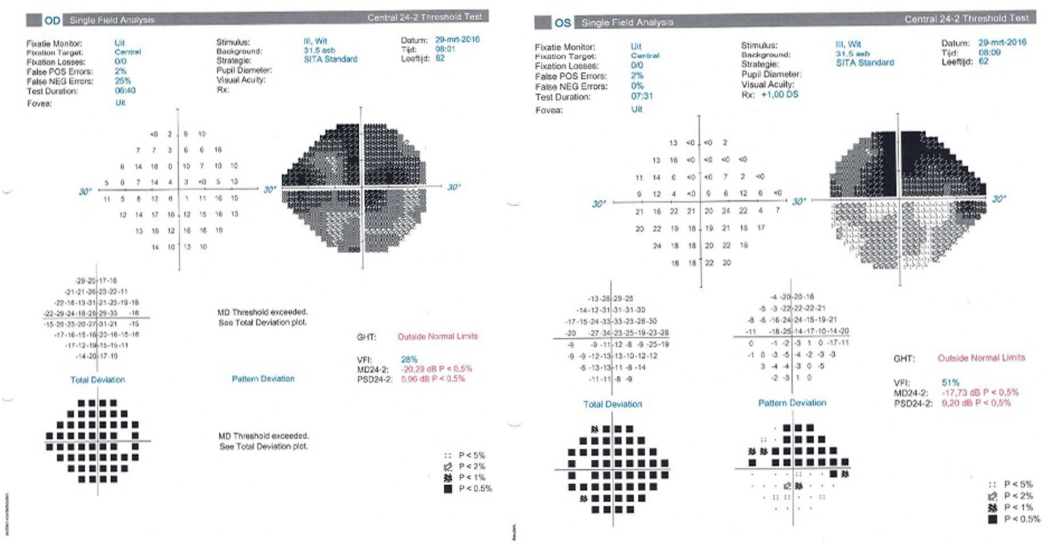

Fig. 1: Visual fields. Right eye (RE): 24.2 SITA standard stimulus III. Left eye (LE): 24.2 SITA standard stimulus III.

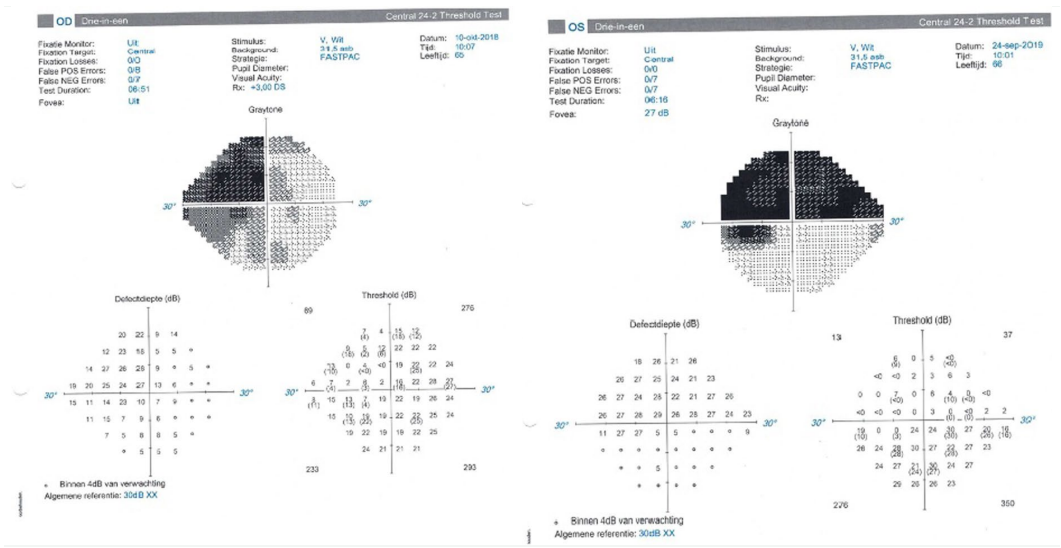

Fig. 2: Visual fields. Right eye: 24.2 FASTPAC stimulus V. Left eye: 24.2 FASTPAC stimulus V.

on the same eye. A mild anterior inflammation was observed 2 months after the surgery but was easily controlled with fluorometholone drops.

Unfortunately, despite topical treatment with bimatoprost and brimonidine/timolol (BE) and IOP of 11 mmHg minimum to 20 mmHg maximum (median 16 mmHg), the vision of the RE decreased to counting fingers (CF). The patient showed important hyperemia and ocular surface disease due to the topical medication. The treatment and regular follow-ups were impeded by the patient's long and frequent travels to and from Africa.

The LE underwent a noncomplicated cataract surgery. IOP ranged from 11 to 20 mmHg (median 15.2 mmHg). Memoptic (Densmore) orally was added because of its neuroprotective properties [4]. Yttrium aluminium garnet (YAG) capsulotomy was performed in both eyes 18 months later.

The mean IOP increased slowly, as did the progression of visual field loss in his best eye (LE) despite the treatment.

The last examination revealed an IOP of 20 mmHg and a BCVA of CF at 35 cm in the RE. In LE, we measured an IOP of 18 mmHg and a BCVA of 0.5. The VFs are shown in Fig. 2.

The slit lamp examination showed a calm pseudophakia and capsulotomy in BE and a nonfunctional superior trabeculectomy in the RE.

A total papillary excavation with no other fundus damage was noticeable in BE.

MPCPC was suggested as a noninvasive treatment to decrease the IOP specifically in this remaining functional eye to prevent further damage and delay a possible trabeculectomy in the LE. In the case of this patient, we were reluctant to perform a trabeculectomy because of the early failure of the trabeculectomy in his RE and the eventuality of a second failure in his last viable eye.

Because of the important ocular surface disease in our patient and the mild effect of adding a fourth hypotensive topical drop, we believed that it was not the best therapy to sufficiently

decrease the mean IOP, to prevent further VF damage. According to Neelankantan *et al.* [5] and Aptel *et al.* [6], the addition of a third or fourth topical antiglaucoma medication does not reduce the IOP significantly.

Aptel *et al.* [6] demonstrated the importance of obtaining the lowest possible IOP to prevent the visual field progression. Taking into consideration the aforementioned elements, we opted for an MPCPC in this patient.

MPCPC was performed under general anesthesia (without a retrobulbar block to avoid potential hemorrhagic complications) on both eyes. The first version treatment parameters recommended by Iridex were 2000 mW of 810 nm infrared diode micropulse laser, 31.3% duty cycle (0.5 ms on-time/1.1 ms off-time), and 90 seconds of laser delivery by "swiping" each inferior and superior hemisphere. The conjunctiva was covered by a layer of hydroxypropyl methylcellulose, and a first-generation probe was used. Subconjunctival steroids, Betamethasone acetate/betamethasone sodium phosphate were injected at the end of the procedure, with no complications being reported during the operation.

Postoperative examination on day 1 revealed a mild anterior inflammation and a lower IOP (12 mmHg) under his concomitant topical treatment (bimatoprost once a day and brimonidine/timolol twice a day) in BE. In the LE, we noticed a thin inflammatory membrane attached to the posterior surface of the posterior chamber intraocular lens (PCIOL).

The vitreous was clear in the RE. In the LE, we observed a mild vitritis with a blurry image of the optic disc and retina. Topical preservative-free dexamethasone drops were added three times a day in the RE and six times a day in the LE.

During the scheduled 1-week follow-up, the patient complained of vision decrease and mild pain in his LE for the last 2 days. The examination reported a BCVA of CF 35 cm in the RE and 0.15 in the LE compared with 0.5 preoperatively. Using topical steroid drops and the usual hypotensive topical treatment, the IOP was 11 mmHg and 10 mmHg in the RE and LE, respectively.

The slit lamp examination was unchanged in the RE but it showed a diffuse punctuate epithelial keratopathy (PEK) in the LE along with a thick inflammatory membrane attached to the posterior surface of the PCIOL.

A moderate anterior chamber inflammation was visible, and the vitritis had progressed relatively to the prior visit. Due to this, a detailed fundoscopic examination was difficult to obtain, but we could still see a blurry image of the optic disc and the retina. There were no signs of retinal detachment nor retinitis. The subconjunctival residues of the betamethasone acetate/betamethasone sodium phosphate celestone were still substantial in both eyes. This inflammatory reaction is visible in Fig. 3.

To manage this complication, the patient was treated with a high dose of topical preservative-free dexamethasone drops once every hour combined with an oxytetracycline + hydrocortisone ointment before bedtime in the LE. The hypotensive medication was changed to carteolol to prevent any further pro-inflammatory effect by brimonidine and prostaglandins.

One week after intensive treatment, there was no clinical improvement of either the posterior inflammatory membrane, nor the vitritis, and the BCVA remained the same (Fig. 4). The IOP was of 11 mmHg in the RE (bimatoprost + brimonidine/timolol drops) and 12 mmHg in the LE

(carteolol). To improve the situation and save the vision of his remaining functional eye, a vitrectomy for the LE was proposed.

The procedure allowed for a clear vitreous, free of inflammation, and the PCIOL remained stable at the end of the intervention. The usual post-vitrectomy topical treatment of combined tobramycin/dexamethasone and diclofenac, four times a day, were started in the LE. In the RE, the IOP-lowering medications (bimatoprost + brimonidine/timolol) were continued without topical corticosteroids.

Day 1 post-vitrectomy, the left BCVA was already improved to 0.2. The IOP was 12 mmHg. Slit lamp examination showed a very mild anterior reaction. The inflammatory membrane behind the intraocular lens was totally removed, and the fundus was clear, with the retina intact.

One week after the vitrectomy, examination of the RE was unchanged with a BCVA of CF 30 cm and an IOP of 7 mmHg under the same hypotensive topical three-therapy treatment.

Examination of the LE revealed a BCVA of 0.1, an IOP of 28 mmHg under the same anti-inflammatory topical treatment but without hypotensive medications; slit lamp examination showed diffuse PEK, a mild residual anterior chamber reaction. As we can see in Fig. 5, the vitreous cavity was clear and the fundus was visible and stable. Bimatoprost + brimonidine/timolol

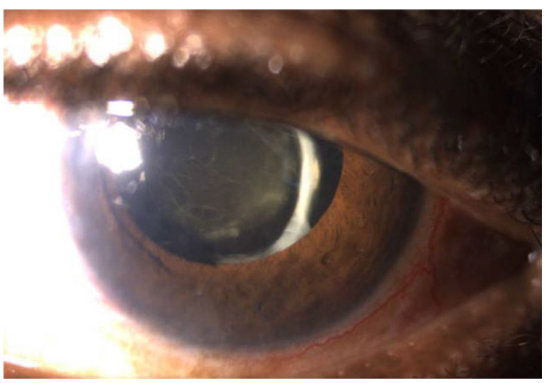

Fig. 3: Left eye 7 days after micropulse cyclophotocoagulation diode.

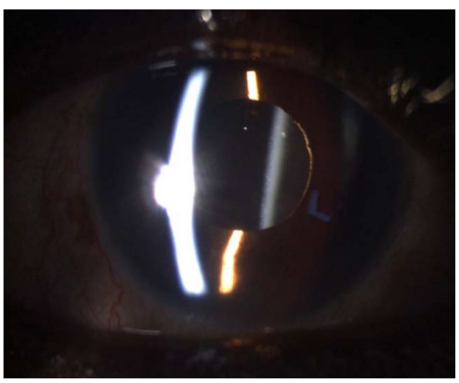

Fig. 4: Left eye 13 days after micropulse cyclophotocoagulation diode.

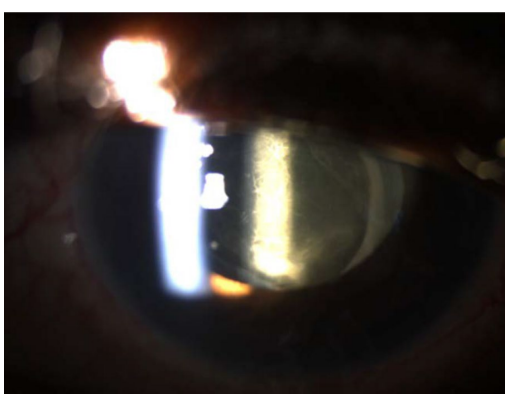

Fig. 5: Left eye after vitrectomy.

drops were administered in BE to maintain low pressure. Artificial tears were given in high quantity to restore proper epithelial integrity. To avoid a new and significant inflammatory reaction, topical corticosteroids (dexamethasone) were administered in the LE, in addition to the normal postoperative treatment.

Discussion

Our case report underlines an unexpected complication with a noninvasive method in a functionally monophthalmic, middle-aged patient There is no discussion about the choice of previous treatments. Consistent and meticulous follow-up with the patient was not possible because he resided in Kinshasa for extensive periods of time. The patient was treated to the best of our ability to stabilize the disease and within the constraints that we had to work with. Bernardi *et al.* [7], in a recent article, insist on the fact that MPCPC is a low-risk procedure, making it applicable to a broad spectrum of glaucoma cases, including patients with good central vision and not only in late-stage refractive cases.

The rapid progression of visual field loss, visual deterioration, and ocular surface disease, despite trabeculectomy in the RE, affected our decision to treat the patient before any further loss of the vision in LE. Our decision residing in our medical oath "*Primum non nocere*" made us opt for a noninvasive (or less invasive) treatment for his best eye. Despite our cautious and guarded approach, the patient had a major complication after micropulse. We were concerned about the vision in his remaining functional eye not improving after high doses of steroids. His social situation was also taken into consideration as he was a single man with little support, having to use public transportation. A vitrectomy was undergone to remove the thick inflammatory membrane from the back of his intraocular implant.

Anterior chamber inflammation, phthisis bulbi, hypotony, cystoid macular edema (CME), and scleral thinning, although at a lesser rate than continuous-wave CPC, have been previously reported. However, and to the best of our knowledge, no case of intermediary inflammation necessitating a vitrectomy as a complication of MPCPC diode has been described before. Aquino *et al.* [8] compared the efficacy and safety of MPCPC versus continuous-wave CPC in refractory glaucoma and reported a lower rate of complications in the micropulse group with a more consistent and predictable effect in lowering intraocular pressure. In their study, only 4% of cases showed prolonged inflammation after micropulse procedure compared with 30% in the continuous-wave CPC group, and the inflammation concerned only the anterior chamber. No case of intermediary inflammation has been reported. We can note the same from the conclusions of Emanuel *et al.* [9], who studied a large cohort of patients having undergone MPCPC; 86% had some degree of anterior chamber cell and/or flare at 1 week, improving to 46% at 3-month follow-up, but none of their patients (84 eyes) has had intermediary inflammatory reaction like our patient.

In the large longitudinal cohort study of Yelenskiy *et al.* [10] (197 eyes), only 2% developed postoperative cystoid macular edema as a complication. They do not report other severe complications.

Dhanireddy *et al.* [11] reported in their retrospective case series of 64 patients 2 patients with severe inflammation and hyphema post-MPCPC procedure. Again, those only concerned the anterior segment.

Even in children, no cases of intermediary uveitis have been reported Abdelrahman *et al.* [12] studied 45 eyes of children. They proved again that the rate of complications is lower with micropulse mode. However, two eyes developed pain and anterior uveitis.

Zaarour *et al.* [13] reported in their study a lower rate of complications after MPCPC procedures compared with those of Emanuel *et al.* or Williams *et al.* In fact, they did not observe any major complications, only transient inflammatory of the anterior chamber, which did not last longer than 1 month postoperation. Zaarour *et al.* pointed out an interesting hypothesis to this fact. They included only Caucasian patients, unlike these two other studies where respectively 4% and 29% African Americans were included. The aforementioned observation could be referenced to our patient, who was African and had a significant inflammatory reaction that we had never witnessed before in other patients.

In fact, it is thought that non-white races have a higher risk of developing prolonged inflammation and hypotony resulting in decreased BVA after diode CPC and other glaucoma surgeries [1].

As a result, we have tried to focus part of our discussion on African people treated by CPC. To our knowledge, there are no other studies of MPCPC other than those reported in this paper, although we did find the study of Abdull *et al.* [14], who investigated the safety and effectiveness of continuous CPC in Nigeria (Africa). In this large cohort of 201 eyes, 11 cases of mild anterior uveitis and one case of severe uveitis have been reported as complications. They did not describe the anatomical location of "severe" uveitis, but because they clearly made the difference with the "mild anterior" uveitis, it can be assumed that they referred to an inflammatory reaction similar to our patient. Furthermore, it is important to remember that Abdull *et al.* [14] analyzed patients treated by continuous CPC and not micropulse CPC like our patient.

To our knowledge, there have been no studies investigating the correlation of the complications with different factors such as age, race, severity of the disease, number of medications, number of previous operations, energy levels delivered by the laser, or time of swiping.

Conclusion

Intermediary uveitis is a rare complication after glaucoma surgery. Micropulse cyclophotocoagulation diode (MPCPC) is nowadays used increasingly and is praised for its safety and fewer complications. This case illustrates that rare, important complications such as intermediary inflammatory reaction can occur. This case is about an unexpected complication with a noninvasive surgery. It demonstrates the importance of informing patients about the possible risks and sometimes rare complications. Patient selection and regular follow-up in cases prone to important complications are crucial (Fig. 6).

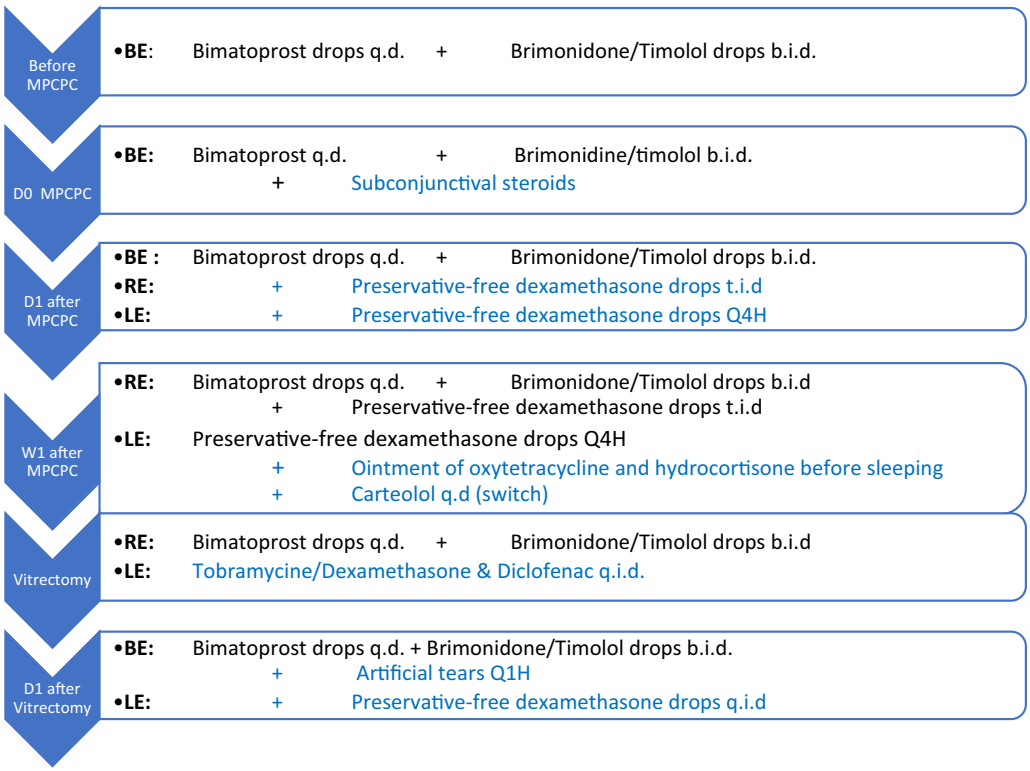

Fig. 5: Timeline of the patient's treatment and medications.

Acknowledgements: To our patient.

Authors' Contributions: GG conducted the literature review and wrote the manuscript. SP reviewed the manuscript and was the supervising glaucoma consultant. AS performed the vitrectomy. All authors read and approved the final manuscript.

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Declarations

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Waardenburg Syndrome Type 4 Coexisting with Open-angle Glaucoma: A Case Report

Li Zhang*, Yue Wan, Ningli Wang

Abstract

Background: Waardenburg syndrome is an autosomal dominant disorder with varying degrees of sensorineural hearing loss as well as abnormal pigmentation in hair, skin, and iris. There are four types of Waardenburg syndrome (1–4) with different characteristics. Mutations in six genes have been identified to be associated with the various types. Herein, we describe a case of Waardenburg syndrome type 4 combined with open-angle glaucoma.

Case Presentation: A 43-year-old Han Chinese man had undergone trabeculectomy due to progression of visual field impairment and unstable intraocular pressure in both eyes. Slit-lamp examination revealed diffuse iris hypopigmentation in the left eye and hypopigmentation of part of the iris in the right eye. Fundus examination showed red, sunset-like fundus due to a lack of pigmentation in the retinal pigment epithelium layer, diffuse loss of the nerve fiber layer, and an excavated optic nerve head with advanced-stage glaucoma. Imaging was performed using anterior segment optical coherence tomography to detect the iris configuration. In the heterochromic iris portion, the normal part of the iris showed a clear hyperreflective signal of the anterior border layer, while atrophy of the pigmented anterior border layer showed a hyporeflective area of the anterior surface resulting in reduced light absorption. Two mutations of the endothelin receptor type B gene were recognized in this study. The first (c.1111G>A on exon 7) leads to an amino acid change from glycine to serine at codon 371. Sanger verification revealed that this mutation is inherited from the mother. The other mutation (c.553G>A) leads to an amino acid change from valine to methionine at codon 185. Sanger verification showed that this mutation was inherited from the father.

Conclusion: Waardenburg syndrome shows a remarkable diversity in clinical presentation and morphology. This disease can also present with open-angle glaucoma. Sequencing analysis revealed two heterozygous mutations in the EDNRB gene in this patient, inherited from his mother and father, respectively. These two sites constitute a compound heterozygous variation.

Keywords: Waardenburg syndrome, *EDNRB* gene, Glaucoma, Genetics

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Background

Waardenburg syndrome (WS) is an autosomal dominant inherited neurogenic disorder presenting a combination of various degrees of sensorineural deafness and pigmentary abnormalities affecting the skin, hair, and eye [1, 2]. WS has myriad clinical features with incomplete penetrance and variable expressivity [3]. WS has an incidence rate of approximately 1 per 42,000 births [4]. Waardenburg syndrome has been described as four different types (WS 1–4) based on genotypic and phenotypic variations [5, 6].

WS 1 is characterized by the distinctive facial features of WS such as dystopia canthorum, a high nasal bridge, synophrys, hypoplasia of the alae nasi, and deafness. There is no dystopia canthorum in WS 2, and over 80% of patients have deafness, while more than 40% have heterochromia iridum [4]. WS 3 (Klein–Waardenburg syndrome) is a severe form of WS 1 presenting with skeletal abnormalities. WS 4 (Waardenburg–Shah syndrome) is characterized by the association of WS features and Hirschsprung disease, which causes severe blockage of the large intestine [7].

Waardenburg syndrome shows a high degree of genetic heterogeneity [4, 8-18]. WS 1 is caused by loss-of-function mutations in the *PAX3* (*paired box 3*) gene [8-11]. WS 2 is a heterogeneous group due, in part to mutations in the *MITF* (*microphthalmia-associated transcription factor*) [12] or *SOX10* (*SRY (sex-determining region Y)-box 10*) genes [13, 14]. WS 3 is caused by mutations in *PAX3* [10], with some patients being homozygous [11]. Five disease-causing genes have been identified in WS 4: *EDNRB* (encoding the endothelin-B receptor) [15], *EDN3* (encoding an endothelin receptor ligand 3) [16, 17], *SNAI2* (*snail-family transcriptional repressor 2*), *MITF* [12-14, 18], and *SOX10* [13].

Although not currently fully understood, all these genes are involved in a complex network in neural crest cells and other derivatives [4, 19, 20]. Therefore, genetic testing is an important method for diagnosing WS and its subtypes. The purpose of this study is to investigate the clinical and molecular characteristics of a patient with WS coexisting with open-angle glaucoma.

Case Presentation

We describe the case of a 43-year-old Han Chinese man with history of blue iris and open-angle glaucoma with severe optic nerve and visual field damage. Blue-colored iris was found since the patient was born. When he was 17 years old, juvenile open-angle glaucoma (OAG) was diagnosed. Trabeculectomy was undertaken in both eyes due to progression of visual field impairment and unstable intraocular pressure (IOP) when he was 18 years old (25 years ago). During 20 years of follow-up, the IOP ranged from 12 to 16 mmHg without antiglaucomatous medications. Bleb function of both eyes was very good.

Recent vision in both eyes was best corrected visual acuity (BCVA) of 0.4 with −9.00 diopters (spheric) in the right eye and hand movement (HM) in the left eye. Twenty-five years ago, when trabeculectomy was undertaken, his BCVA was 0.8 with −6.00 diopters (spheric) in the right eye and 0.1 with −7.00 diopter (spheric) in the left eye. The central corneal thickness (CCT) of the patient was measured by anterior segment optical coherence tomography (AS-OCT), giving measurements of 494 nm in the right eye and 499 nm in the left eye. His sight with both eyes was

worsening with glaucoma progression. Five years ago, the vision in his left eye decreased to hand movement, and from that time on, he began to take antiglaucomatous medication with prostaglandin eye drops. Exotropia was found due to low vision and disuse of his left eye. Horizontal nystagmus in both eyes was detected. He has no dystopia canthorum.

Slit-lamp examination revealed wide iris hypopigmentation in the left eye, just sparing a section between 1 and 2 o'clock, and in part of the iris of the right eye, sparing sections between 3:30 and 8:30 o'clock and between 10:30 and 12:00 o'clock.

It also showed clusters of pigmented granulations on the anterior lens capsule (Fig. 1).

Fundus examination showed red, sunset-like fundus due to a lack of pigmentation in the retinal pigment epithelium (RPE) layer, diffuse loss of the nerve fiber layer, and an excavated optic nerve head with advanced-stage glaucoma (Fig. 2).

Gonioscopic observation of the patient revealed heavy trabecular meshwork pigmentation. The angle between the iris and the surface of the trabecular meshwork was 45°. Normal iris vessel was seen located in the peripheral iris (Figs. 3 and 4).

Imaging was performed using anterior segment optical coherence tomography (AS-OCT) to detect the iris configuration (Figs. 5 and 6).

In the heterochromic portion of the iris of the right eye (heterogeneous color in the temporal part of the iris that includes normal and abnormal iris tissues), the normal part of the iris shows a clear hyperreflective signal of the anterior border layer, where increased light absorption causes optical shadowing and decreased visualization of the posterior pigmented epithelium. Atrophy of the pigmented anterior border layer (devoid of pigmentation or melanin pigment in the anterior border layer) shows a hyporeflective area of the anterior surface resulting in reduced light absorption. The OCT signal is therefore able to penetrate more deeply, which exaggerates the typical signal of the posterior pigmented epithelium. The nasal and temporal portions of the iris, including both abnormal and normal portions, show part of the hyporeflective signal of the anterior border layer, while reverse shadowing occurs with an obvious signal from the posterior pigmented epithelium, or part of the hyperreflective signal of the anterior border layer, while shadowing occurs with little signal from the posterior pigmented epithelium.

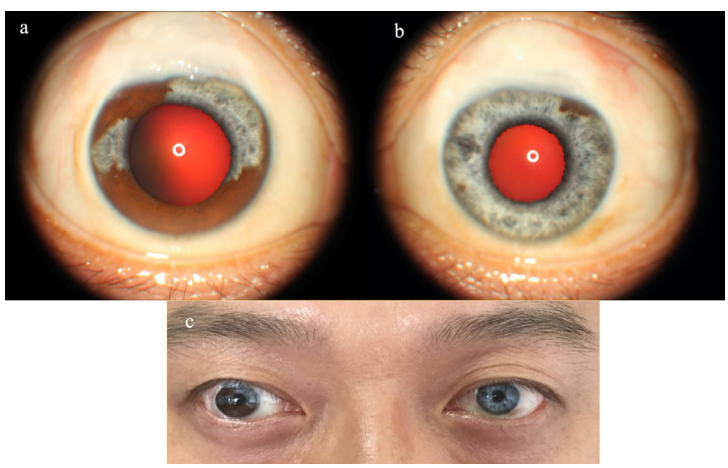

Fig. 1: Functional filtrated blebs were seen in both eyes (**a, b**). Slit-lamp examination revealed hypopigmentation of part of the iris in the right eye (**a**) and diffuse iris hypopigmentation in the left eye, just sparing a section between 1 and 2 o'clock (**b**).

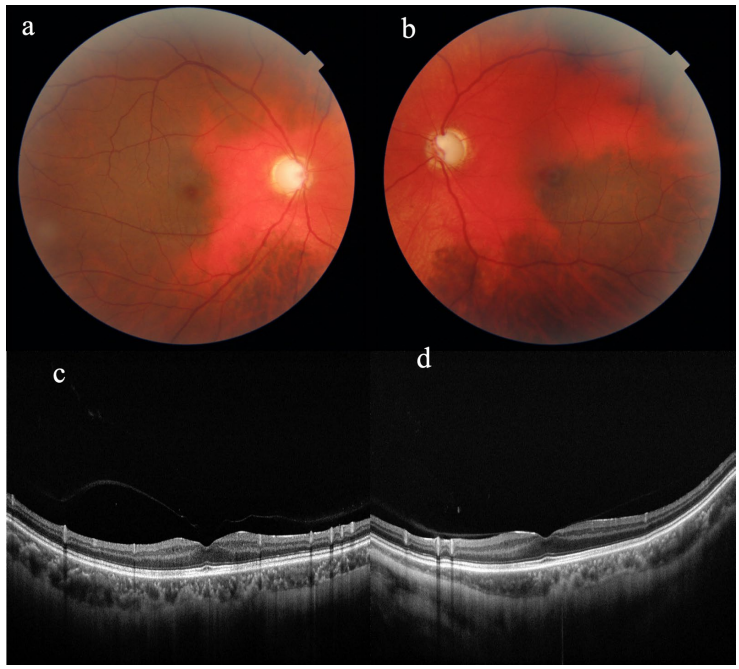

Fig. 2: Fundus examination showed diffuse loss of the nerve fiber layer and an excavated optic nerve head with advanced-stage glaucoma. The red, sunset-like fundus around the optic disc was seen due to a lack of pigmentation in the RPE layer. A normal retinal appearance can be seen in the area two or three optic disc distances away from the optic disc. Posterior segmental OCT showed abnormal retina with thinning of choroidal tissue at the parafovea in the left eye. **a** Fundus photograph of the right eye; **b** Fundus photograph of the left eye; **c** Macular image with OCT of the right eye; **d** Macular image with OCT of the left eye.

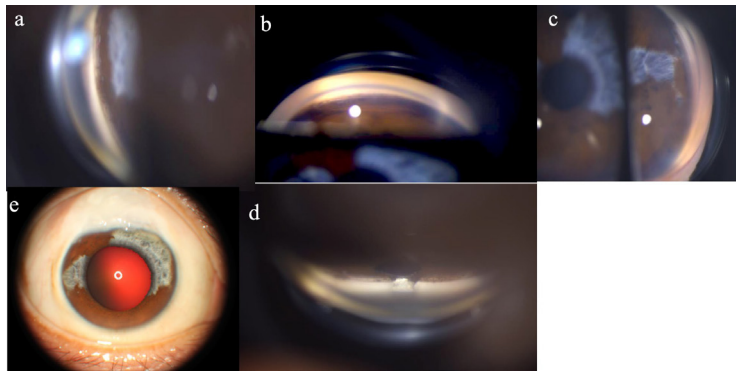

Fig. 3: Gonioscopic view of right eye showing that the angle was open, with heavy trabecular meshwork pigmentation seen. **a** Nasal angle. **b** Inferior angle. **c** Temporal angle. **d** Superior angle; inner opening of filtering surgery was seen. **e** External photograph of right eye.

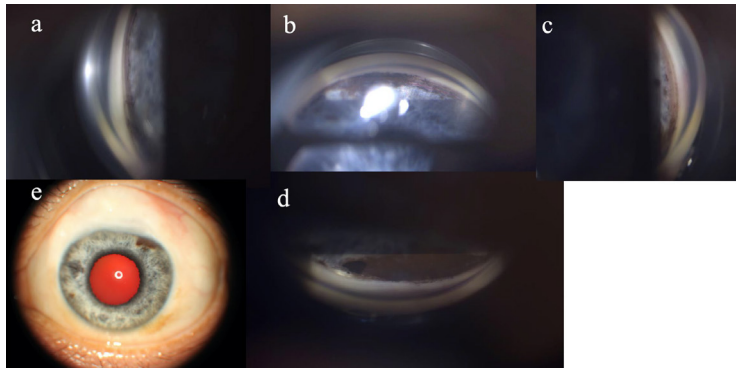

Fig. 4: Gonioscopic view of left eye shows that the angle was open, pigmentation of the trabecular meshwork increased, and iris vessel was exposed in the inferior angle (**b**). **a** Temporal angle. **b** Inferior angle. **c** Nasal angle. **d** Superior angle, inner opening of filtering surgery was seen. **e** External photograph of right eye.

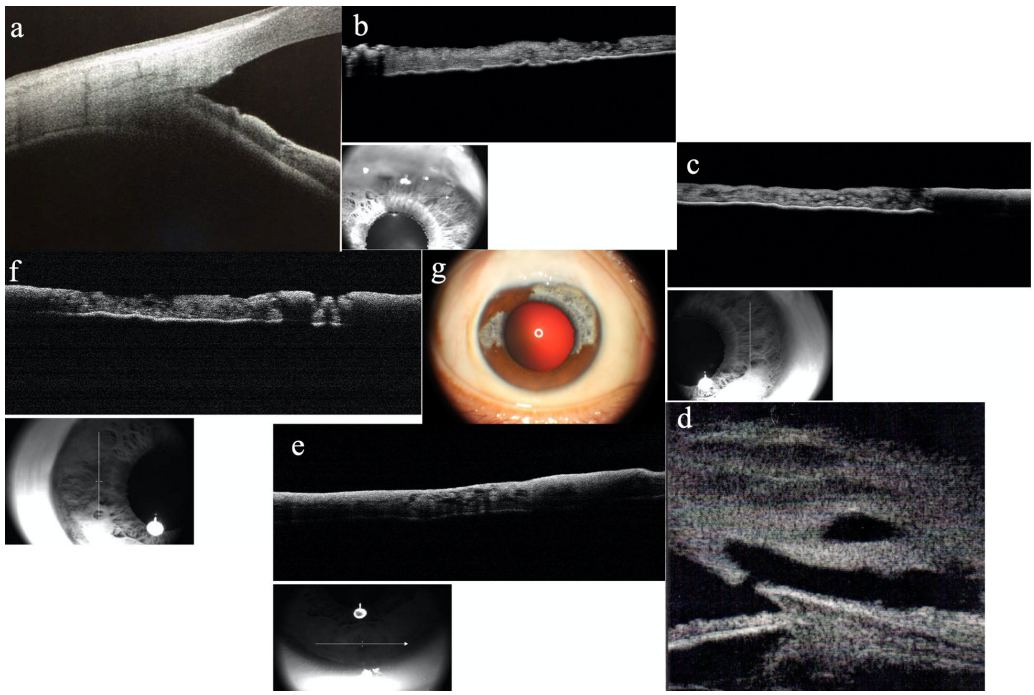

Fig. 5: AS-OCT of iris configuration and ultrasound biomicroscopy (UBM) of filter bleb in the right eye. **a** Open angle was seen. **b** Superior part of iris, showing atrophy of the pigmented anterior border layer (devoid of pigmentation or melanin pigment in the anterior border layer) resulting in a hyporeflective area of anterior surface and reduced light absorption. The OCT signal is therefore able to penetrate more deeply, which exaggerates the typical signal of the posterior pigmented epithelium. **c, f** Heterochromic iris in the nasal (**c**) and temporal part (**f**). Normal part of iris shows a clear hyperreflective signal of the anterior border layer, increasing light absorption and resulting in optical shadowing and decreased visualization of the posterior pigmented epithelium. In the part with a hyporeflective signal of the anterior border layer, reverse shadowing occurs with an obvious signal of the posterior pigmented epithelium. **d** Filter bleb in the right eye. **e** The inferior part of the iris is normal. AS-OCT shows a hyperreflective signal of the anterior border layer, while shadowing occurs with little signal from the posterior pigmented epithelium. **g** The part of the iris with hypopigmentation in the right eye, sparing sections between 3:30 and 8:30 o'clock and between 10:30 and 12:00 o'clock.

Posterior segment OCT shows abnormal retina with thinning of the choroidal tissue at the parafovea in the left eye. Analysis of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) (Optic disc cube 200 × 200) revealed an average RNFL thickness of 47 μm in the right eye and 49 μm in the left eye (Fig. 7a).

Severe visual field defects were found in the right eye with mean deviation (MD) of −13.52 dB (Fig. 7b), versus −27.87 dB in the left eye (Fig. 7c).

The patient's hearing test showed no neurosensorial hearing loss. Temporal bone findings were normal according to computed tomography (CT), and magnetic resonance imaging (MRI) did not show any cranial abnormality.

Ocular examinations were performed on the patient's parents, revealing no abnormal results except for cataract. The physical and ocular examinations of the patient's son were normal.

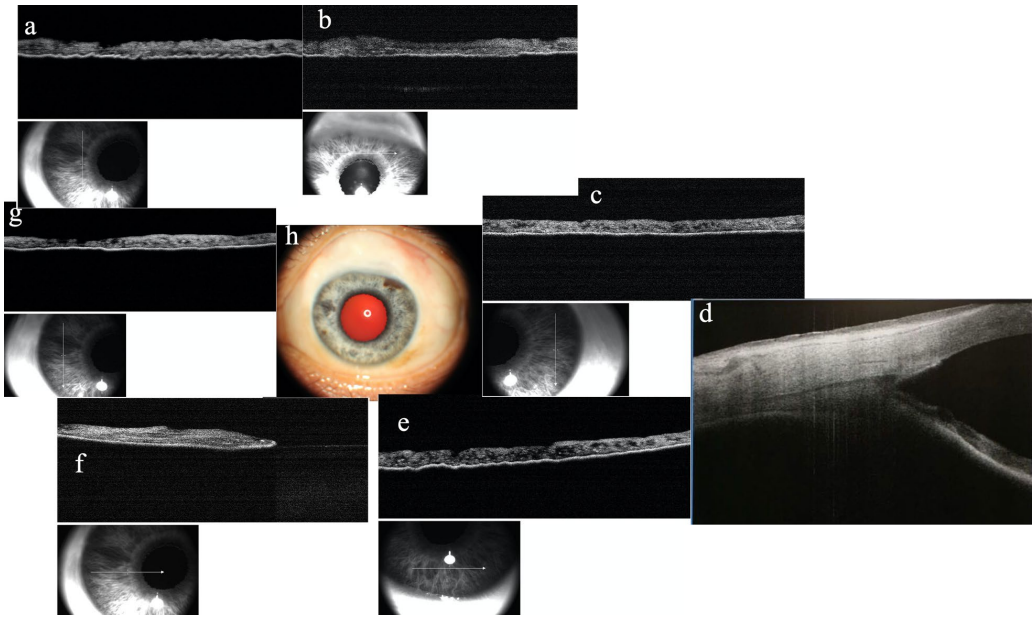

Fig. 6: Wide iris hypopigmentation in the left eye, just sparing a section between 1 and 2 o'clock. Most areas of the iris were devoid of pigmentation in the anterior border layer. The hyporeflective signal in the anterior border layer demonstrates shadowing with a hyperreflective signal in the posterior pigmented epithelium. **a** Nasal part of iris. **b** Superior part of iris. **c** Temporal part of iris. **d** Open angle. **e** Inferior part of iris. **f, g** Nasal part of iris. **h** External photograph of left eye.

For genetic testing, blood samples (with EDTA anticoagulant) were collected from the patient and his family members (mother, father, and son). The genomic DNA was extracted using the QIAampBlood Midi Kit (QIAGEN, Valencia, CA) according to the instructions. Candidate pathogenic mutations were identified by Sanger sequencing for all family members. The mutation was sequenced on an ABI 3730 analyzer (Applied Biosystem). Sites of variation were identified by comparison of DNA sequences with the corresponding GenBank (www.ncbi.nlm.nih.gov) reference sequences using Mutation Surveyor software.

The patient was diagnosed with juvenile open-angle glaucoma with Waardenburg syndrome based on his clinical features. No mutations in the gene associated with glaucoma were found in the patient.

Two mutations of *EDNRB* gene were recognized. The first (c.1111G>A on exon 7) leads to an amino acid change from glycine to serine at codon 371. This mutation is not found in the 1000 Genome, ESP6500, ExAC_ALL, or ExAC_EAS population databases. To confirm the c.1111G>A (p.G371S) variant, the patient and his parents were evaluated using Sanger sequencing, revealing that this mutation was inherited from the mother (Fig. 8).

The second mutation (c.553G>A) leads an amino acid change from valine to methionine at codon 185. The frequency of the mutation is extremely low in the 1000 Genome, ESP6500, ExAC_ALL, and ExAC_EAS population databases. Sanger verification revealed that this mutation was inherited from the patient's father (Fig. 9).

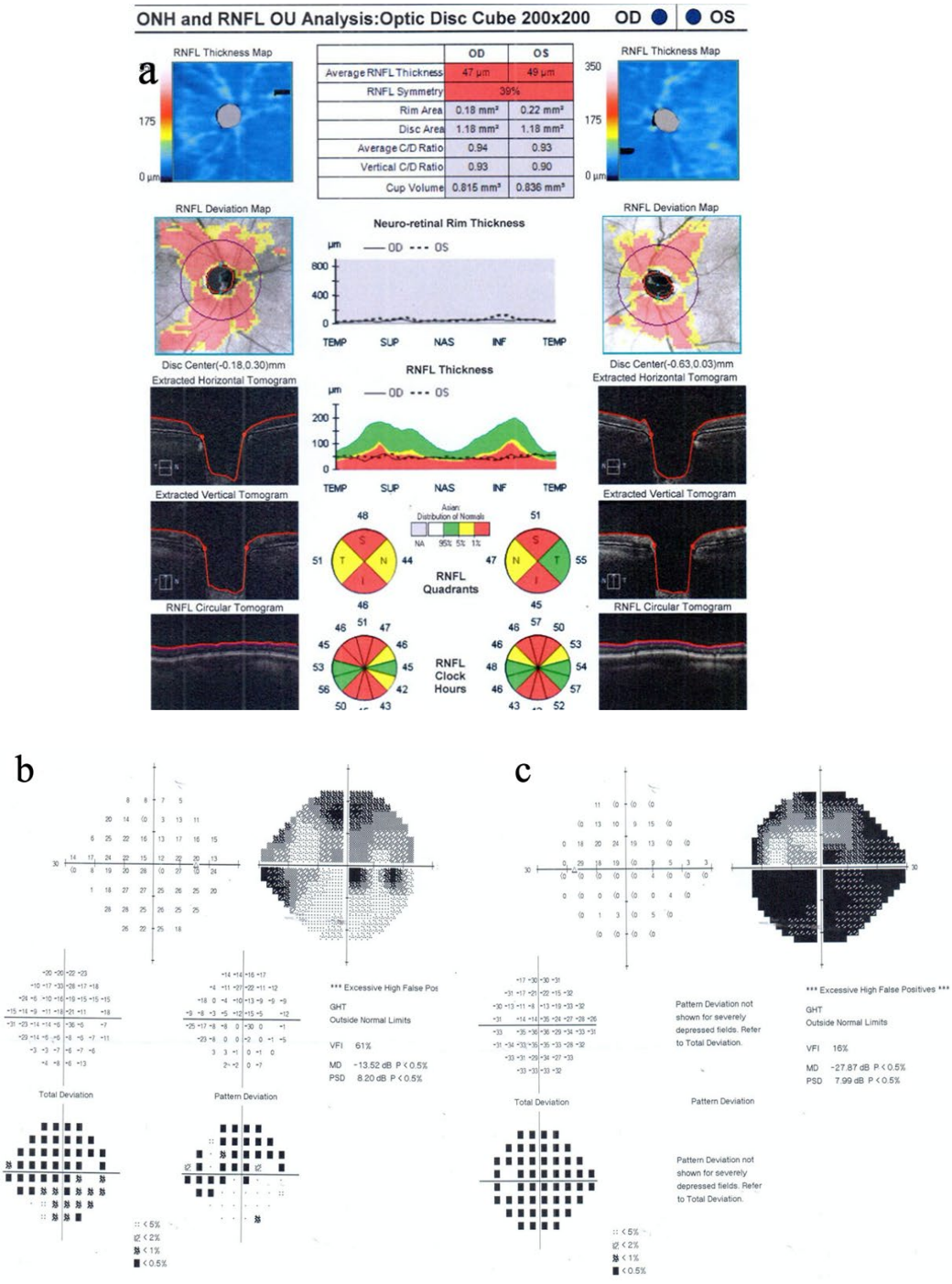

Fig. 7: PS-OCT shows diffuse loss of the retinal nerve fiber layer (**a**). Visual field damage is moderate in the right eye (**b**), but damage is severe in the left eye (**c**).

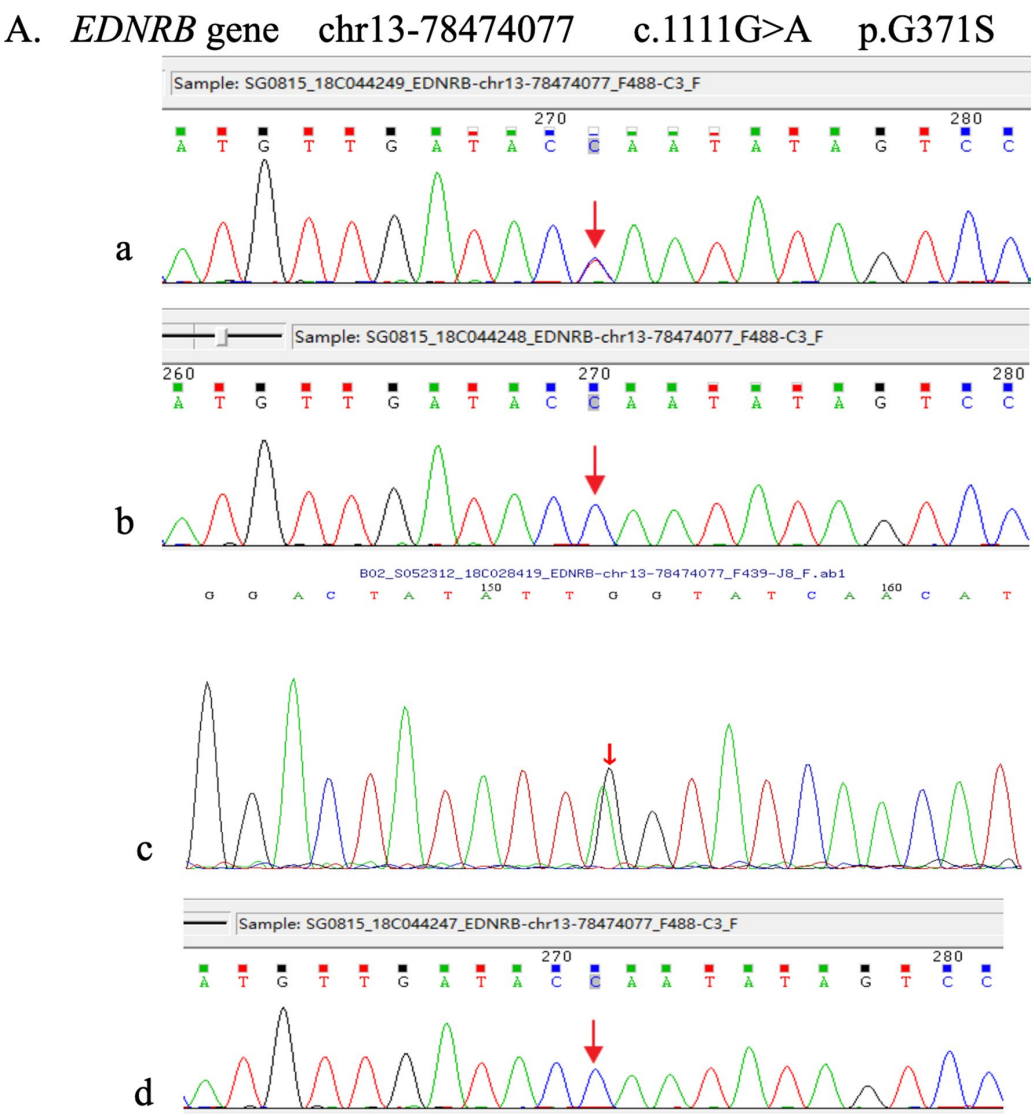

Fig. 8: To confirm the c.1111G>A (p.G371S) variant, the patient and his parents were evaluated by Sanger sequencing, revealing that this mutation was inherited from the mother. **a** The patient's mother. **b** The patient's father. **c** The patient. **d** The patient's son.

Predictions using SIFT, Ploy phen-2, and Mutation Taster revealed that both mutations were deleterious, while GEREP++ predicted that both mutations lay in conservative regions.

The *EDNRB* gene shows an AR inheritance pattern. Sequencing analysis revealed that there were two heterozygous mutations in the *EDNRB* gene in this patient, inherited from his mother and father, respectively. These two sites constitute a compound heterozygous variation.

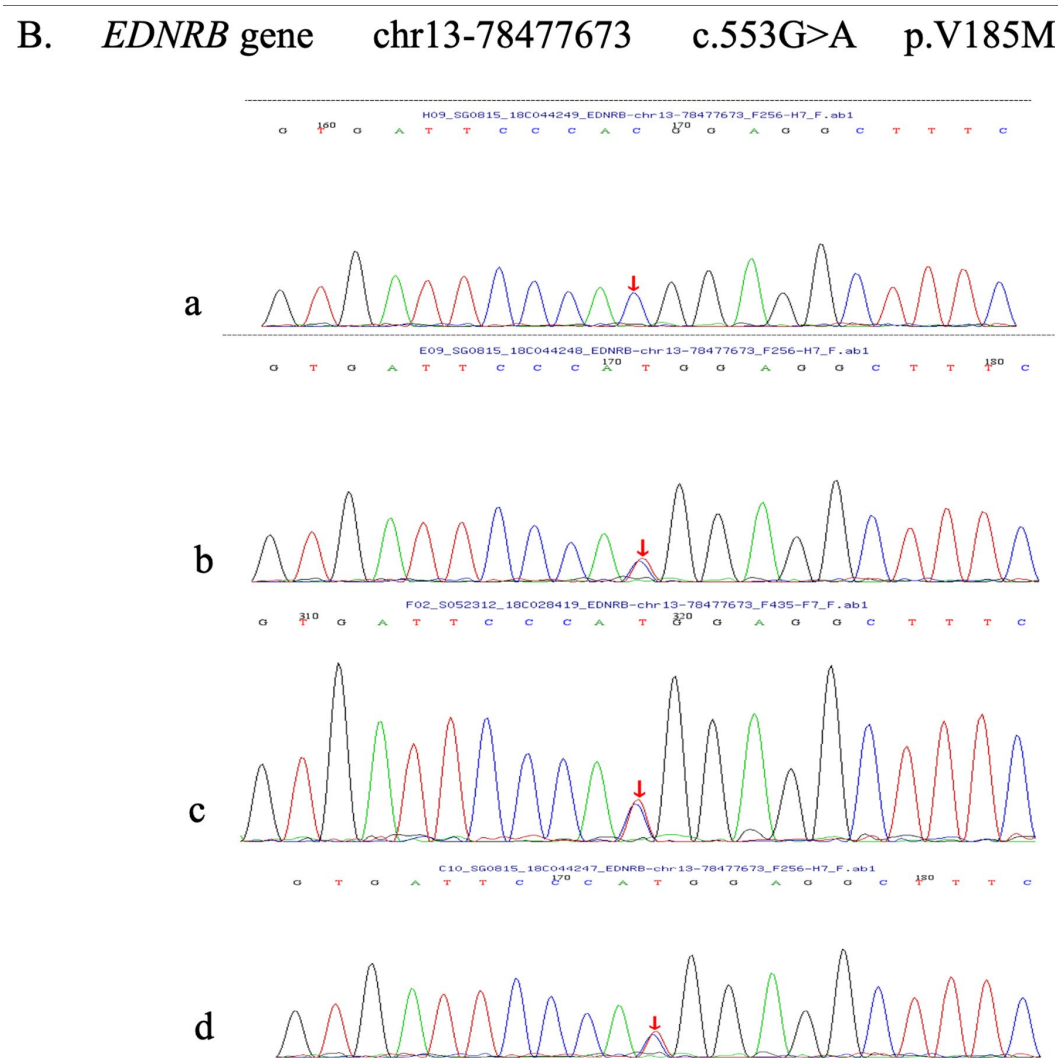

Fig. 9: The c.553G>A mutation leads to an amino acid change from valine to methionine at codon 185. Sanger verification revealed that this mutation was inherited from the patient's father. **a** The patient's mother. **b** The patient's father. **c** The patient. **d** The patient's son.

Discussion

Ophthalmological evaluation of the four types of WS reveals synophrys, ptosis, epicanthal folds, strabismus, telecanthus, iris hypopigmentation or heterochromia, high intraocular pressure, and choroidal hypopigmentation [21-25]. Beside iris heterochromia, WS patients show iris thickness changes in areas of hyper- and hypopigmentation [22]. Müllner-Eidenböck *et al.* reported patients with WS type II who presented with a fundus photo with ipsilateral connections between the iris

and fundus [26]. Kadoi *et al.* [27] reported a case of WS with hypopigmented fundi, branch retinal vein occlusion, and high intraocular pressure. Cortés-González *et al.* [28] suggested that posterior microphthalmos may be associated with WS type 2A. Shrinkhal *et al.* [24] reported a case of WS type 2 with bilateral blue iris, hypopigmented fundus, and a rare association of bilateral aqueous deficient type dry eyes. Nork *et al.* [29] and Gupta *et al.* [30] reported cases of WS with bilateral glaucoma. Abdelrahman reported a case of WS with juvenile open-angle glaucoma [31]. Meire *et al.* [32] reported a patient with WS who presented with Marcus Gunn ptosis with jaw-winking. Not only the external abnormalities, but also the intraocular defects, of patients with WS have been found in clinic.

In the present study of a patient with WS4, several abnormal characteristics of the eyes were reported, including nystagmus, thinner central corneal thickness, iris hypopigmentation and structure changing, choroidal hypopigmentation, and juvenile open-angle glaucoma. To date, glaucoma has not been considered as an associated characteristic of WS. No mutations in the gene associated with glaucoma were found in this patient.

WS is caused by mutation of six genes that affect the division and migration of neural crest cells during embryonic development. Six genes involved in Waardenburg syndrome include *PAX3* (encoding the paired box 3 transcription factor), *MITF* (microphthalmia-associated transcription factor), *EDN3* (endothelin 3), *EDNRB* (endothelin receptor type B), *SOX10* (encoding the Sry bOX10 transcription factor), and *SNAI2* (snail homolog 2) [4, 8-18]. Approximately 400 mutations including missense/nonsense mutations, frameshift mutations, insertions/deletions, and copy number variants (CNVs) have been identified in genes associated with WS [33-35]. Three causative genes have been identified for WS4, WS 4A, and WS 4B, including mutation of *EDNRB* and *EDN3*, respectively, while WS 4C is caused by heterogeneous mutation in the *SOX10* gene, which plays a major role in the development and migration of neural crest cells [25, 36, 37]. The interaction of these genes during the formation and development of melanocytes could be the pathogenesis of WS and related diseases [4, 19, 34].

Neural crest cells (NCCs) are multipotent stem cells with migratory ability that arise from the dorsal neural tube during embryonic development. The contribution of the major cranial neural crest to ocular development includes the periocular mesenchyme (POM), formed of migratory mesenchymal cells composed of neural crest cells and paraxial mesoderm cells [38]. The POM undergoes three migratory waves that give rise to various structures in the eye [39]. The first wave migrates into the region between the surface ectoderm and the newly invaginated optic vesicle, eventually condensing to form the corneal endothelium. The second wave migrates between the corneal epithelium and corneal endothelium, giving rise to the corneal stroma. Finally, the third wave migrates into the space adjacent to the anterior rim of the developing optic cup, contributing to the stroma of the ciliary body and iris, as well as the trabecular meshwork [39, 40].

WS and juvenile open-angle glaucoma coexisted in the patient of this present study. A possible mechanism could be that ocular melanocytes may be derived from the neural crest and a defect in pigmentation may therefore lead to developmental abnormalities in cornea, iris, iridocorneal angle structures, and trabecular meshwork.

In the present study, the patient had high intraocular pressure (before trabeculectomy) and enlarged cup-to-disc ratio, and decreased RNFL attributed to glaucoma. This patient was treated with antiglaucoma eye drops, and follow-up observation was needed regularly. This finding suggests that examination of intraocular pressure, optic disc ratio, and RNFL measurements may be necessary for patients with WS.

Mutations in the *EDNRB* and *EDN3* genes are inherited in an autosomal recessive manner in most cases, with patients carrying homozygous mutations manifesting WS4, whereas some individuals who are heterozygous for mutations in either gene may occasionally present with one or more features of the disease [15-17].

The patient in this study presented characteristics of iris heterochromia and choroidal hypopigmentation of WS. Anterior segment dysgenesis (ASD) is a group of developmental disorders in which structures found in the anterior segment of the eye, many of which receive neural crest contributions, develop abnormally [20, 40]. Waardenburg syndrome is one of those rare neural crest diseases. Decreased central corneal thickness and dysfunctional trabecular meshwork may be associated with juvenile open-angle glaucoma. External abnormalities such as nystagmus and strabismus in this patient were speculated to be secondary to severe damaged visual function attributed to glaucoma.

Gosain *et al.* reported that *EDNRB* was deleted from the neural crest, resulting in mutants with defective neural crest cell migration [41]. The mutations in *EDNRB* may explain both ophthalmic features of WS and juvenile open-angle glaucoma in this patient.

Despite many efforts to differentiate clinically between the subtypes of WS on the basis of diagnostic criteria [42], its rarity and highly varied expression have limited the ability to make an accurate diagnosis in individual patients. Thus, the accuracy of WS diagnosis needs to be improved by using additional diagnostic procedures such as genetic testing.

Conclusion

Waardenburg syndrome exhibits a remarkable diversity in clinical presentation and morphology. In this study, the patient was first diagnosed as having juvenile open-angle glaucoma. Waardenburg syndrome was diagnosed based on clinical features and genetic testing. Two mutations of *EDNRB* gene were recognized, thus WS type 4A was subtyped diagnosed. Since ocular melanocytes and the trabecular meshwork derive from the neural crest cell, mutations in the *EDNRB* gene can contribute to defective neural crest cell migration and developmental abnormality in anterior and posterior segment dysgenesis.

Abbreviations: WS: Waardenburg syndrome; IOP: Intraocular pressure; ONH: Optic nerve head; OCT: Optical coherence tomography; AS-OCT: Anterior segment optical coherence tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; RPE: Retinal pigment epithelium; MD: Mean deviation; RNFL: Retinal nerve fiber layer; AD: Autosomal dominant; AR: Autosomal recessive; PAX3: Paired box 3; SOX10: SRY-box 10; EDN3: Endothelin 3; MITF: Melanogenesis-associated transcription factor; EDNRB: Endothelin receptor type B; SNAI2: Snail-family transcriptional repressor 2.

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Declarations

Ethics approval and consent to participate: Institutional review board waived the approval to publish the case details.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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