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March 2014
OPTOMETRISTS
ASSOCIATION AUSTRALIA
ADVANCING OPTOMETRY

Glaucoma

SPECIAL ISSUE

Optometric diagnosis and management

FOR wAMD†

20/200

20/100

20/70

20/50

20/40

20/30

20/25

20/20

ONE INJECTION EVERY TWO MONTHS*

***EYLEA® wAMD† TREATMENT IS INITIATED WITH ONE INJECTION PER MONTH FOR THREE CONSECUTIVE MONTHS, FOLLOWED BY ONE INJECTION EVERY TWO MONTHS[1]**

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Required information for wet AMD. EYLEA is not PBS listed for CRVO.

BEFORE PRESCRIBING, PLEASE REVIEW FULL PRODUCT INFORMATION AVAILABLE ON REQUEST FROM BAYER AUSTRALIA LTD, ABN 22 000 138 714, 875 PACIFIC HIGHWAY, PYMBLE, NSW 2073 or go to www.ebs.tga.gov.au

MINIMUM PRODUCT INFORMATION EYLEA® [aflibercept (rch)] INDICATIONS: EYLEA (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wet AMD); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*. **DOSAGE AND ADMINISTRATION:** Injection volume of 50µL EYLEA (equivalent to 2mg aflibercept). For wet AMD: Treatment is initiated with one intravitreal injection per month for three consecutive months, followed by one injection every two months. For CRVO*: Treatment is initiated with one intravitreal injection per month. After the first three monthly injections, the treatment interval may be extended based on visual and anatomic outcomes. The treatment between doses should not be shorter than one month. Monitoring should be done at the injection visits. During treatment interval extension, the monitoring should be determined by the treating physician based on the individual patient's response. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; arterial thromboembolic events*; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: conjunctival haemorrhage, eye pain. Common: retinal pigment epithelium tear, detachment of retinal pigment epithelium, cataract, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, corneal oedema, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, conjunctival hyperaemia, ocular hyperaemia. Others: see full Product Information. Date of most recent amendment: November 2013

*Please note changes in Product Information.

Reference: 1. EYLEA Product Information. †wAMD = Wet age-related macular degeneration

EYLEA®
aflibercept (rch)
solution for intravitreal injection

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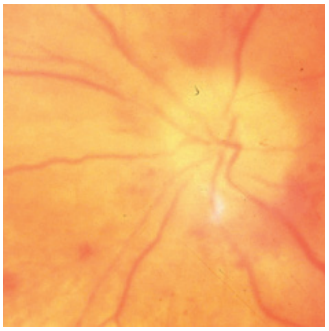
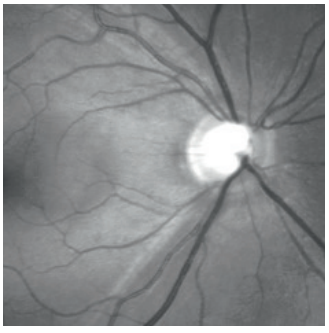
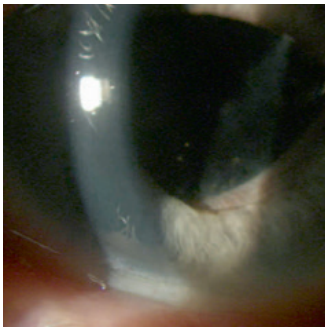
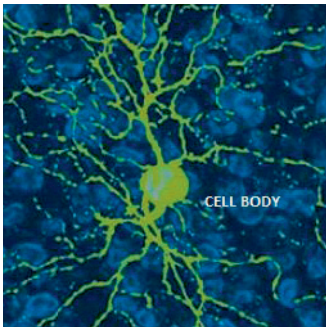
March 2014 Glaucoma issue









Editor
JEFF MEGAHAN

National Publications Manager
SANDRA SHAW

Clinical Editor
Associate Professor MARK ROTH FAAO
Department of Optometry and Vision Sciences, The University of Melbourne

Graphic design
GORAN NIKOLIC

Optometrists Association Australia
ABN 17 004 622 431

204 Drummond Street
Carlton VIC 3053
Tel (03) 9668 8500
Fax (03) 9663 7478

j.megahan@optometrists.asn.au
www.optometrists.asn.au

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Pseudoexfoliation syndrome

Clinical signs, lens and glaucoma

Kristen Lambert
BS

Leonid Skorin Jr

OD DO MS FAAO FAOCO
Mayo Clinic Health System, Albert Lea MN, USA

PSEUDOEXFOLIATION syndrome (PXF) is a systemic condition that primarily affects the eyes. It is not a true exfoliation but consists of white, flaky material that is deposited on the lens capsule and other anterior eye structures. True exfoliation is extremely rare and is usually seen in glassblowers whose exposure to infrared radiation over time causes the delamination of the anterior lens capsule. There is some argument about whether pseudoexfoliation should actually be named exfoliation syndrome because true exfoliation is uncommon, and both nomenclature can be found in the literature.[1,2]

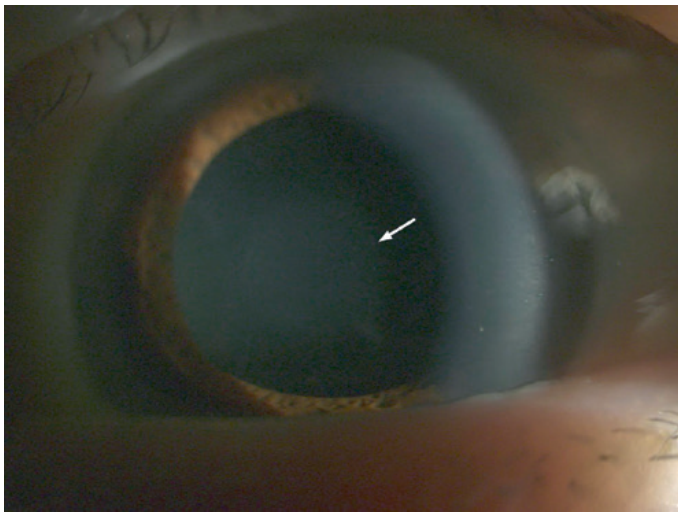
Pseudoexfoliation syndrome is traditionally described as affecting people of Scandinavian decent; however, it can also be found in other European ethnic groups as well as in the Middle East, Southeast Asia, India, South Africa, and South America.[2] The incidence increases with age and is rarely seen in those younger than 50 years old. An incidence of one per cent in ages 52-64 and five per cent in those over 75.6 years old has been reported in the United States.[3] England, Germany and France have a prevalence of 1-5 per cent.[3] In older Scandinavians (over 60 years), the prevalence has been reported to be as high as 20-25 per cent.[3] The condition is familial and seems to portray autosomal dominant inheritance, according to recent studies.[1,3] Prevalence appears to be equal between the sexes.[1,2,4] Other studies indicate a higher prevalence in women.[3]

Risk factors are thought to be high altitude, diet and exposure to ultraviolet light, although the aetiology is still poorly understood.[2] PXF is not associated with any specific systemic disease, but pseudoexfoliation material deposits in tissues that are histologically similar to those in the anterior segment of the eye including the skin, heart, lungs, liver, kidneys, meninges and gall bladder.[1] There is no evidence that PXF causes an increase in mortality.[4]

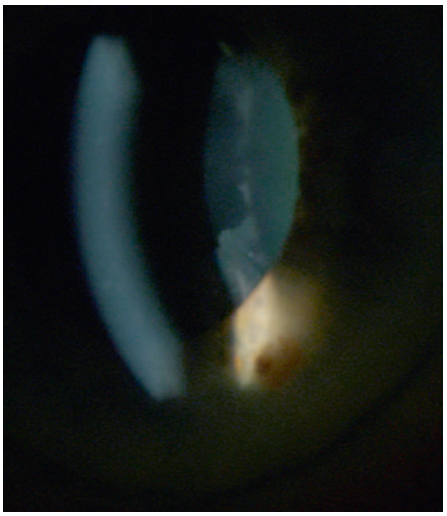
Although it has been extensively researched, the exact composition of the white, dandruff-like material is still unknown. The substance is a fibriller glycoprotein material and is believed to be the result of either abnormal metabolism or overproduction of glycosaminoglycans from the basement membrane of pre-equatorial lens epithelium, non-pigmented ciliary epithelium, iris pigment epithelium, corneal and trabecular endothelium, and iris stromal cells.[3]

Clinical signs

Diagnosis of PXF is usually based on the slitlamp finding of deposits on the lens capsule.[4] The pseudoexfoliative material classically appears on the anterior lens capsule in a 'bull's eye' or 'target' pattern (Figure 1) with a central disc, clear middle zone and granular peripheral zone often with serrated edges which is best seen with pupil dilation (Figure 2). The clear area is due



▲ Figure 1. 'Bull's eye' appearance of pseudoexfoliative material where physiological dilation and constriction of the pupil create a clear zone on the anterior lens capsule surrounding a central disk (arrow)



▲ Figure 2. Serrated presentation of pseudoexfoliative material on anterior lens capsule

complications, cataract formation associated with PXF

Intraoperative	Postoperative
Shallow anterior chamber	Acute rise in IOP
Small pupil	Capsular contraction (phimosis)
Zonular dehiscence	Corneal oedema
Capsular rupture	Cystoid macular oedema
Lens displacement	IOL deposits
Vitreous prolapse	IOL dislocation
	Posterior capsular opacification

▲ Table 1. Complications associated with cataract surgery in PXF.[3,5] Note: not a complete list

to the rubbing of the posterior iris on the capsule during physiologic dilation and constriction of the pupil. This also leads to liberation of iris pigment causing iris transillumination defects and pigment deposition in the trabecular meshwork that can be seen with gonioscopy.[1,3] The white, flaky material deposits on the pupillary border in 32-94 per cent of patients.[3] Loss of pupillary ruff may occur leading to an inverted ruff in some cases.

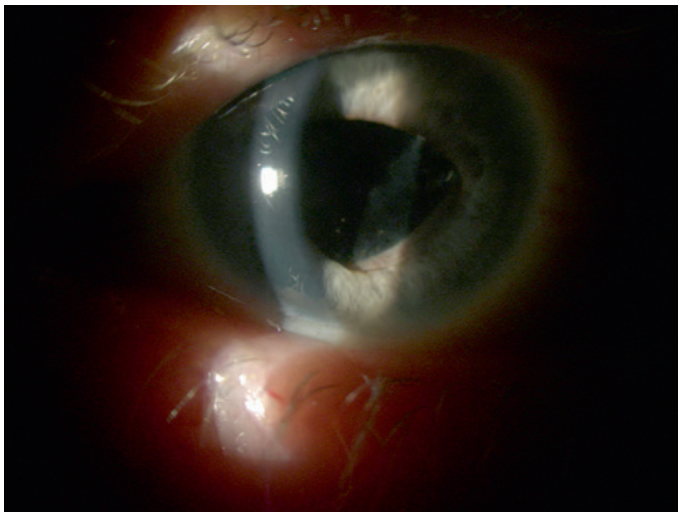
Pupils often dilate poorly in PXF because the iris is more rigid than normal in this condition or, more likely, because of sphincter and dilator muscle degeneration.[3] Posterior synechiae formation is also possible.[1] The corneal endothelium may have a dusting of pseudoexfoliative material and iris pigment granules resembling Krukenberg's spindle in pigmentary dispersion syndrome. However, in PXF, the deposits are larger and more diffuse. The liberated pigment may settle anterior to Schwalbe's line creating a distinct Sampaolesi's line that may be viewed with gonioscopy. The deposits first accumulate on the zonules and ciliary body where the material is actively produced. Pseudoexfoliative material may be seen on the vitreous face, posterior capsule, and the intraocular lens (IOL) after cataract extraction.[3] PXF is bilateral but asymmetric in the vast majority of cases.[1]

Lens complications

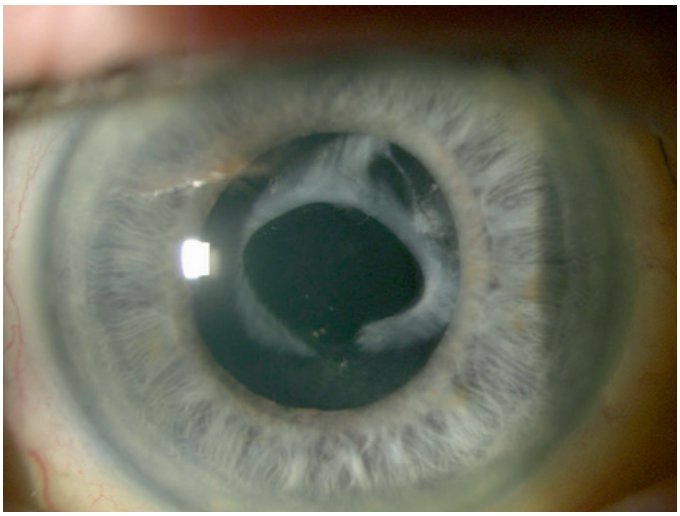
Patients with PXF have accelerated cataract formation, particularly with nuclear sclerotic cataracts.[1,3] Deposition of pseudoexfoliative material on the zonules is believed to cause proteolytic damage leading to zonular weakness and breakage, which may result in phakodonesis or spontaneous subluxation of the natural lens or IOL.[2,5] It stands to reason that the more pseudoexfoliative material present, the more likely phakodonesis or pseudophakodonesis may occur, although it has been reported that the degree of zonular weakness does not seem to correlate with the amount of material visible.[3,5]

Patients with PXF are about 10 times more inclined to have cataract surgery

Continued page 4



▲ Figure 3. Iris capture due to IOL subluxation post-cataract extraction



▲ Figure 4. Anterior capsule phimosis right eye in patient with PXF

Pseudoexfoliation syndrome

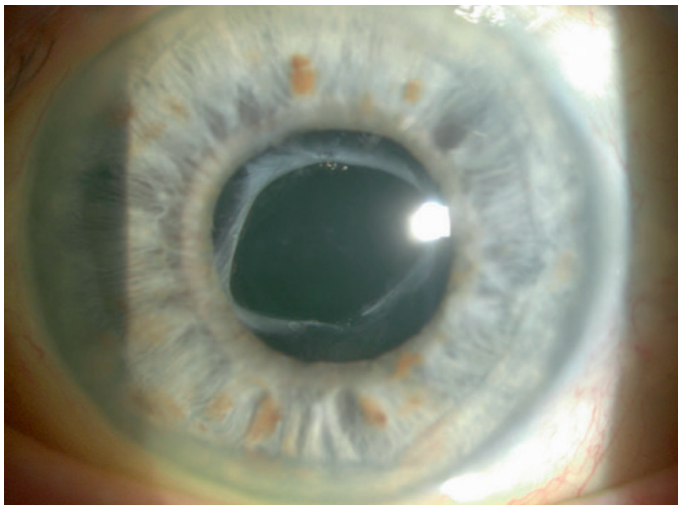
From page 3

complications, both intraoperatively and postoperatively (Table 1).[6] Intraoperative complications include poor pupil dilation, capsular rupture, zonular dehiscence, lens displacement and vitreous loss.[1,3] The risk of vitreous loss is up to 10 times higher than in eyes without PXF. Complications can be minimised by mechanically dilating pupils smaller than 6.0 mm with iris hooks especially since progressive pupil constriction may occur during surgery.[4]

If capsular wrinkling is present during the initial capsulotomy, significant zonular weakening is present and capsular tension rings to stabilise the capsular bag may need to be used. Making a larger capsulorhexis can also help reduce stress on the zonules. If there is a high amount of zonular dehiscence, suturing the IOL implant or using an anterior chamber IOL should be considered.[2] Postoperative complications include posterior capsular opacification, IOL and capsular bag decentration (Figure 3), capsular contraction (phimosis) (Figures 4 and 5) and transient intraocular pressure (IOP) elevation. In one study, the average time between IOL implantation and dislocation was seven years.[3]

Pseudoexfoliative glaucoma

Pseudoexfoliative glaucoma (PXG) is the most common cause of secondary open-angle glaucoma in the world, accounting for 20-25 per cent of all chronic open-angle glaucoma,[3,6] and 40-50 per cent of patients with PXF go on to develop PXG.[2,3,6] In one study, 44 per cent of patients with PXF were diagnosed with PXG within 15 years.[7] Although there is disagreement on whether PXF is more prevalent in males or females, there is little disagreement in the literature that there is equal gender prevalence in PXG.[1,3] It is unknown why some patients with PXF develop PXG, but according to recent studies, the most important risk factor for predicting the conversion was initial IOP.[3]



▲ Figure 5. Anterior capsule phimosis left eye in patient with PXF

In PXF, white, flaky material and pigment are deposited passively in the trabecular meshwork, but there is no glaucomatous increase in IOP. Mechanical clogging of the trabecular meshwork by pigment granules is thought to be the main cause of decreased aqueous outflow leading to a rise in IOP and subsequent damage of the nerve fibre layer in PXG. In one study, the amount of pseudoexfoliative material in the trabecular meshwork was similar in PXG and non-glaucomatous PXF eyes while the degree of pigment was much greater in eyes that were considered glaucomatous.[1] Other possible mechanisms of PXG include cellular dysfunction of the trabecular meshwork or of the endothelium of Schlemm's canal.[3]

Most cases of PXG are secondary open-angle glaucoma. In some instances, IOP can rise suddenly and an acute form of open-angle glaucoma with similar signs and symptoms as acute angle-closure can occur.[2] Patients may experience blurred vision, red eyes, corneal oedema, and IOPs 50 mmHg or higher. Eyes with PXF are also more likely to have narrow angles that may lead to angle-closure glaucoma. This occurs because of the formation of posterior synechiae or from pupillary block caused by zonular weakness and forward displacement of the natural lens.

PXG is more difficult to manage than primary open-angle glaucoma (POAG) and has a worse prognosis. Compared to POAG, PXG usually has a poorer response to medications, more frequent need for surgical intervention, more diurnal fluctuation of IOP and worse visual field defects at the time of diagnosis. Glaucomatous changes to the optic nerve are more diffuse in PXG than in POAG where cupping is usually observed inferotemporally or superotemporally.[3] The optic nerve may be especially vulnerable in PXG due to elastosis of the lamina cribrosa.[2]

Treatment for pseudoexfoliative glaucoma

There is no known mechanism to prevent PXF from progressing to PXG. Since IOPs can rise within a matter of months, it is important to monitor patients with PXF every four to six months to check IOP and perform yearly dilated fundus exams and visual fields. PXF patients with concomitant ocular hypertension should be treated earlier and more aggressively to delay glaucomatous damage.[3]

PXG is treated much like POAG. First-line therapy is pharmaceutical with prostaglandin analogs which can successfully lower IOP by increasing uveoscleral outflow. Medications that decrease aqueous production (beta-blockers, carbonic anhydrase inhibitors, and alpha-agonists) have also been shown to be effective in lowering IOP.[1] Theoretically miotics should be a first-line therapy because they can also slow progression by preventing the rubbing of the iris on the lens and decreasing the amount of iris pigment liberated while the pupil is constricted. However, miotics are not the drug of choice because posterior synechiae

may develop and many patients also have nuclear sclerotic cataracts which contraindicate the use of miotics.[3]

Cataract extraction helps to decrease IOP and helps to prevent liberation of iris pigment because the iris rarely continues to rub along the IOL implant. Extraction is not a cure because pseudoexfoliative material still accumulates in pseudophakic eyes.[4]

Surgical treatment is often needed as an adjunct therapy. Argon laser trabeculoplasty (ALT) is more effective in PXG than in POAG initially, particularly because of the high pigment deposition in the trabecular meshwork. Unfortunately, the success rate of ALT in both PXG and POAG decreases to 35-55 per cent in three to six years.[1] Selective laser trabeculoplasty (SLT) has similar initial and diminishing success rates as ALT. Trabeculectomy success rates also decline with time. In one study, successful IOP control (considered 21 mmHg or less) was maintained in 52 per cent of patients after four years.[3] Success rates improved if cataract extraction was performed at the same time as the trabeculectomy with 2-4 mmHg lower at 12 months.[3]

Other surgical options include increasing aqueous outflow by bypassing the trabecular meshwork with Trabectome or iStent and decreasing aqueous production with endoscopic cyclophotocoagulation.[6,8] If a patient with PXF or PXG also has a narrow angle, laser iridotomy should be considered.[6]

Conclusion

PXF is more common in certain ethnicities but can be found worldwide. It is important to have an understanding of the clinical and surgical implications this condition presents. Natural lens and IOL dislocation, cataract surgery complications and PXG are constant considerations for any patient with pseudoexfoliation. There is no cure but as clinicians, we must be diligent in managing this condition.

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Is adherence an issue with generic eye-drops for glaucoma?

Joseph Halwagy

BPharm FSHP MBA
Medical Manager
Global Established Pharma
Pfizer Australia and New Zealand

A STUDY PUBLISHED in 2011 notes that Australian pharmacists recommended generics for 96.4 per cent of the prescription items which were eligible for substitution.[1] The study, which looked at generic substitution across a nationally stratified sample of 500 community pharmacies, revealed that patients with chronic diseases demonstrated a significantly lower rate of acceptance of generic medicines (72.4 per cent) than patients with acute conditions (81.6 per cent).

Challenges to adherence to therapy

Similar substitution rates have been reported in the United Kingdom (UK) with 74 per cent of glaucoma patients having their prescriptions substituted with generic latanoprost.[2]

The study, published in the *British Journal of Ophthalmology* in 2013, demonstrated that 35 per cent of patients found the generic latanoprost drops more difficult to use, and 19 per cent of patients were unable to use them afterwards. This would suggest an emerging issue with adherence to therapy for up to one in three previously stabilised glaucoma patients.

Although changes in a medication name and attributes of the physical packaging can be a major source of confusion,[3] upwards of 20-27 per cent of glaucoma patients in the UK reported changes in effectiveness and/or side-effects when switched to generic medication.[4] Although these were self-reported outcomes, and whether factual or perceived, this may cause certain patients to use their drugs inappropriately or cease their use.

The pharmacological management of primary open angle glaucoma in Australia is similar to that in the UK where latanoprost as monotherapy, or in combination with timolol maleate accounts for ≥ 75 per cent of all prescribed prostaglandin analogues.[5,6]

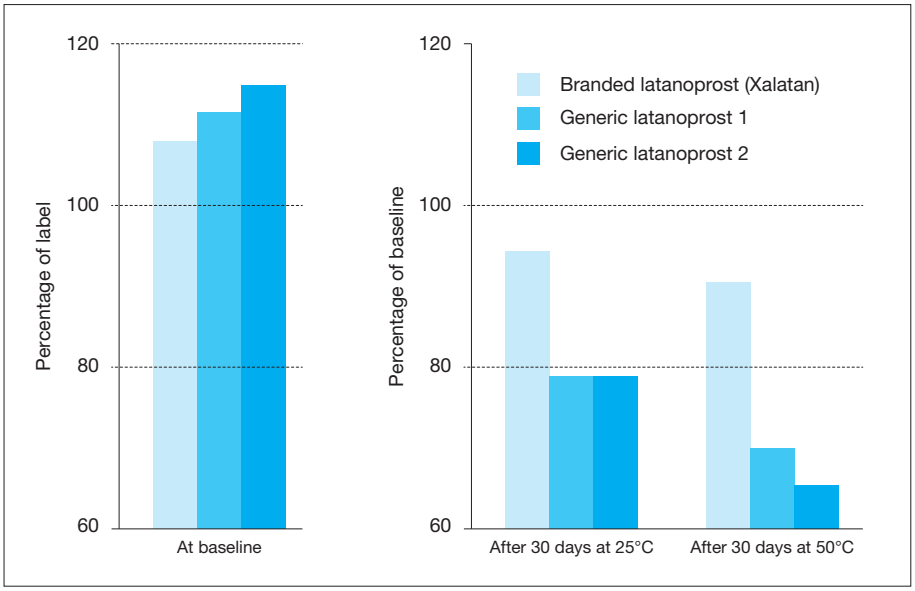
Given the availability of no less than five generic formulations for latanoprost eye drops in the Australian market,[7] glaucoma patients here may also be likely to exhibit similar issues with adherence after generic substitution.

Generic medicines

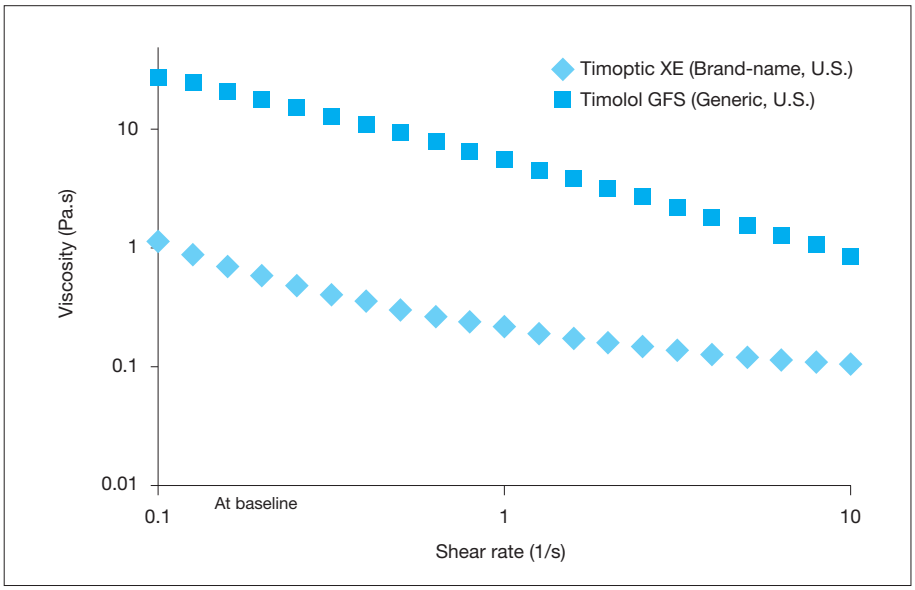
In general, the clinical effectiveness of a generic medicine is considered to be similar to that of the branded product.

The Therapeutic Goods Administration (TGA) requires generic medicines to contain the same active ingredient as the brand-name drug and to be identical in strength.[8] However, a recent US study looking at drug formulations, concentrations and stability of generic latanoprost versus the originator brand (Pfizer Xalatan) found large discrepancies, particularly over time, with up to a 10 per cent increase in drug concentration and more particulate matter in the generic formulations.[9] Malik Kahook, one of the authors of this study, is Professor of Ophthalmology and Chief of the Glaucoma Service at the University of Colorado School of Medicine. At the 2013 annual meeting of the American Academy of Ophthalmology, Kahook argued that although the active and non-active ingredients may be similar, other differences may impact the effectiveness and safety of generic use. He noted that changes in bottle shape and size as well as alteration in plastic stiffness may cause installation difficulties in an elderly population even if laboratory testing shows no difference between the generic and branded agent.[10]

The TGA does not stipulate that generic formulations must be identical to the originator brand product and indeed, side by side comparison of generic versus originator brand product information documents suggests that inactive ingredients can be different



▲ Figure 1. Changes in the active ingredient concentration for brand name and generic formulations of latanoprost at baseline and after exposure to different temperatures for 30 days (Adapted from Kahook et al)



▲ Figure 2. Average rheological measurements (log-log scales) of American brand-name Timoptic XE and American generic Timolol GFS (Adapted from Mammo et al)

from those in the original product.[11,12]

A recent study comparing North American branded timolol maleate versus 11 other generic preparations showed significant differences in drop volume, viscosity, surface tension, bottle design and bottle tips, with the authors recommending 'careful consideration should be given to drop viscosity and bottle design when generic ophthalmic products are evaluated for interchangeability and market entry'.[12]

Beyond the formulation and efficacy factors, originator companies may provide patient aids such as eye-drop instilling devices. These devices may make the administration of eye-drops easier compared with the dropper bottle, especially in the elderly.[13] To date, generic glaucoma products have been supplied in the standard round eye-drop bottles that do not fit into originator brand eye-drop aid devices available in Australia.

Conclusion

The switching of glaucoma eye-drop medications to generics is occurring at the pharmacy. Available data suggest compliance with generic glaucoma eye-drops may be an issue in up to one in three glaucoma patients previously stabilised with originator branded medicines. Clinicians' re-evaluation of intraocular pressures and that control is being maintained may be useful for glaucoma patients switching from originator to generic formulations. Educating patients on the value of brand compliance could be a way forward for maximizing adherence and persistence with therapy.

Due to the increase in generic switching, it is recommended that optometrists and ophthalmologists ask their patients to bring in their medication bottles to each visit. By doing this, clinicians can track each type of generic medication switch and watch for any tolerability issue or intraocular pressure change.

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Generic drugs

Generic drugs as defined by the Therapeutic Goods Administration* are medicines that in comparison to the originator product** have the same quantitative composition of therapeutically-active substances, contain substances of similar quality to those in the originator product; have the same pharmaceutical form; are bioequivalent or for topical products, are considered to be therapeutically equivalent; and have the same safety and efficacy properties.

* Therapeutic Goods Administration, ARGOM Appendix 1: Guidelines on efficacy and safety aspects of OTC applications, V1.0; October 2012

** An 'originator' product (sometimes referred to as the 'innovator' product) is a medicine that has been approved for marketing in Australia on the basis of a full dossier which may include chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data.

What is the earliest test for glaucoma?

Use of the ganglion cell complex as a new diagnostic indicator

Dr Adrian S Bruce

BScOptom PhD FAAO FACO
Australian College of Optometry
and The University of Melbourne

Iris Huang

BOptom PGDipAdvClinOptom
PGCertOcTher
Australian College of Optometry

GLAUCOMA IS AN OPTIC neuropathy characterised by the loss of retinal ganglion cells and the retinal nerve fibre layer.[1] There is a diversity of factors that may lead to glaucoma but key issues in common are the effect on the retinal ganglion cells and potentially devastating visual loss.[2]

What is the earliest test for glaucoma? The answer depends on the type of glaucoma. If the pressure is consistently high, that measurement alone will alert the clinician that further work-ups, monitoring and possible treatment are required. However, in many patients the pressure is not that high but the discs are asymmetrical or suspicious, or there are other risk factors. What should we be assessing?

As retinal ganglion cell (RGC) loss cannot be visualised in a standard clinical examination, the standard procedure for glaucoma assessment often relies on detection of secondary changes in the optic nerve head (ONH), careful examination of the retinal nerve fibre layer (RNFL) and visual field test.

Optic nerve head

Classic glaucomatous signs at the ONH include thinning or notching of the neuroretinal rim (NRR), asymmetry of NRR, excavation and enlarged cup to disc ratio over a period of time, Drance haemorrhage, or bayoneting and baring of blood vessels.

Retinal nerve fibre layer

In some glaucoma patients, a diffused loss of RNFL can be seen as a wedge of diminished light reflection. This is best appreciated with a red-free (green or blue) filter. However, early glaucoma RNFL loss often appears as subtle attenuation of the light reflection and can be difficult to detect.

Visual field

Glaucomatous visual field defects include an early paracentral scotoma, which may slowly merge and form an arcuate defect that continues to the blind spot. A nasal step may be present and one hemifield more depressed than the other. The visual field defect should correspond to the NRR change and/or RNFL loss.

As clinical examination is subjective and clinician dependent, early glaucoma signs can be overlooked from time to time. Early treatment opportunities may be missed if relying primarily on a visual field defect. This is because a substantial reduction in RGC population can occur before clinically significant visual field defect can be detected. Since the introduction of optical coherence tomography (OCT), the technology has assisted clinicians in the detection of RNFL loss associated with glaucoma. Due to advances in OCT technology, we can now acquire a 6 x 6 mm cube of data in the peripapillary region in less than 1.5 seconds. Using OCT ONH scan to analyse peripapillary RNFL is now a widely employed parameter for diagnosing glaucoma.

More recently, the measurement of the perimacular ganglion cell layer has emerged as a new diagnostic parameter in glaucoma with spectral domain OCT. Various OCT machines now use this technique to capture the thickness of the innermost three retinal layers around the macula. These three layers, known as the macular ganglion cell complex (GCC), are the retinal nerve fibre layer, ganglion cell layer and inner plexiform layer.[3] The GCC contain the axons, cell bodies and dendrites of the ganglion cells, respectively, which have been shown to be preferentially affected by glaucoma.[4] This new parameter may assist early glaucoma detection, especially in cases where the ganglion cell loss is predominately macular rather than peripheral.

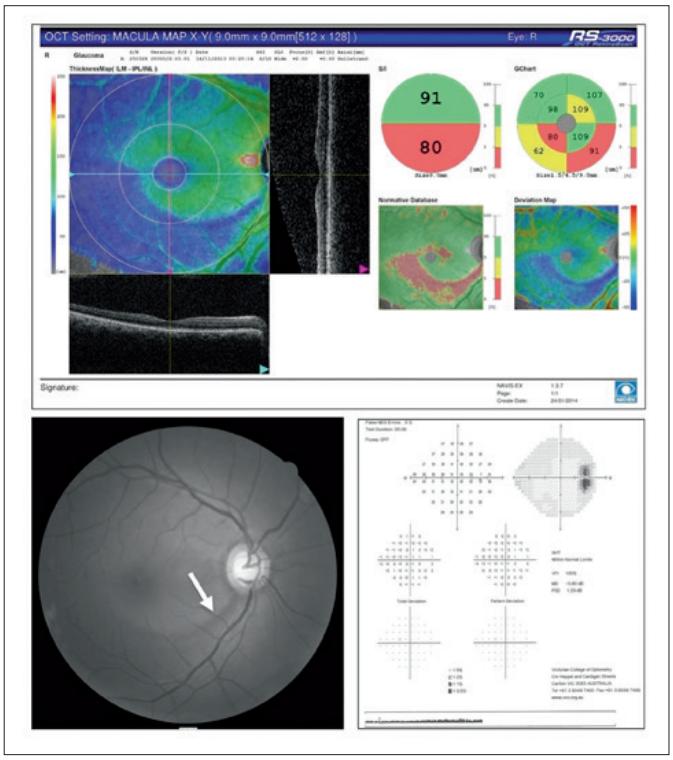
CASE REPORTS

Examples of using GCC measurement in assisting glaucoma diagnosis

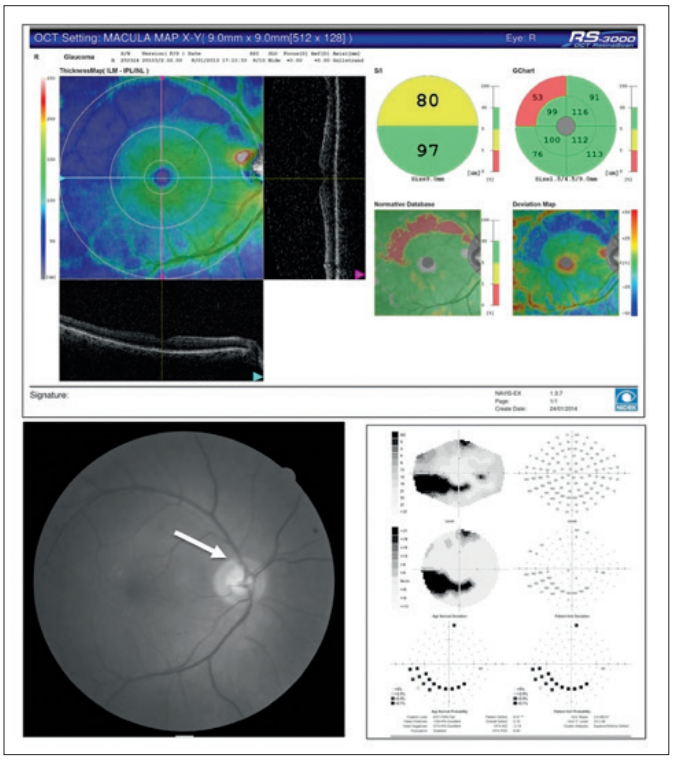
Case 1 (Figure 1) shows a large glaucomatous cupping with a slit of inferior RNFL defect (as shown in the red free photo). The Nidek OCT macular scan highlighted the inferior arcuate loss, enabling us to quantify the total GCC loss and compare superior and inferior hemifields. Note that there is no visual field defect in this case, once again echoing the previous studies that structural loss can precede detectable functional loss by up to five years.[5]

Case 2 (Figure 2) shows an exemplary structure-function relationship with a classic glaucomatous inferior arcuate field loss, which corresponds to the superior temporal rim notch. RNFL loss is not readily detectable in the red-free photo; however, the Nidek OCT macular GCC scan shows a clear superior arcuate loss.

Since the new macular GCC scan has gained popularity in glaucoma management, many studies have been performed in the past few years to investigate its diagnostic ability. Studies comparing the diagnostic performance of the GCC parameter to peripapillary RNFL have found a



▲ Figure 1. Nidek OCT scan of the macular ganglion cell complex (GCC) shows right inferior shallow arcuate loss in a 57-year-old female with early glaucoma. The right inferior GCC is 15 µm thinner than the left inferior GCC (not shown). The red-free fundus image shows inferior nerve fibre loss (arrow) but the visual field is normal.



▲ Figure 2. Nidek OCT scan of the macular ganglion cell complex (GCC) shows right superior arcuate loss in a 64-year-old male with glaucoma. The right superior GCC is 19 µm thinner than the left superior GCC (not shown). The red-free fundus image shows superior temporal rim notch (arrow) and the visual field shows a corresponding inferior arcuate loss.

GCC scan to be comparable with the ONH scan in detecting early, moderate and advance glaucoma.[4] The studies also found that GCC measurements and ONH scan had similar structure-function relationships with visual field sensitivity.

Limitations of GCC parameter were also discussed in many of these papers. Common issues that are also shared with peripapillary RNFL scan includes signal quality and image artifact. Any coexisting macular pathology such as ARMD may affect GCC thickness measurement. In addition, most GCC scans cover a 7 x 7 mm grid on the macula; patients who present with RNFL defect outside of this area may escape detection.

This is less of an issue now as imaging technology has advanced. Nidek OCT RS 3000 software V2.0.0 or higher allows 3-D scanning over a 9 x 9 mm square in only 1.6 seconds. This function provides clinicians with the opportunity to measure GCC thickness across a wider area. Furthermore, GCC measurement has a theoretical advantage in glaucoma diagnosis as RGC loss occurs early in the pathogenesis of the disease. Besides, ONH scanning may be complicated by other non-glaucomatous conditions, such as extensive peripapillary atrophy in high myopia.

In summary, macular GCC scan is able to illustrate areas of glaucomatous ganglion cell loss with the advantage of correlation with visual field defects point by point, as shown in Case 2 above. Clinicians should carefully interpret the individual patient's clinical signs and consider including macular GCC thickness as part of the glaucoma assessment procedure.

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Dr Laura Downie

BOptom PhD(Melb) PGCertOcTher FACO FAAO DipMus(Prac) AMusA

ABSTRACTS

In vivo test confirm viability of drug-eluting contact lens

The concept of utilising contact lenses as a means of ocular drug delivery was proposed nearly 50 years ago but successfully achieving controlled release of therapeutic agents has remained a considerable challenge.

A recent paper described a drug-eluting contact lens designed for prolonged delivery of latanoprost for glaucoma treatment. The contact lens was created by encapsulating latanoprost-poly(lactic-co-glycolic acid) films in methafilcon by ultraviolet light polymerisation. *In vitro* and *in vivo* studies showed an early burst of drug release, followed by sustained release for at least one month.

Using an *in vivo* animal model, a single contact lens was able to achieve latanoprost concentrations in the aqueous humour that were comparable to those achieved with topical latanoprost eye-drops. The contact lens was reported to appear safe both in cell culture and animal studies.

The authors proposed that this contact lens design may offer a viable alternative to the current treatment of glaucoma with topical eye-drops and may also serve as an ocular drug delivery platform for treating other ocular diseases.

Biomaterials 2014; 35: 1: 432-439

Quality of social media for patients with glaucoma highly variable

Analysis confirms that social media platforms may be a useful adjunct to current ophthalmic care models by providing a supportive and educational online community—provided that their limitations are understood.

Researchers in the United Kingdom assessed the ophthalmic content of five social media platforms: the International Glaucoma Association (IGA) forum, Facebook, Twitter, YouTube and PatientOpinion.org.uk. A total of 3,785 items were scraped from the sites, collated and analysed using simple thematic analysis by two coders.

A total of 14 themes were identified. The most commonly discussed topics included treatments, care experiences, promotions and support. Unmoderated sites were found to contain misleading information. Complementary therapies and treatments with a poor evidence base were presented more positively than established, evidence-based treatments.

The authors concluded that while online forums provide patients with a space to air questions, grievances and suggestions, and to offer mutual support, there is a risk of exposure to misleading content which is heightened in unmoderated sites.

Ophthalmic Physiol Opt 2014; 34: 1: 46-52

IOP changes in medically-versus surgically-treated eyes

A study comparing posture-induced intraocular pressure (IOP) changes in (non-operated) medically-treated eyes versus previously trabeculectomised eyes with open angle glaucoma

Study shows optometrist referrals are more comprehensive and legible than referrals written by ophthalmologists

When researchers in Canada conducted a cross-sectional study to assess the quality of referral letters to glaucoma specialists, they found that optometrist referrals contained more information and were relatively more legible than those of ophthalmologists. They also found that many clinicians often omitted vital information.

The study involved a survey of 135 glaucoma specialists and an audit of 200 consecutive referrals to a tertiary glaucoma unit. The survey asked respondents to detail what they considered the most important data to be included in a glaucoma referral. The referral letters were assessed with regard to their content on the basis of the survey results and information in current Canadian glaucoma guidelines.

Of the 200 referral letters, 46 per cent were from ophthalmologists, 42 per cent from optometrists, 10 per cent from family medical doctors and two per cent from other sources.

The top five most important data that glaucoma specialists suggested for inclusion in a referral letter for progressive glaucoma were serial visual fields (VFs), current glaucoma therapy, current intraocular pressure (IOP), maximum IOP and serial disc imaging.

Approximately one-quarter of referrals were illegible (18 per cent from ophthalmologists vs six per cent from optometrists, $p < 0.01$). Optometrists were more likely than ophthalmologists to provide visual acuity, IOP, refraction and VF details ($p < 0.01$ for each). Only 24 per cent of referrals for glaucoma progression included more than 10 of 14 information points suggested by glaucoma guidelines and 34 per cent included fewer than eight of 14 points.

Overall, optometrist referrals were more comprehensive and more legible than ophthalmologist referrals. Referrals to glaucoma specialists frequently did not include important information. The authors suggested that practitioners would benefit from having a check-list of clinical details when referring patients for specialist glaucoma care that includes maximum and current IOP, disc evaluation, serial VFs and serial disc imaging.

Ophthalmology 2014; 121: 1: 126-133

suggests that trabeculectomy may not only decrease IOP but may also reduce postural-related IOP deviations, compared with medical glaucoma intervention.

Post-trabeculectomised open angle glaucoma eyes with a cystic filtering bleb (n = 51) and medically-treated OAG eyes (n = 51) with a baseline IOP less than 12 mmHg were studied using Goldmann tonometry. IOP was measured in the sitting and lateral decubitus position (upper eye after five minutes) using an iCare rebound tonometer.

The study authors found that there was no significant difference in IOP between groups at baseline using Goldmann tonometry (p = 0.892) or in the sitting position using the iCare tonometer.

On average, a greater increase in IOP (+3.3 mmHg) was observed in the medically-treated group compared with the surgically-treated group (+1.00 mmHg, p < 0.001) for the lateral decubitus position.

Invest Ophthalmol Vis Sci 2014; Epub Jan 7 ahead of print

Habitual sleep positions may be associated with visual field loss

The results of a retrospective, cross-sectional study suggest that the sleep position habitually preferred by glaucoma patients may be associated with greater visual field loss.

The study sought to investigate the relationship between preferred sleeping position and asymmetric visual field loss, defined as a difference in mean deviation between eyes of at least 2dB, in open-angle glaucoma.

Patients (n = 692) with either bilateral normal tension glaucoma or high-tension glaucoma were consecutively enrolled. A questionnaire was used to determine preferred sleeping position.

Of the participants, 60.6 per cent with normal tension glaucoma and 66.5 per cent with high-tension glaucoma demonstrated asymmetric visual field loss between the two eyes. Among these normal tension glaucoma patients, approximately one-third preferred the lateral decubitus position; of these, 66 per cent preferred the worse-eye-dependent lateral decubitus position (p = 0.001).

Among the high-tension glaucoma patients, about one-quarter preferred the lateral decubitus position and of these 72 per cent preferred the worse-eye-dependent position (p = 0.013).

Am J Ophthalmol 2013; Epub Dec 14 ahead of print

Intraocular lens glistening in glaucomatous eyes

There is a relationship between the number of topical daily glaucoma medications that a patient uses and the degree of intraocular lens (IOL) glistening after cataract surgery, it has been shown.

The prospective study involved 67 consecutive glaucomatous eyes (47 patients) who previously had phacoemulsification with a hydrophobic acrylic IOL implanted in the capsular bag. IOL glistening was graded by severity: GO (< 50 micro-vacuoles per mm^2), G1 (50-100 micro-vacuoles per mm^2) and G2 (>150 micro-vacuoles per mm^2). Eyes were examined for visual acuity, visual fields, contrast sensitivity and wave-front analysis of higher-order aberrations.

Grading of the degree of glistening was G0 for 39 per cent, G1 for 18 per cent and G2 for 43 per cent of eyes. The mean follow-up after cataract surgery was significantly higher for G1 and G2 groups compared with G0 eyes (p < 0.001). A higher number of topical glaucoma medications was associated with a higher IOL glistening grade (p < 0.05). G1 and G2 eyes had significantly lower mean contrast sensitivity at high spatial frequencies and significantly higher loss variance values on visual field testing (p < 0.05). There was no difference in visual acuity between groups (p > 0.05).

It was concluded that in glaucomatous eyes, IOL glistening increased with time and was significantly associated with the number of topical daily glaucoma medications being utilised. It was also suggested that because IOL glistening had some impact on visual performance, it should be a consideration in the management of glaucoma patients.

Acta Ophthalmol 2013; Oct 7 Epub ahead of print

FDT rates predictive of glaucoma progression

Rates of frequency doubling technology (FDT) pattern standard deviation (PSD) change were found to be predictive of the development of standard automated perimetry (SAP) visual field (VF) loss in patients suspected of having glaucoma.

The prospective, observational cohort study was conducted with the purpose of determining the utility of longitudinal frequency doubling technology (FDT) (Humphrey Matrix, Carl Zeiss Meditec Inc) to predict the development of glaucomatous visual field loss on standard automated perimetry (SAP) in glaucoma suspects.

This study included 587 eyes of 367 patients with suspected glaucoma (defined as IOP > 21 mmHg or an optic disc appearance suspicious of glaucoma, with normal or non-repeatable abnormal SAP) at baseline, selected from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). The eyes had an average of 6.7 ± 1.9 FDT tests during a mean follow-up time of 73.1 ± 28.0 months. The study end-point was the development of three consecutive abnormal SAP test results.

Sixty-three (11 per cent) of eyes developed SAP visual field loss during follow-up. The mean rate of FDT pattern standard deviation (PSD) change in eyes that developed SAP visual field loss was 0.07 dB/year versus 0.02 dB/year in those that did not (p < 0.001). Baseline FDT PSD and slopes of FDT PSD change were significantly predictive of glaucomatous visual field progression, with hazard ratios of 1.11 per 0.1dB higher (95% CI: 1.04-1.18, p = 0.002) and 4.40 per 0.1 dB/year faster (95% CI: 1.08-17.96, p = 0.04), respectively.

The study authors concluded that longitudinal frequency doubling technology (FDT) evaluation may be useful for risk stratification for patients with suspected glaucoma.

Ophthalmology 2013; Epub Nov 26 ahead of print

Managing neuro-ophthalmic emergencies

Dr Joseph Sowka

OD FAAO Diplomate

WHEN THINKING of ocular emergencies, retinal detachment, acute angle closure and chemical burns typically come to mind. While these conditions carry a high burden in potential visual loss, there exist several neuro-ophthalmic conditions that clinicians cannot afford to miss that carry an even higher risk of not only visual morbidity but even potential patient mortality.

Cranial nerve III palsy

A patient with acute cranial nerve (CN) III palsy will usually present with a sudden onset of unilateral ptosis and ophthalmoplegia, which is frequently accompanied by significant eye or head pain dependent on the cause.[1-4] The patient often complains of double vision, though in some cases the diplopia may be masked by the ptosis which obscures the vision in the affected eye; however, if the lid is manually elevated, the patient will experience diplopia. (Figure 1)

CN III palsy produces a non-comitant exotropic, hypotropic eye position (down and out). There is limitation of elevation, depression and adduction. There is an underaction of the superior, inferior and medial recti muscles and inferior oblique muscle.[1-3] In any case of CN III palsy, the pupil may be dilated and minimally reactive to light (pupillary involvement), or totally reactive and normal (pupillary non-involvement) or may be sluggishly responsive (partial pupillary involvement).[3,4,7-10]

The main concern in an isolated CN III palsy occurring within the subarachnoid space is compression of the nerve by an expanding aneurysm of the posterior communicating artery. Additionally, aneurysmal compression can occur from the internal carotid, basilar, anterior communicating or temporal arteries.[8,9] Aneurysmal compression is marked by head or retro-orbital pain and anisocoria with ipsilateral pupil dilation as the expanding aneurysm compresses the pupillomotor fibres within CN III as well as pain sensitive dura and other such structures.

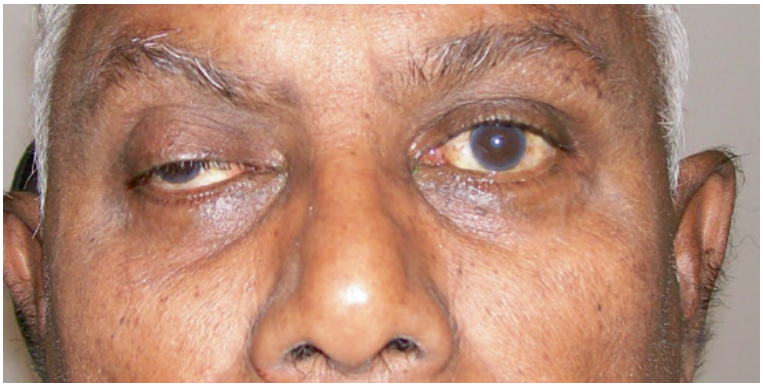
Approximately 15 per cent of isolated CN III palsies occurring secondary to damage within the subarachnoid area are due to aneurysms.[11] In these cases, there is a high risk of morbidity or mortality from aneurysm rupture and subsequent subarachnoid haemorrhage. Approximately 20 per cent of patients with aneurysmal CN III palsy will die within 48 hours from rupture and intracranial haemorrhage. In cases of CN III palsy caused by subarachnoid aneurysm, immediate neurosurgical intervention is necessary. Common endovascular treatment involves direct clipping of the aneurysm or embolisation with detachable coils. These patients need to be sent immediately to the hospital emergency department, by ambulance, if necessary, with detailed notes on the suspected diagnosis.

Vision loss from giant cell arteritis

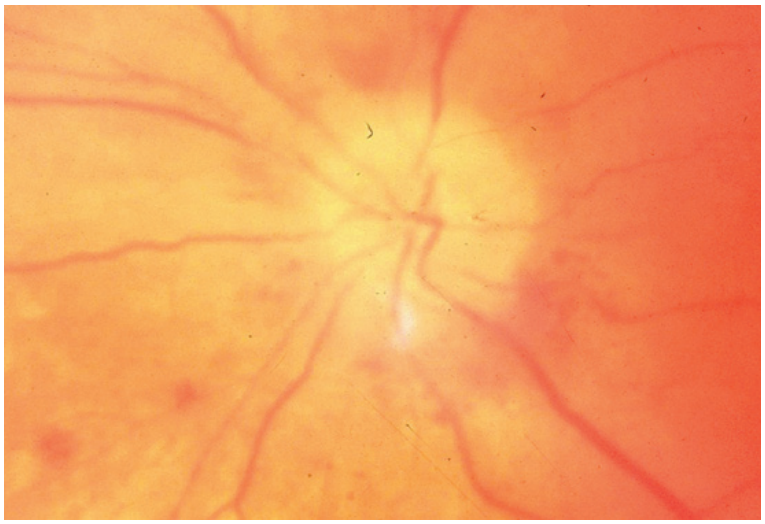
Giant cell arteritis (GCA) is a granulomatous inflammation of medium and large-sized arteries.[12] There is cellular infiltration of the muscular wall of these vessels by T lymphocytes, macrophages, histiocytes, plasma cells and multinucleate giant cells.[13,14]

The inflammatory cells produce matrix metalloproteinases that digest the arterial walls, fragmenting the elastic lamina and causing tissue destruction. Vascular endothelial growth factor (VEGF) produced by multinucleate giant cells causes smooth muscle proliferation and migration towards the vessel lumen. This in combination with neoangiogenesis causes intimal hyperplasia with obliteration and occlusion of the vessel lumen.[13,14]

The patient suffering from giant cell



▲ Figure 1. A 63-year-old man with sudden onset head pain, diplopia, down-and-out position of the right eye, ptosis, and mid-dilated, unreactive right pupil from CN III palsy caused by an intracranial aneurysm



▲ Figure 2. Pale, swollen optic disc from arteritic anterior ischaemic optic neuropathy in a patient with giant cell arteritis

arteritis (GCA) is invariably elderly, with the mean age of 71 years at presentation. There is an increasing incidence with advancing age.[1] This condition is generally considered only after the age of 50 years. There is a 2:1 female to male ratio and a higher incidence in Caucasian patients.[15]

There is a multitude of systemic manifestations that can accompany and signal the presence of GCA, including malaise, weight loss and anorexia, headache about the temporal or occipital region, pulseless and indurated temporal arteries, night sweats, tongue necrosis and oral ulceration, dental abscess, scalp pain, scalp necrosis, jaw claudication when eating, head and neck swelling, anaemia, depression, mental disturbance, neck pain, low grade fever, transient ischaemic attack and stroke, proximal myalgia, breast masses, gynecological disorders, malignant disease, persistent flu-like illness, chronic pharyngitis, vertigo, muscle aches, cardiac arrhythmia, congestive heart failure and myocardial infarction.[16,17]

Too often, patients with GCA are diagnosed following sudden, devastating vision loss in one or both eyes. The cause typically is arteritic anterior ischaemic optic neuropathy (AAION). (Figure 2) In approximately 10 per cent of GCA cases, central retinal artery occlusion (CRAO) is the underlying cause of vision loss.[17] Sudden, permanent vision loss is preceded by the ominous warning sign of bouts of amaurosis fugax in approximately 30 per cent of cases.[13] Progression to bilateral vision loss has been known to occur with a time interval of 1-14 days between involvement of the two eyes; hence, the emergency nature of this disease.

Management begins with the recognition that GCA may be a potential cause of the aforementioned findings in an elderly patient. Any unexplained ocular findings, involvement of multiple vessels, or idiopathic systemic deterioration in an elderly patient should immediately raise suspicions. Once GCA is recognised as a potential cause, immediate referral to a hospital emergency department for testing to include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) must be undertaken.

The ESR, a non-specific index of illness, is typically elevated in cases of GCA; however, there will be a small percentage of cases that will not manifest an elevated ESR. In these cases, supplemental confirmatory evidence provided by the CRP (a marker of inflammatory activity) is helpful. Additionally in these cases, the ophthalmic findings and systemic history become diagnostically more important. If the ESR or CRP is elevated, or if there are obvious constitutional symptoms, a temporal artery biopsy must be performed to conclusively diagnose GCA.[18,19] Again, patients suspected of having vision loss from GCA should be sent immediately to the emergency department with detailed notes on the presumptive diagnosis and recommended management.

Unquestionably, systemic steroids are needed to preserve vision and reduce morbidity and mortality;[18,19] however, steroids should not be withheld pending biopsy results. If history, examination findings and serology indicate GCA, steroids must be started without delay. Biopsy results will not be immediately affected after initiation of steroid therapy.

Unquestionably, GCA is an ocular and systemic emergency. Untreated, progression involving the fellow eye occurs in a high number of cases within hours to days. Frequently, vision loss in GCA is devastating and irreversible, and may progress despite seemingly adequate treatment. Giant cell arteritis may present insidiously without vision loss. Headache arising de novo in elderly patients is uncommon and a reason to suspect GCA. It is not unreasonable to recommend that a patient's general practitioner obtain ESR and CRP testing on elderly patients complaining of headache despite a normal ophthalmic examination.

Horner syndrome

Horner syndrome is characterised by an interruption of the oculosympathetic nerve supply somewhere between its origin (in the hypothalamus) and the eye. The classic clinical findings associated with Horner syndrome are ptosis, pupillary miosis, facial anhidrosis, apparent enophthalmos, increased amplitude of accommodation, heterochromia of the irides (if congenital or occurring before the age of two years), paradoxical contralateral eyelid retraction, transient decrease in intraocular pressure and changes in tear viscosity.[20] (Figure 3)

Apraclonidine 1% and 0.5% (Iopidine, Alcon Laboratories, Ft Worth, TX) can be used effectively to diagnose Horner syndrome.[21-23] The theory is that the Horner syndrome pupil undergoes denervation hypersensitivity with upregulation of both the number and sensitivity of available receptors. When

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Managing neuro-ophthalmic emergencies

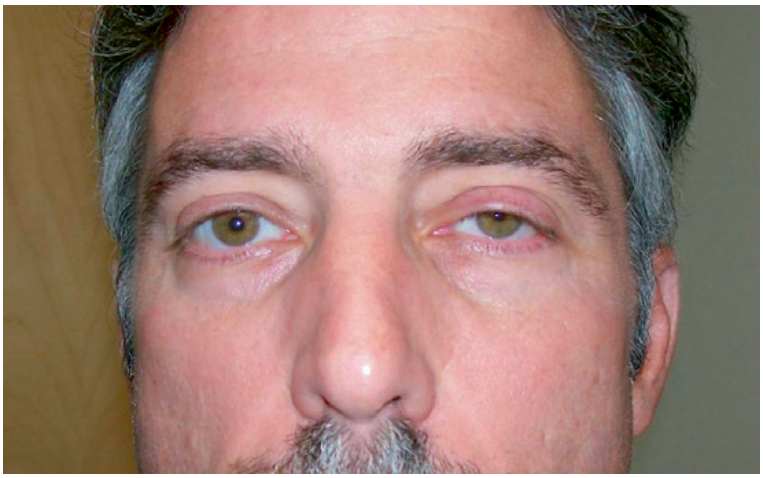
From page 13

a very weak alpha-1 adrenergic agonist is applied, the hypersensitive pupil dilates while the normal pupil has no effect. In most cases, there will be a reversal of the anisocoria.

The common aetiologies of acquired Horner syndrome include but are not limited to: trauma, aortic dissection, carotid dissection, tuberculosis, and Pancoast syndrome.[24-25]

If the patient reports recent ipsilateral neck trauma, neck and face pain, ipsilateral transient monocular visual loss, or contralateral transient weakness or numbness, acute cervical carotid dissection must be immediately suspected. Cervical carotid dissection is a relatively common cause of acute onset Horner syndrome.[26] In this case, there is a substantial risk of hemispheric (middle cerebral artery distribution) stroke within the first two weeks of onset. Patients presenting with Horner syndrome suspected to be caused by carotid dissection should be considered to be in an emergency situation and referred promptly to the emergency department for diagnosis and treatment to prevent cerebrovascular stroke.

In general, the treatment for Horner syndrome depends on the cause. In many cases, there is no treatment that improves or reverses the condition. Treatment in acquired cases is directed toward eradicating the cause. Recognising the signs and symptoms is tantamount to early diagnosis, as is making expedient referrals to appropriate medical specialists.



▲ Figure 3. Left ptosis and miosis in a patient with new onset Horner Syndrome

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Pigment dispersion syndrome

Dr Andrew Whatham

BOptom(Hons) DPhil GradCertOcTher

Agnes Choi

BOptom MOptom GradCertOcTher

Michael Yapp

BOptom(Hons) MOptom GradCertOcTher

Centre For Eye Health
The University of New South Wales

CASE REPORT

A 45-YEAR-OLD Caucasian male was referred to the Centre for Eye Health for further testing in light of a family history of glaucoma (father).

Best correctable acuities were 6/7.5^{+2} R and L with a moderately high myopic prescription. Intraocular applanation pressures were R 20mmHg and L 18mmHg at 11 am. Corneal thicknesses at the pupil centre were thinner than average at 508 µm OD and 514 µm OS. Slitlamp examination (Figure 1) revealed peripheral iris transillumination defects in the right eye. Gonioscopy (Figures 2A and 2B) revealed open anterior chamber angles with the level of pigmentation in the pigmented trabecular meshwork being dense in the right eye and moderate in the left, in particular inferiorly. Stereoscopic optic nerve assessment (Figures 3A and 3B) showed average-sized discs with no significant peripapillary atrophy and no evidence of Drance haemorrhages.

The neuroretinal rim (NRR) showed superior shelving in both eyes being more pronounced in the right. The right NRR also showed focal thinning inferiorly. A superior and an inferior wedge retinal nerve fibre layer (RNFL) defect were also noted in the right eye (Figure 4). Fundus examination was otherwise unremarkable in each eye.

Cirrus OCT RNFL analysis (Figure 5) showed the average RNFL thickness to be borderline in the right eye and within normal limits in the left; however, the superior and inferior RNFL quadrants in the right eye were classified as outside normal limits.

Humphrey 24-2 threshold SITA Standard perimetry (Figures 6A and 6B) revealed adjacent points of reduced sensitivity infero-nasally and superiorly in the right eye and an essentially normal visual field in the left eye. Considering the clinical appearance is consistent with pigmentary dispersion glaucoma and the complicated nature and relatively high progression rate of this type of glaucoma, the patient was referred to a glaucoma specialist ophthalmologist for further assessment.

Discussion

Pigment dispersion syndrome (PDS) is characterised by two or more of iris transillumination, pigment deposition on the central corneal endothelium (Krukenberg spindle) and increased pigmentation of the trabecular meshwork.[1] Pigmentary ocular hypertension (POH) refers to the co-existence of PDS with elevated IOP but without glaucomatous optic neuropathy. The term pigmentary glaucoma (PG) refers to PDS in conjunction with glaucomatous optic neuropathy.

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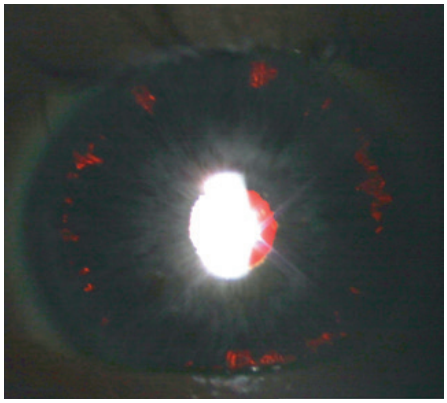
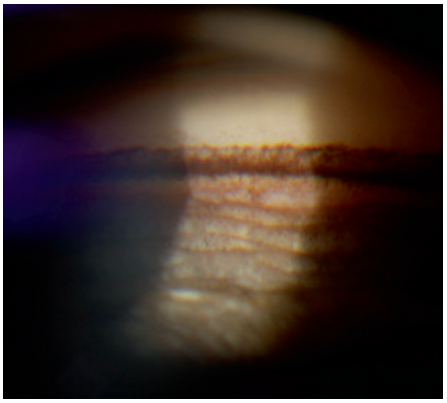
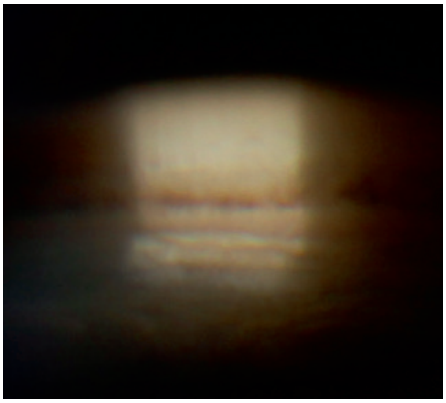


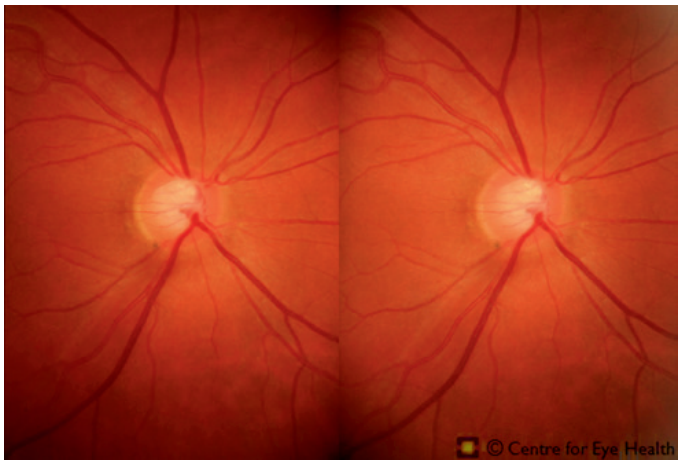
▲ Figure 1. Peripheral iris transillumination defects in the right eye



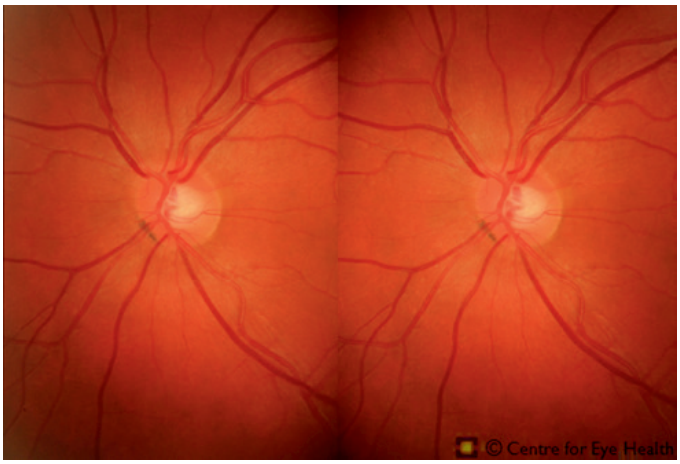
▲ Figure 2A. Dense pigmentation in the pigmented trabecular meshwork in the right eye



▲ Figure 2B. Moderate pigmentation in the pigmented trabecular meshwork in the left eye



▲ Figure 3A. Large optic nerve cupping and thin neuroretinal rim in the right eye



▲ Figure 3B. Left optic nerve showing smaller cupping and thicker neuroretinal rim

Pigment dispersion syndrome

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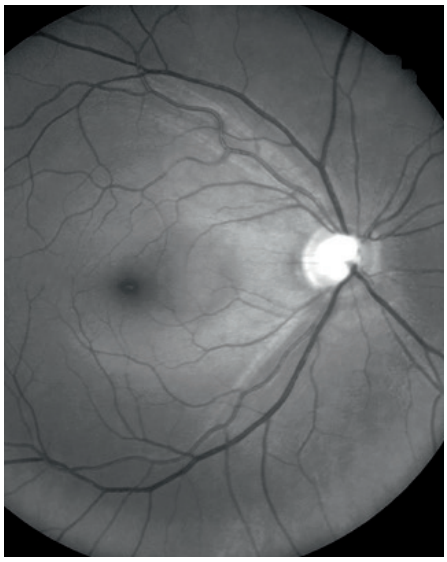

▲ Figure 4. Superior and inferior wedge RNFL defects in the right eye

PDS is typically bilateral but can be asymmetric.[2,3] PDS classically affects young Caucasians between 30 and 50 years of age with myopia[4] but all ethnicities can be affected. Men and women appear equally likely to develop PDS, although males appear much more likely to convert to PG.[2,5]

In newly diagnosed eyes with PDS, conversion rate to PG has been estimated to be 10 per cent at five years after diagnosis and 15 per cent at 15 years after diagnosis.[4] Risk factors for increased likelihood of conversion from PDS to POH and PG include male gender, higher myopic refractive error, presence of a Krukenberg spindle and higher IOP.[2]

Iris transillumination defects arise from loss of pigment from contact between the posterior iris pigmented epithelium and the lens zonules; however, they are not always present or of this form in individuals with PDS.[6]

Specific anomalous anatomical relationships between the iris and lens are believed to give rise to release of pigment from the posterior iris. In particular, the phenomenon of reverse pupil block has been postulated. This is believed to arise from differential pressure in the anterior and posterior chambers so that the higher anterior chamber pressure bows the peripheral iris posteriorly (increasing iris concavity) with the area of irido-lenticular contact acting as a one-way valve preferentially allowing aqueous flow from the posterior to anterior chamber and inhibiting flow in the reverse direction. The consequence of this is that the iris posterior pigmented epithelium comes into contact with the lens zonules, which abrade the epithelium, leading to pigment release into the aqueous.

Research with anterior OCT and ultrasound biomicroscopy has shown that accommodation, Pilocarpine 2% and laser peripheral iridotomy[7,8,9] can eliminate the iris concavity. Alternatively, exercise has been shown to show a significant increase in iris concavity in both eyes with and without pigment dispersion.[10]

Pigmentation on the corneal endothelium is frequently present in a vertical spindle formation, referred to as Krukenberg's Spindle. This particular pattern of pigment distribution is believed to arise as a consequence of the direction of aqueous convection currents in the eye.[2,11]

Increased trabecular meshwork pigmentation, visualised during gonioscopy, is a prominent characteristic of PDS and the most relevant when considering glaucoma risk. The released iris pigment travels to the anterior chamber angle via the aqueous convection currents and is phagocytosed by the trabecular endothelial cells. The trabecular endothelial cells readily phagocytose pigment, and provided the pigment load is not excessive, the architecture of the trabecular meshwork remains undisturbed.[11] Histological characteristics of a small group of eyes with PDS, POH and PG showed that PG seems to occur when the excessive

pigment in the anterior chamber angle results in loss of normal trabecular architecture, increasing outflow resistance.[12]

A number of reports have shown PG 'burnout' with increasing time, in which pigment dispersion is no longer active, IOP normalises and progressive optic neuropathy is halted.[2] The reason for this may be that as the eye's crystalline lens continues to grow throughout life, iris profile changes and reverse pupil block is no longer an issue. As such, new pigment dispersion no longer occurs. If the trabecular meshwork is relatively undamaged, optic nerve health may be stable; however, if the trabecular meshwork has become irreversibly damaged, progressive optic nerve damage may continue to occur with or without normalisation of IOP.[2]

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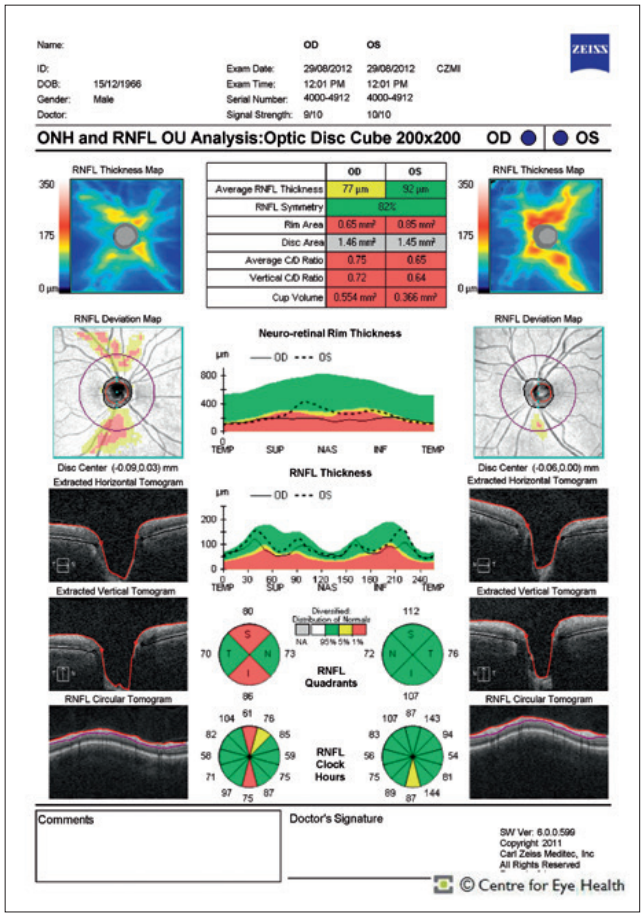
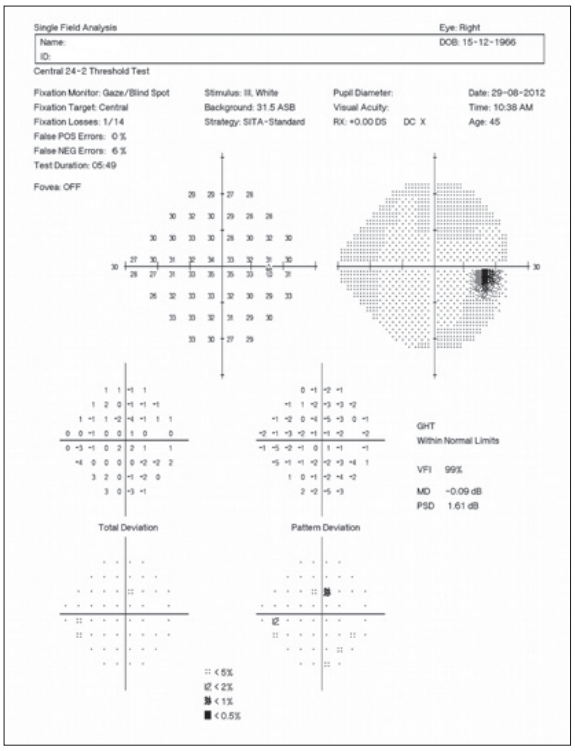
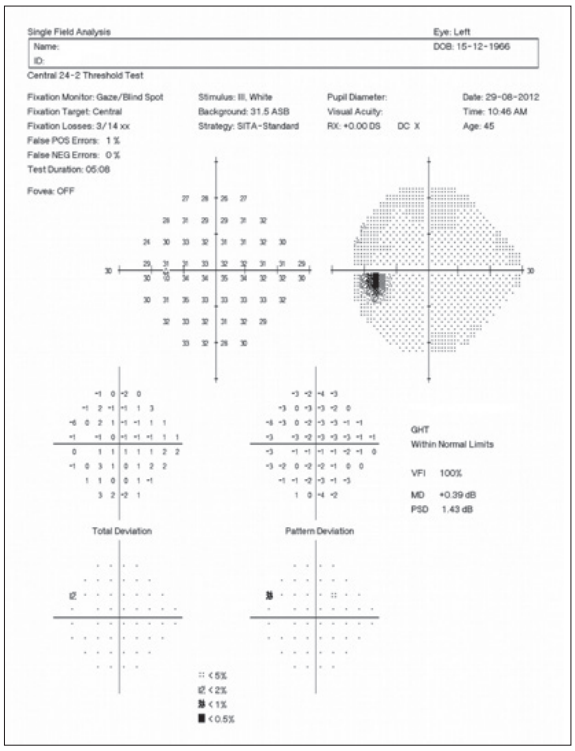


▲ Figure 5. Superior and inferior RNFL quadrants OD classified as outside normal limits and the 6 o'clock RNFL sector OS as borderline on Cirrus OCT



▲ Figure 6A. Visual field examination showed reduced sensitivity inferiorly in the right eye



▲ Figure 6B. Left eye showed an essentially normal visual field

Pigment dispersion syndrome

From page 17

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Anatomic landmarks used in new OCT software

Novel approach to the clinical assessment of the optic nerve head

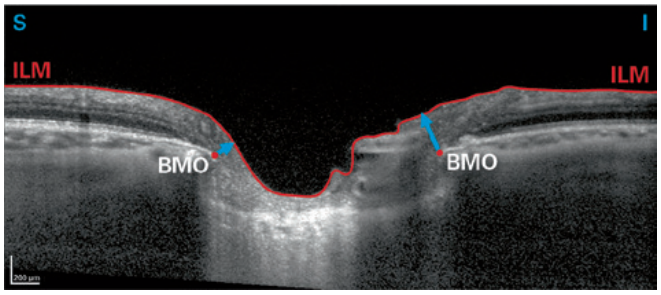
HEIDELBERG ENGINEERING has unveiled its new Anatomic Positioning System (APS) as part of its software for the Spectralis SD-OCT. The innovative system accurately places all OCT-scans relative to the position of the fovea and Bruch's membrane opening (BMO) which serve as anatomic landmarks for each individual eye.

The new optic nerve head assessment is based on research done by the groups of Balwantray Chauhan PhD of Dalhousie University in Halifax, Canada, and Claude Burgoyne MD of Devers Eye Institute in Portland, Oregon, USA. Their work demonstrated the importance of making an anatomically and geometrically accurate neuroretinal rim measurement using BMO, the anatomical outer border of the rim, rather than the clinical disc margin.

The Spectralis software makes a measurement from the BMO to the nearest point at the internal limiting membrane, quantifying the minimum cross-section of the nerve fibres exiting the eye, which allows the BMO-based minimum rim width (BMO-MRW) to be assessed. BMO-MRW data are acquired and regionalised relative to the axis between BMO and the fovea (the FoBMO axis) in each individual eye allowing meaningful and accurate analyses.

The Glaucoma Module Premium Edition also offers comprehensive analyses for retinal nerve fibre layer and posterior pole asymmetry.

The system appeared at the October 2013 meeting of the European Society for Cataract Refractive Surgery in Amsterdam, the Netherlands.



▲ Automatic detection of Bruch's membrane opening (BMO) (blue arrows) and the internal limiting membrane (ILM) in each cross sectional scan.

Integrate SD-OCT into glaucoma diagnosis and management

Dr Blair B Lonsberry

MS OD MEd FAAO

Optical coherence tomography is fast becoming the standard for evaluating glaucomatous change

GLAUCOMA IS DEFINED as an optic neuropathy characterised by progressive damage to the optic nerve and surrounding retinal nerve fibre layer (RNFL).[1] Traditionally, standard automated perimetry (SAP) is the most commonly used method for 'diagnosing', assessing the rate of visual function loss and estimating risk of impairment from glaucoma.[2] A variety of clinical signs will make a patient a glaucoma suspect, including a positive family history of glaucoma, elevated IOP, enlarge optic nerve cupping and RNFL defects.[3]

Diagnosis of glaucoma typically involves finding a visual field defect (for example, nasal step) that corresponds with a defect located on the optic nerve or RNFL. A visual field examination is standard for measuring glaucoma progression and many clinical trials have evaluated glaucoma progression using a SAP visual field examination.[4] However, some glaucomatous eyes show only structural changes, for example, in the RNFL and/or the optic nerve head (ONH), without changes in visual function. Complete assessment of glaucoma progression requires not only functional but also structural evaluation.[2,4]

Since the 1960s, it has been known that the size of the cup relative to the size of optic disc, or the cup-to-disc ratio (CDR), is a useful measure of glaucomatous damage.[5] In glaucoma, there is a loss of retinal ganglion cells (RGCs) and their axons, resulting in a consequent thinning of the neuroretinal rim and progressive enlargement of CDR occurs. Loss of the neuroretinal rim tends to occur first in the superior and inferior poles, and consequently, the vertical CDR has become a more commonly used parameter in clinical practice.[6]

The ability to detect glaucoma based on CDR is limited due to the wide variability of CDRs in the normal population. This variability is partially explained by the relationship between the CDR and the size of the optic disc. Eyes with large optic discs tend to have large cups, whereas eyes with small discs tend to have small cups. Despite the large variation in 'normal' CDR, CDRs are still used extensively in clinical practice to document the optic disc and determine those patients suspected of having glaucoma.[5,6] By documenting CDRs, clinicians hope to be able to better diagnose the disease and detect progressive structural damage.

However, relatively large interobserver variability has been reported for CDR measurements.[7] Such variability would be most likely to allow only large changes in this parameter to be detected over time, such as CDR changes of at least 0.2.[5] A study by Tatham and colleagues showed that assessment of CDR is an insensitive method for evaluation of progressive neural losses in glaucoma. Even relatively small changes in CDR may be associated with large losses of RGCs, especially in eyes with large CDRs. Subjective evaluation of photographs of the optic disc is often used for assessing glaucomatous structural change but this approach is qualitative rather than quantitative, and even expert opinions vary.[6]

RNFL evaluation also has an important role in the diagnosis and management of glaucomatous patients. At early stages of the disease, significant losses of RGCs have been found to correspond to relatively small changes in visual field measured by SAP.[8] There is mounting evidence indicating that progressive CDR or RNFL changes can frequently be seen before the appearance of statistically significant defects on SAP.[2] In fact, experimental studies have shown that as many as 25 per cent to 50 per cent of RGCs may need to be lost before the decrease in SAP threshold sensitivity values exceed normal variability and reaches statistical significance. Several studies have shown significant rates of structural damage in eyes with early glaucoma in the absence of apparent visual field deterioration.[8,9]

With the advent of optical coherence tomography (OCT) technology, diagnosis and management of glaucoma has been revolutionised. OCT technology was introduced in the early 1990s and gave clinicians their first opportunity to obtain repeatable and reliable objective assessment of the RNFL and to a more limited degree, optic nerve. With the introduction of spectral domain OCT (SD-OCT), there is the ability to obtain detailed 3-D imaging of the retina and optic nerve, allowing a much more accurate and repeatable evaluation.[3,9,10,11]

OCT technology uses a low-coherence infrared beam to cause interference patterns as they pass through the retina/optic nerve. Scans of the optic nerve and surrounding RNFL are analysed and compared to normative databases determined for the specific type of OCT being used.[3]

The normative databases vary depending on the manufacturer, for example, age, race, refractive error.[3] The standard has been to use fundus photographs (stereo) to track

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Integrate SD-OCT into glaucoma diagnosis and management

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progression changes in the optic nerve.[4,5,9] With the introduction of the OCT, are optic nerve photographs still the standard?

A study by Sharma and colleagues compared the clinical assessment of optic nerve photos with the assessment using a Cirrus HD-OCT. The optic disc size designated by the SD-OCT is smaller than that designated by observers of colour fundus images, probably because the SD-OCT considers the optic disc margin to be the easily identified opening in Bruch's membrane, whereas designation of the optic disc boundary during readings from photographs may be influenced by the contrast of reddish optic disc tissue with surrounding peripapillary tissues of darker colour, and the edge of Bruch's membrane is not always evident.

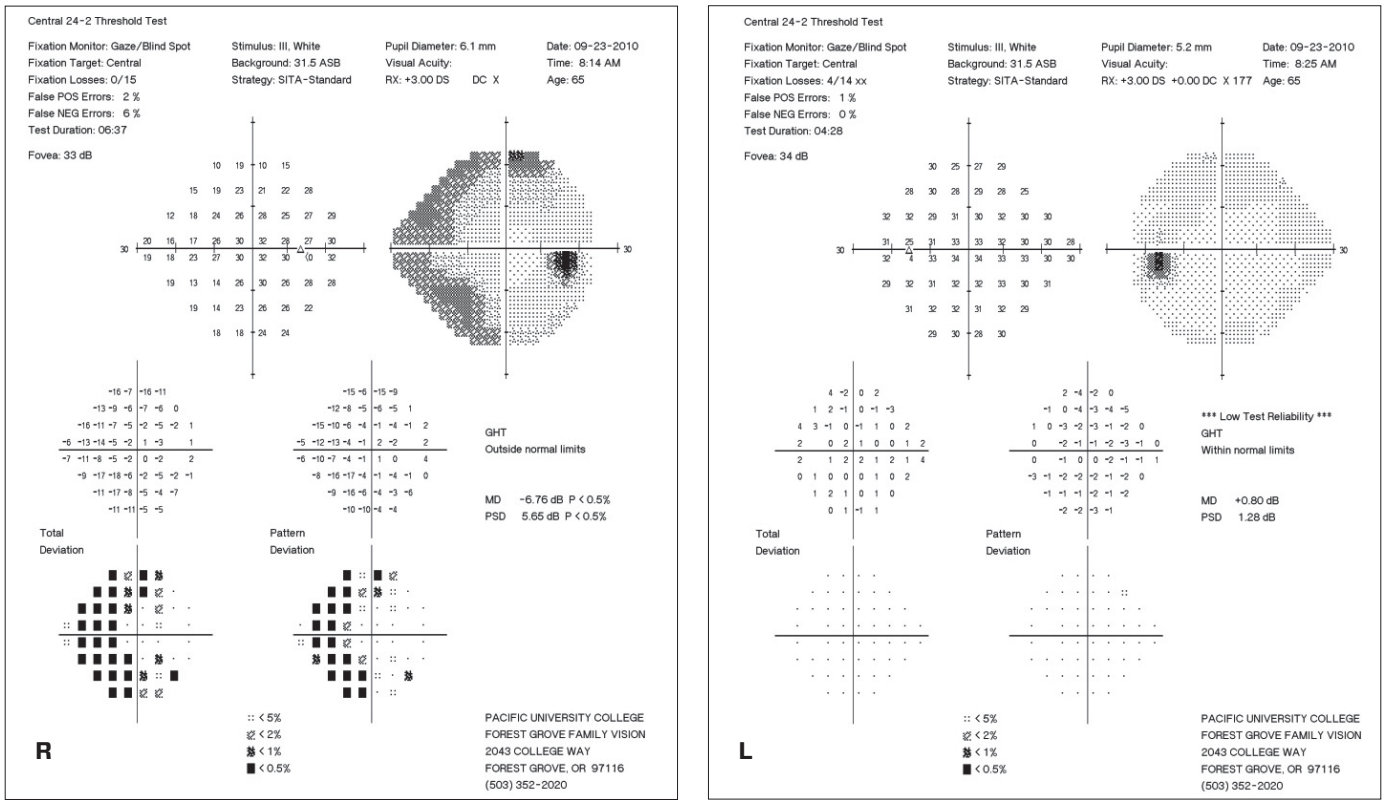
They concluded the Cirrus HD-OCT algorithm for calculating optic disc, cup and rim size is qualitatively in keeping with a clinician's traditional evaluation. What was found to be superior was the repeatability of the measurements in the HD-OCT images and this reduced variance should narrow the region of uncertainty between values found in normal eyes and the values found in glaucoma. High repeatability also is an important feature when monitoring for progressive change.[5]

Figure 1 shows a case of a patient with unilateral glaucoma in his right eye secondary to IOP spikes secondary to steroid injections. Note the superior and inferior nasal visual field defects in the right eye with an apparently normal visual field in the left eye.

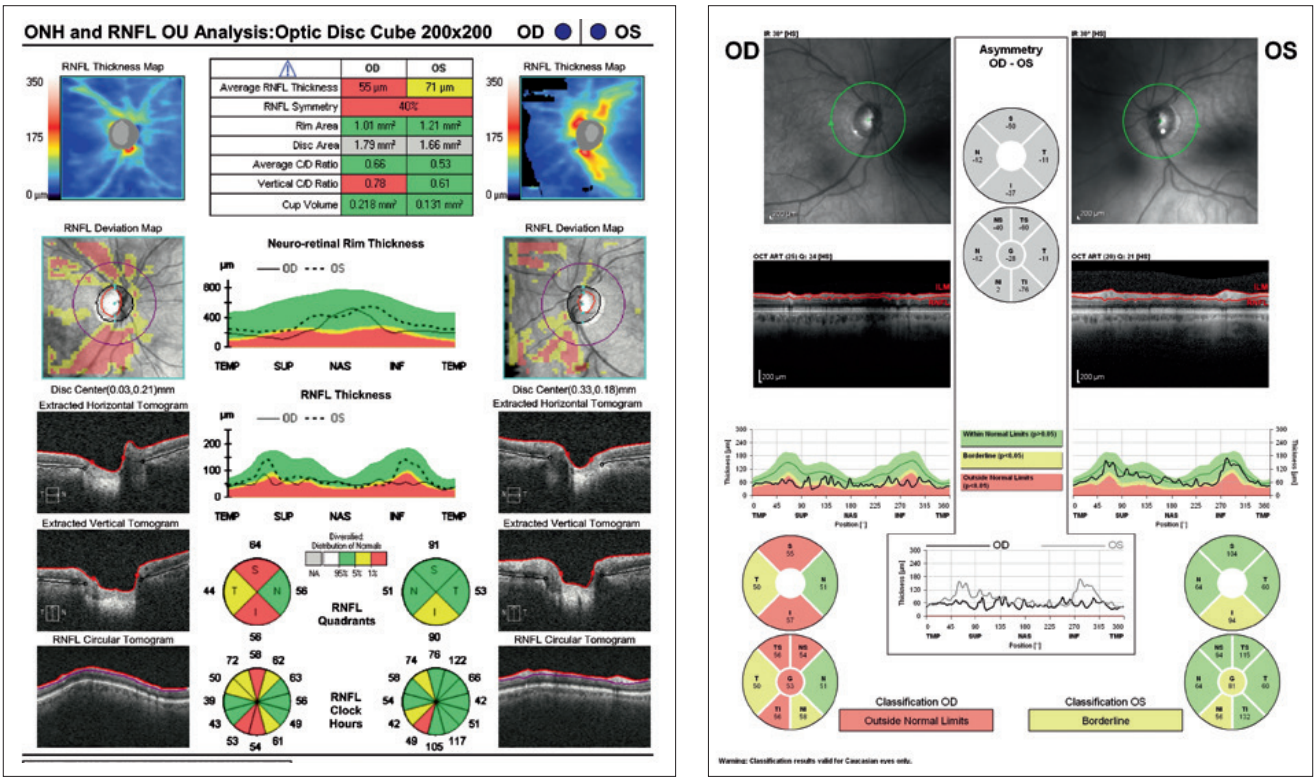
Figure 2 is a print-out of a combined optic nerve and RNFL scan on the patient using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) and a print-out from the Spectralis OCT (Heidelberg Engineering, Carlsbad, CA). The Cirrus HD-OCT shows a corresponding thinning in the superior and inferior temporal RNFL quadrants as shown on the TSNIT graphs. Average NFL thickness is in the red or abnormal zone in the right eye compared to a normative database, with a 'suspicious' (yellow) thickness in the left eye. Average NFL thickness is used as it has been found to be the most clinically useful in separating out normal from 'abnormal' NFL thickness.[3,10,11]

Note the symmetry index is flagged as abnormal. Glaucoma is an asymmetrical disease and it is crucial to look at the symmetry index. It is possible that the average NFL thickness could be in the green (normal) range in both eyes, but if the symmetry index is abnormal it may suggest that patient is suspicious for glaucoma, which would be overlooked if the clinician is only looking at the 'normal' NFL thickness.

Looking at the pie graphs, the superior and inferior quadrants in the right eye



▲ Figure 1. Visual field from a 60-year-old white male with history of IOP spikes secondary to steroid injections for lower back stenosis. Asymmetry noted in CDR with vertical elongation noted in the right eye. Note the superior and inferior nasal defects (steps) in the right eye, and apparently normal visual field in the left eye.



▲ Figure 2. Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) and Spectralis OCT (Heidelberg Engineering, Carlsbad, CA) for the 60-year-old white male with the visual field presented in Figure 1. Note the 'red' flagged average NFL thickness and symmetry index in the Cirrus OCT parameters and the flattened TSNIT curve (compared to the left eye curve), with additional red flagged superior and inferior sections of the pie graphs which corresponds with the inferior and superior nasal defects noted on the right visual field. Similarly, the Spectralis has the same flattened right TSNIT curve for the right eye and the similar red flagged superior and inferior RNFL thickness in the pie graph associated with the superior and inferior visual field defects noted on the visual field. Note that both the Cirrus HD-OCT and the Spectralis OCT have flagged the inferior NFL in the left eye as 'suspicious' or thinner than age expected norms with no apparent visual field defect noted in the left visual field, potentially picking up an early preperimetric thinning of the patient's NFL that has not manifested as an observable visual field defect.

are red indicating that the patient's NFL is abnormally thin compared to age expected norms. Additionally, the optic nerve parameters are also represented, which shows a vertically elongation of the CDR and a thin neuroretinal rim. Also shown is a print-out from the Spectralis OCT, showing patterns similar to those noted with the Cirrus HD-OCT. The TSNIT graph shows a 'normal' left eye but a flattened line graph in the right eye with the line dipping into the abnormal thickness range in the superior and inferior temporal quadrants corresponding to the inferior/superior nasal visual field defects.

Interesting to note is that the visual field in the left eye appears to be normal with no significant visual field defects noted in the pattern standard deviation (PSD) plot. However, when looking at the Cirrus HD-OCT and the Spectralis print-out, you note that the inferior temporal NFL is flagged in yellow or suspicious. Is there a preperimetric thinning of the left NFL that is not showing as an observable visual field defect? Remember, it is estimated that 25-50 per cent NFL loss maybe needed to get an observable visual field defect.[8] The use of SD-OCT technology may allow the clinician to pick up preperimetric visual field defects, allowing the clinician to more closely monitor that patient or potentially initiate therapy at an early stage in the disease process.

It is well known that the circa parapappillary NFL (cpNFL) and the optic nerve are critical in the diagnosis of glaucoma[9-12] but evidence is accumulating that measurements of the inner retinal layers in the macular region may be additional parameters for glaucoma detection.[12] The ganglion cell complex (GCC) consists of the RNFL, the ganglion cell layer and the inner plexiform layer. The GCC is becoming an increasingly important area to assess, particularly in patients with early glaucoma.

Studies have shown that GCC and cpRNFL thickness exhibit similar diagnostic performance for the detection of early glaucoma.[9,10,11] Nakatani and colleagues demonstrated that macular parameters (GCC) in SD-OCT had comparably high discriminating power for early glaucoma and high reproducibility comparable with peripapillary RNFL parameters. SD-OCT increased the diagnostic value of macular parameters for early glaucoma.[12] Akashi and colleagues demonstrated that the diagnostic performances of average cpRNFL thickness and average GCC thickness to identify early glaucoma and all-stage glaucoma were similar among Cirrus, RTVue and 3-D OCT measurements in our study population.[10]

Figure 3 shows a patient who presented with asymmetrical IOPs (24 OD, 20 OS) and asymmetrical CDR (0.75/0.75 OD, 0.6/0.6 OS). FDT visual field shows no apparent visual field defects in either

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Integrate SD-OCT into glaucoma diagnosis and management

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eye; however, the GCC as measured by the Cirrus SD-OCT is normal in the left eye but abnormal in the right eye compared to age normative database. Note that the Cirrus SD-OCT measures the GCC by removing the NFL for the GCC and utilises only the ganglion cell layer and the inner plexiform layer combined thickness.

This is compared to the Spectralis OCT, which utilises a posterior pole retinal thickness map where retinal thickness around the macula is measured and symmetry of retinal thickness is compared between corresponding 'grids' between right and left eyes, and additionally between the interior and superior corresponding quadrants in the same eye.

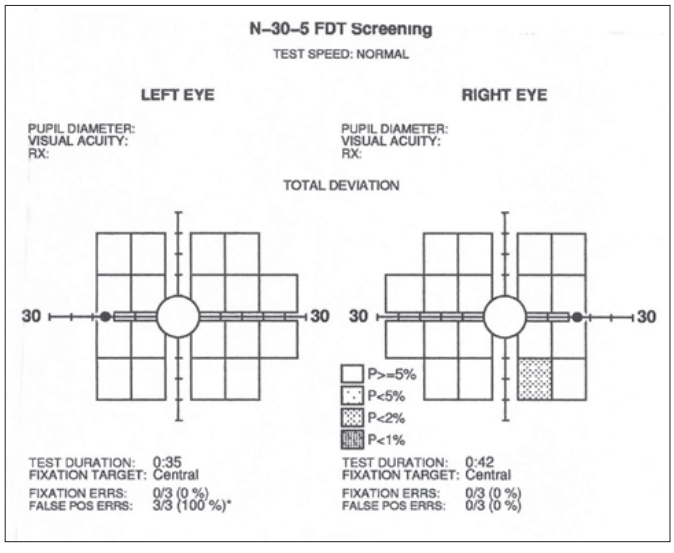
Is it appropriate to treat this patient who has asymmetrical and above 'normal' IOP, asymmetry in his CDR and an abnormal GCC but no observable visual field defect? To add to the clinical picture, Figure 4 depicts the RNFL and ONH scan performed on this patient and there is noticeable thinning in the NFL in the superior quadrant correlating with the abnormal GCC noted in Figure 3. Traditionally, patients are not 'diagnosed' with and begun treatment for glaucoma unless there is an observable and repeatable visual field defect. With the advent of SD-OCT, the paradigm of when to treat is shifting.

Glaucoma is a progressive disease with no cure, but with early detection and treatment there is the hope of slowing progression and preventing significant vision loss. A subjective evaluation of the disc and the RNFL status is currently the reference standard for the assessment of glaucomatous structural change. This approach is qualitative rather than quantitative, and even expert opinions vary on what is considered progression.[4,8,9,10] What is needed is an objective, qualitative and repeatable means to monitor progression in patients.

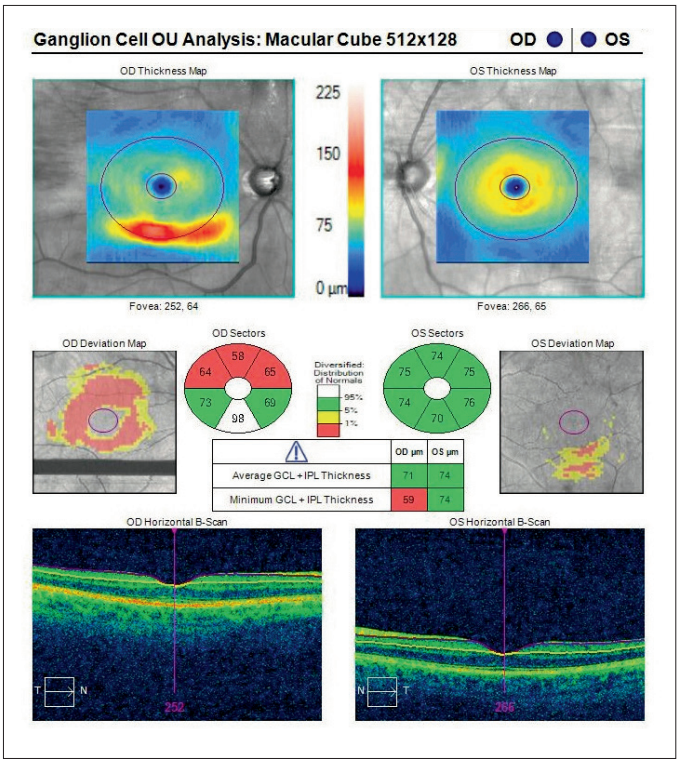
Progressive visual field loss has traditionally been the measure of functional loss with respect to glaucoma and is often the determining factor on whether treatment is modified.[1,9] However, reliability is always a concern when performing visual field testing due to its reliance on the patient and their subjective assessment during the testing process.

Guided progression analysis (GPA) has been introduced to visual field testing in instruments such as the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA) attempting to take patient variability into consideration and determine if there is progressive loss in visual function over time. Similar to the guided progression analysis that is found in the Humphrey Visual Field, OCTs also have a form of GPA and is useful for progression detection in an objective and structural capacity (versus the subjective and functional with visual field testing) in glaucoma to complement other reference standard strategies.[9]

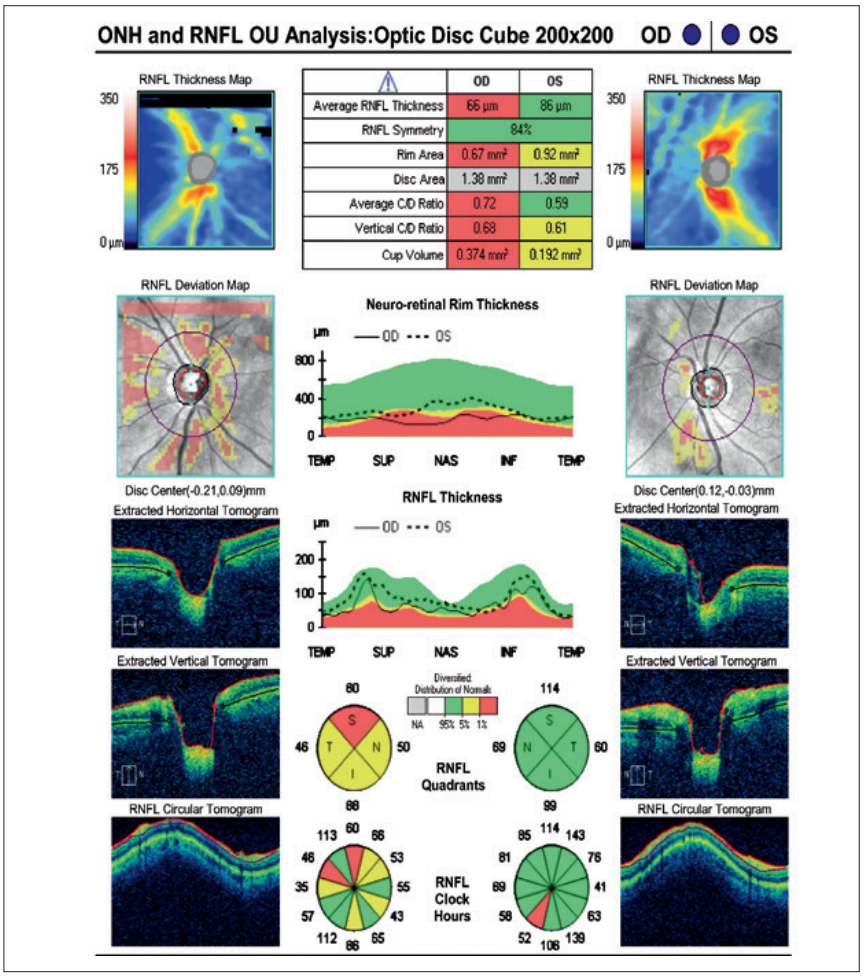
It also has to be remembered that as the disease progresses, testing and the emphasis placed on particular tests also has to change. For example,



▲ Figure 3A. FDT screening visual field of a 66-year-old male patient who presented with asymmetrical IOP (24 OD, 20 OS) and asymmetrical CDR (0.75/0.75 OD, 0.6/0.6 OS). No glaucomatous visual field defects noted on the screening FDT visual field.



▲ Figure 3B. GCC analysis print-out from the Cirrus SD-OCT for this patient. Note the superior GCC thinning (flagged in red on the pie graph) and the normal GCC in the left eye.



▲ Figure 4. Print-out of a Cirrus SD-OCT ONH and RNFL from the patient depicted in Figure 3. Note the abnormal (red flagged) average NFL thickness and the superior quadrant on the pie graph representing a superior NFL thinning compared to age norms. ONH parameters in the right eye are also flagged in red with an average CDR of approximately 0.72 compared to 0.59 in the left eye and an abnormal neuroretinal rim area compared to age norms. The NFL thinning noted in the superior quadrant correlates with abnormal thinning noted on the GCC printout in Figure 3; however, no corresponding visual field defect was noted on the FDT screening.

traditionally a 24-2 visual field is used in the diagnosis and early progression testing for glaucoma, but with more advanced visual field loss the clinician may have to change to a 10-2 visual field and potentially more emphasis being placed on changes in the visual field compared to imaging equipment dependent on the reliability of the scan that can be obtained. In addition, 10-2 visual field testing may also need to be considered in the early diagnosis of glaucoma as paracentral VF defects are thought to be an early visual field defect seen particularly in normal tension glaucoma,[13] which may also correspond to the new GCC scans that we are obtaining. With the advances in technology, our 'traditional' approach to glaucoma diagnosis and management will also have to advance.

Summary

OCT technology has revolutionised how eye-care professionals diagnosis and manage their patients, in particular when it comes to glaucoma. OCT technology has developed into a reliable and repeatable quantitative assessment of retinal and optic nerve structure. The potential of this advanced technology is to identify those patients who present with glaucoma, even preperimetric glaucoma, without completely relying on a subjective and often unreliable visual field assessment. With the added advanced glaucoma tools like ganglion cell analysis and guided progression analysis, the OCT is becoming a mainstay in the diagnosis and management of patients.

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Visual field defects and glaucoma

Dr Jack Phu

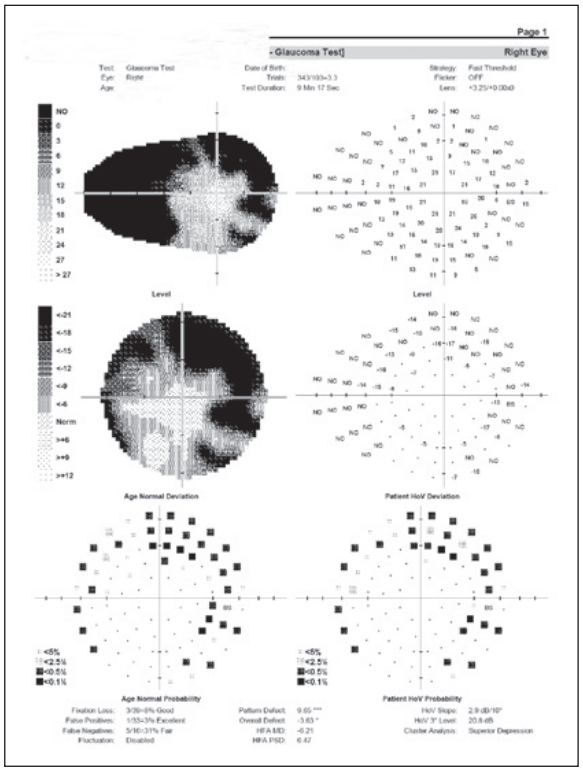
BOptom (Hons) BSc

CASE REPORT

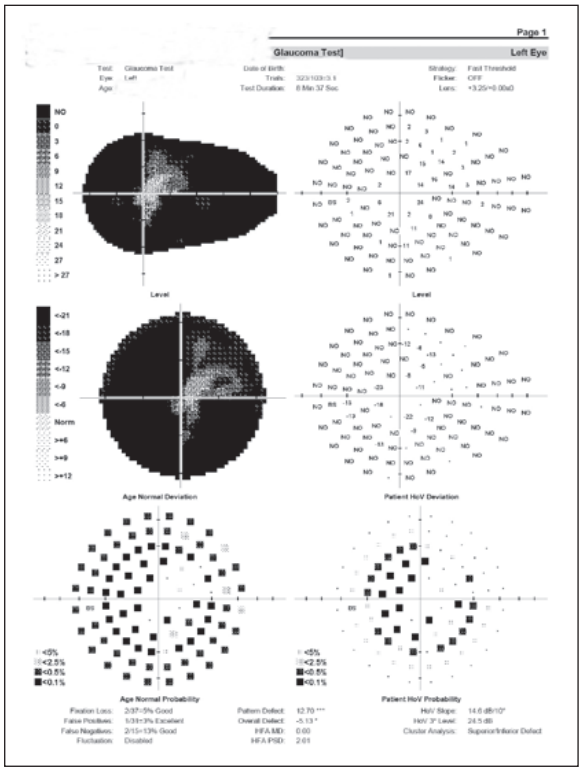
HC IS AN 87-YEAR-OLD Chinese woman who first presented to the practice on 13 August 2013 for routine eye examination. The patient complained of blurry vision with her old spectacles. She had no other complaints of red, sore or itchy eyes. The patient had had cataract surgery with posterior capsular intraocular lenses in the left eye in Australia about three years previously. She had a systemic history of type 2 non-insulin dependent diabetes mellitus, hypertension, hyperlipidaemia, cardiac arrhythmia, and gastroesophogeal reflux disease, and was taking medications for these conditions. The patient reported no history of asthma, renal disease or any medical allergies. There was no family history of vascular or ocular disease.

Best corrected visual acuities were 6/45 at distance and 6/45 at near OD and 6/18 at distance and 6/12 at near OS with manifest refraction of +0.25 DS OD and +0.25 DS OS. Pupils were equal, round, reactive to light and with no afferent pupillary defect OU. Extraocular motilities were smooth, accurate, full and extensive OU. Anterior examination showed open angles with deep anterior chambers OU. Corneas were clear OU. There were grade 2+ pterygia on the bulbar conjunctiva OU, and grade 3+ meibomian gland dysfunction OU. There was grade 3+ mixed cataract OD. The posterior chamber intraocular lens was clear OS. Intraocular pressures measured by Goldmann applanation tonometry were 15 mmHg OU at 5:36 pm.

Dilated fundus examination with Superfield lens showed cup-disc ratios of 0.95 with deep cupping OU. Neuroretinal rims were notched superior and inferior OU, and there was a Drance haemorrhage at 10:30 on the disc OD. There were grade 2+ epiretinal membranes OU, and numerous dot-blot haemorrhages and microaneurysms in the fundus OU. Vitreous body was clear OU. Confrontation visual fields showed slight restriction of temporal and nasal fields OU.



▲ Figure 1. HC's right visual field result. Reliability indices were mostly reliable except for high false negatives which may have been due to poor understanding of the task. It shows a superior scotoma with nasal defects, and enlarged blind spot with possible inferior defect.



▲ Figure 2. HC's left visual field result. Reliability indices were better compared with right eye. The raw data shows severe restriction of the visual field inferior more than superior. The pattern deviation shows a similar arcuate defect inferior more than superior; however, such a defect could possibly be due to poor understanding of the task.

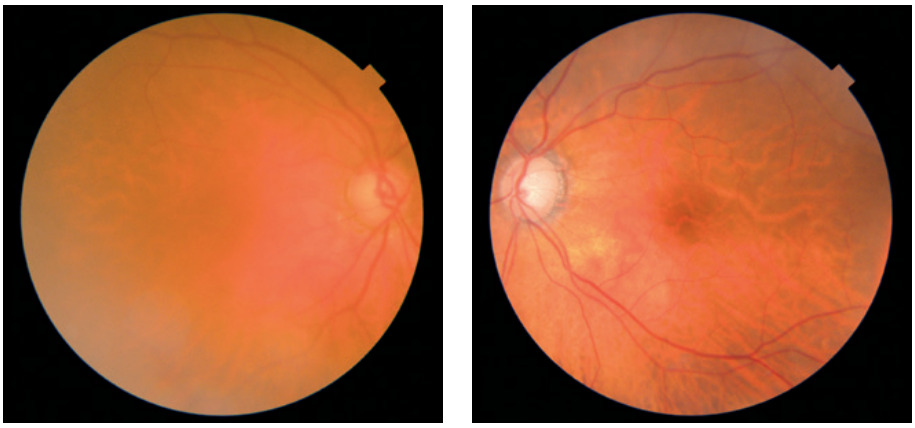
The patient was asked to come back in one week for automated perimetry and OCT imaging.

The patient was seen on 21 August 2013 for glaucoma assessment. Automated perimetry (M700 Automated Perimeter, Medmont Pty Ltd, VIC Australia) results were reliable and showed superior scotoma, nasal defects and enlarged blind spot with possible inferior defect OD though it was difficult to separate the cataractous defects (Figure 1), and very restricted visual fields OS (Figure 2).

Colour fundus photography showed notching and pallor of the superior and inferior neuroretinal rims with adjacent peripapillary atrophy right more than left (Figure 3). The microaneurysms and dot-blot haemorrhages were also seen. The Drance haemorrhage OD was still present. Spectral-domain OCT (3D OCT-1 Maestro, Topcon, Device Technologies, Australia) was unreliable in the right eye due to cataracts but showed corresponding thinning of the nerve fibre layers superior and inferior OU (Figure 4). Intraocular pressures measured by applanation were 15 mmHg OD and 16 mmHg OS at 12:25 pm. Gonioscopy (Sussman G4 goniolens, Volk, Designs For Vision, Australia) showed angles open to the ciliary body OU with no synechiae and light pigmentation of trabecular meshwork. Central corneal thicknesses were 498 um OD and 480 um OS by ultrasound pachymetry (Pachmate DGH55, DGH Technology, Inc PA, USA).

Differential diagnoses for this patient included compressive optic neuropathy and secondary glaucoma. Signs of secondary glaucomas such as inflammation, exfoliation, and pigmentation were all absent. In light of classical cupped appearance, rather than diffuse pallor, age, and pattern of visual field defect, neuroimaging was not performed for compressive optic neuropathy.

With clear correlation of optic nerve head appearance, visual fields and OCT imaging, HC was diagnosed with advanced glaucoma OU and moderate non-proliferative diabetic retinopathy OU. She was referred to a local ophthalmologist for glaucoma co-management. Because the ophthalmologist was fully booked for the next proceeding weeks, she was started on latanoprost 0.005% (Xalatan, Pfizer, Australia) nocte to both eyes to at least lower the pressure to slow progression of the disease. An appointment was scheduled for three months ahead to discuss the treatment and to ensure that she was compliant and agreed with the management plan. She was to repeat visual field tests after six months. Based on these findings, the ophthalmologist agreed with the diagnosis. The post-treatment IOP was 10 mmHg, which is a 30 per cent reduction from baseline.



▲ Figure 3. HC's colour fundus photos. (Left) Right eye fundus photo, slightly blurred due to cataract. Despite blurriness, the notching of the neuroretinal rim, inferior more than superior, is easily detected. There is also a small Drance haemorrhage visible at 10:30 o'clock on the disc. (Right) Left eye fundus photo, much clearer with intraocular lens implant. There is also significant thinning and pallor of the neuroretinal rims superiorly and inferiorly with loss of retinal nerve fibre layer. The small microaneurysms are easily seen in the left macula.

Management of glaucoma with significant visual field defects presents a challenge to both the optometrist and the ophthalmologist. There are numerous methods of staging glaucoma. One uses the Bascom-Palmer method, or Glaucoma Staging System (GSS).[1] Based on this scoring system, HC has moderate-advanced defect from this visual field result.

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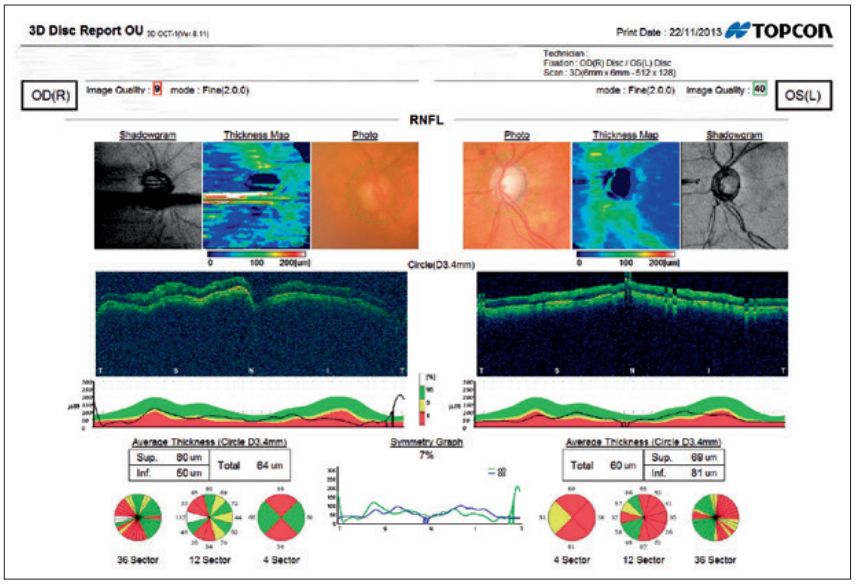

VF defects and glaucoma

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Different studies suggest different target IOP for normal-tension glaucoma. The Collaborative Normal-Tension Glaucoma Study group refers to a target IOP of 30 per cent;[2] the Early Manifest Glaucoma Trial reported a resultant pressure reduction of 25%;[3] and the Advanced Glaucoma Intervention Study and similar studies suggest a reduction of 50 per cent, or to 10 mmHg.[4,5] Controversy still exists regarding the recommended target IOP for patients with NTG.[6] however, a recent study showed any reduction in IOP is beneficial for the patient in helping to preserve visual function and should be titred according to severity of disease.[7] This should be further refined from the individual's rate of progression.

Studies of topical ophthalmic anti-glaucoma drops show that a reduction of about 20-30 per cent is expected with prostaglandin analogue medications in patients with NTG. Because HC's baseline IOP was 15 mmHg, the resultant IOP is expected to be 10-12 mmHg. A prostaglandin analogue was selected as first-line therapy due to its ease of dosing—once at night, 24-hour maintenance of IOP reduction, its minimal systemic side-effects, and long-term sustained effect.[8] In comparison to timolol, latanoprost has a superior 24-hour IOP reduction profile and is more favourable towards ocular perfusion pressure.[7,9]

However, prostaglandin analogues have a number of well-documented ocular side-effects, including conjunctival hyperaemia, hypertrichosis, iris and eyelid pigmentation, and prostaglandin-associated periorbitopathy.[10] To a lesser extent, prostaglandin analogues have also been linked to inflammatory disease such as uveitis, recurrent ocular herpes and cystoid macular oedema.[10] These need to be monitored closely. In addition to topical treatment, HC was counselled on the importance of blood sugar, cholesterol and hypertensive control, as vascular comorbidities may be associated with progression of glaucomatous disease.[11,12]

Advanced glaucoma with normal-range IOP can present a challenge to the optometrist and ophthalmologist as reduction in IOP alone may be insufficient to prevent progression of glaucomatous disease. Ocular perfusion pressure should be considered in these cases.[6] Such a late presentation requires regular follow-up with disc assessment, IOP measurements, and trend analysis by perimetry and optic nerve imaging.

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Dr P Pathmaraj

FRANZCO FRCS MRCOphth MBBS
Consultant Ophthalmologist
Vision Eye Institute and Royal Victorian Eye and Ear Hospital
Melbourne

SELECTIVE LASER trabeculoplasty (SLT) is a form of laser surgery that is used to lower intraocular pressure (IOP) in glaucoma. There are reports of progression to blindness in 25 per cent of glaucoma patients under treatment for 20 years.[1] There are many reasons why patients with glaucoma go blind, of which one is non-compliance with medical therapy. SLT averts the compliance (Table 1), side-effects (Table 2) and inconvenience issues associated with medical treatment.

The introduction a decade ago of SLT to the treatment regimen for glaucoma has changed the treatment algorithm in the management of glaucoma.

Who is a candidate for SLT?

Any patient with glaucoma whose trabecular meshwork is visible on gonioscopy is a candidate for this procedure. SLT helps to lower IOP in open angle glaucoma or high-risk ocular hypertension as well as stabilise the intraocular pressure fluctuation, which causes the damage to the optic nerve.

How does it work?

SLT uses a Q-switched (that is, pulsed), three nanosecond frequency-doubled Nd:Yag, 532 nm wavelength green laser. Low energy and larger spot size allow the ophthalmologist to easily focus the laser onto the trabecular meshwork (TM) and distribute the laser energy evenly, so that all the target cells receive equivalent doses of laser energy. The laser energy targets pigmented trabecular meshwork endothelial (TME) cells. As this targeting is highly specific, the laser energy does not cause coagulative damage to the TM or other collateral thermal effects to the TM.

The treated TME cells release cytokines, which bind with Schlemm's canal endothelial (SCE) cells, and open the cellular tight junction barrier that has been acting as a control site

Selective laser trabeculoplasty

for aqueous outflow. The opening of the SCE barrier results in increased aqueous drainage leading to decreased IOP. Additionally, the newly released cytokines attract circulating monocytes to the laser site. These monocytes becomes macrophages, which perform phagocytosis of cellular debris in TM so that aqueous is drained easily from the anterior chamber in to Schlemm's canal, resulting in reduction of IOP.

Why is it called 'selective'?
A high degree of selectivity of target tissue by the laser and the use of a brief pulse duration, which last for just nano-seconds, produce minimal pain and scar tissue.

What are the risks?
One key aspect of SLT is a favourable side-effect profile, even when compared with glaucoma medication. Postoperative inflammation is common but generally mild and treated with observation or non-steroidal anti-inflammatory drops. There is a five per cent incidence of elevated IOP after laser, especially in heavily pigmented TM.[2] By using lower laser energy, high IOP is averted in patients at risk. The elevated IOP can be managed easily by glaucoma medications and usually resolves after 24 hours but rarely may require surgery to control the IOP.

How effective is it?
SLT is effective as primary, replacement or adjunctive treatment. SLT lowers the IOP by about 30 per cent when used as initial therapy. This effect may be reduced if the patient is already on glaucoma medication. Treating 360 degrees of trabecular meshwork gives the greatest IOP lowering effect. It must be also noted that the patients most likely to have a significant response are those with the highest base line pressures, regardless of any prior medical or therapeutic intervention.

The clinical efficacy of SLT is comparable to the IOP lowering of the most commonly used class of medication, the prostaglandin analogue (PGA). In a study conducted by Dr Nagar and colleagues,[2] it was found that there was a slightly higher reduction in IOP as a result of commonly used PGA latanoprost but it was explained that SLT offers the benefit of being a one-time intervention not requiring ongoing patient compliance. The authors noted that as a rule of thumb, with SLT they expected a 20 per cent drop in IOP when the base line pressure was 20 mmHg and a 30 per cent drop for a base line pressure of 30 mmHg. In another study,[3] it was found that approximately 93 per cent of patients were expected to respond to SLT as primary therapy, and more than 50 per cent of all patients receiving SLT as replacement therapy will not need any medication post-treatment

Complicated prescription regimens
Medication costs
Unpleasant side-effect (see Table 2)
Physically unable to place eye-drops
Forgetfulness and changes in routine

▲ Table 1. Reasons for non-compliance

Allergic reaction
Ocular surface disease
Hyperaemia, increased pigmentation of lids and iris
Reduced blood pressure and pulse rate
Shortness of breath in patients with respiratory disorders
Fatigue and drowsiness

▲ Table 2. Side-effects with eye-drops

How long does it last?
The effect will generally last from one to five years and in rare cases, longer than that. There is a higher non-responder rate among normal tension glaucoma (NTG) versus primary open angle glaucoma (POAG) (25-30 per cent versus 20-22 per cent) as well as a lower five-year survival rate (30 per cent versus 50 per cent). SLT is useful in NTG patients only if there is concern about either compliance or intolerance to PGA or significant IOP fluctuation. Duration of response also seems to be shorter in pseudoexfoliation compared to POAG.

What happens if effectiveness of SLT diminishes?
If SLT is effective for more than six to 12 months at lowering IOP but its effectiveness wears off over several years, the procedure can be repeated. The second treatment may not be effective as the first and may not have long-lasting impact. Glaucoma medication can be used if the effect diminishes over time.

What happens if it doesn't work?
If SLT fails to lower the IOP, then the glaucoma is treated by other means such as medications or conventional surgery (trabeculectomy). The laser does not affect the success of these other types of treatment.

What is the cost?
Because the procedure is an accepted form of glaucoma treatment and is a TGA approved treatment, Medicare covers most of the cost but co-payments may vary.

Is there a need to use glaucoma medication after SLT?
Some patients can be controlled with just SLT; others require additional IOP reduction and may need to use glaucoma medication as well. SLT can be thought of as equivalent to one glaucoma medication. Just as some patients will require more than one glaucoma medication to control their IOP, some may require laser plus one or more medications. It is important to remember that SLT is not a cure for glaucoma, just as medication and surgery are not. Whatever method is used, appropriate follow-up and testing are required to monitor the progress of glaucoma to prevent blindness.

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The ganglion cell complex and glaucoma

Graham Lakkis

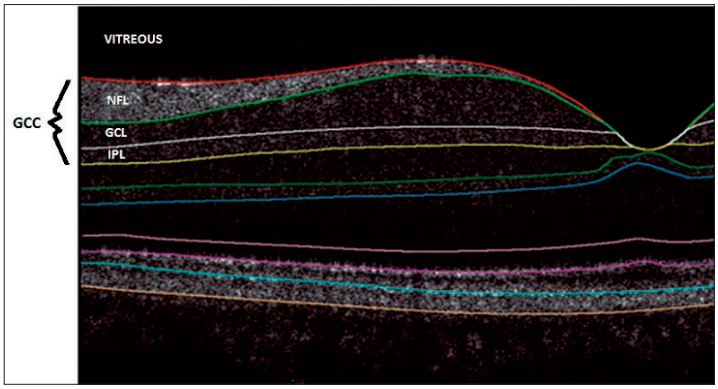
BScOptom GradCertOcTher FACO
Lead Optometrist, University of Melbourne Eyecare Glaucoma Clinic

GLAUCOMA IN ALL its manifestations and clinical variants ultimately leads to destruction of retinal ganglion cells.

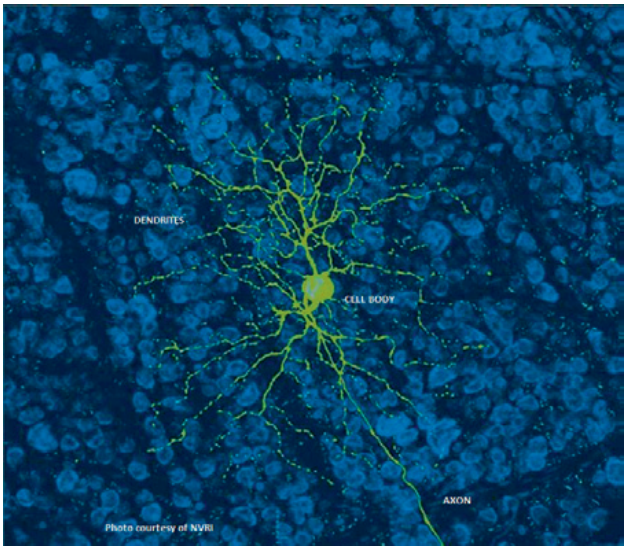
Different methods are available to detect ganglion cell damage, such as structural losses at the optic nerve head (for example, increased C/D ratio, neuroretinal rim thinning or notching) or changes in ganglion cell function such as threshold visual field defects. Existing clinical methods are limited in their ability to detect ganglion cell damage until there is significant loss. Approximately 40 per cent of ganglion cells need to be lost before an early glaucomatous threshold visual field defect is manifested,[1] and the typically slow progression in optic nerve head changes makes structural glaucoma detection difficult until significant rim tissue is lost.

With the advent of scanning laser clinical instruments, newer methods have been developed to enhance earlier detection of glaucomatous damage. The Heidelberg Retinal Tomograph (HRT) tracks changes in optic nerve head physical characteristics such as rim area and cup volume. The GDx (Carl Zeiss Meditec) looks for loss of ganglion cell birefringence in the circumpapillary retinal nerve fibre layer. Time domain (TD) and spectral domain (SD) OCTs measure the ganglion cell axons around the optic nerve head to determine nerve fibre layer thickness and the TSNIT curve. These existing clinical instruments concentrate on measuring the axons of the retinal ganglion cells adjacent to and on the optic nerve head.

However, retinal ganglion cells are large and complex cells extending from the inner retina all the way to the lateral geniculate nucleus (LGN) in the midbrain. Ganglion cells begin at the inner plexiform layer (IPL) where they synapse with the bipolar and amacrine cells of the middle retina. Their cell bodies (soma) make up the ganglion cell layer (GCL) of the inner retina, and the ganglion cell axons that emerge are the retinal nerve fibre layer (NFL). These axons traverse the retina, converging at the scleral foramen where they form the neuroretinal rim of the optic nerve head, before continuing on to the optic chiasm and LGN. On a cross-sectional OCT scan,



▲ Figure 1. The ganglion cell complex (GCC) consists of the three innermost layers of the retina: IPL (inner plexiform layer), GCL (ganglion cell layer), NFL (nerve fibre layer)



▲ Figure 2. An en face view of a retinal ganglion cell; the extensive dendritic arbour makes up the inner plexiform layer (IPL)

all three segments of the ganglion cells (IPL, GCL and NFL) are known as the ganglion cell complex (GCC) (Figure 1). In an en face view (Figure 2) we see that the ganglion cell synapses of the IPL are the largest area of the cell, forming an extensive branching dendritic arbour. The cell body (GCL) and axon (NFL) are relatively small compared to this dendritic tree.

How retinal ganglion cells die

Research in animal models shows that when a retinal ganglion cell is damaged either by axotomy (severing the retrobulbar optic nerve) or raised intraocular pressure, the ganglion cell dies in a characteristic way. The earliest changes are seen as a loss of the dendritic arbour (IPL) due to mitochondrial fission (splitting).[2] Subsequently, the cell body (GCL) dies. Studies on axonal death show that first there is a loss of microtubules inside the axons (detected as a change in birefringence on GDx scans) prior to the eventual phagocytosis of the outer axon itself (detected as RNFL thinning on OCT scans) which in animal models may occur many months later.[3]

The advent of spectral domain (SD) OCT allows us greater optical resolution to accurately segment the inner layers of the retina into their constituent IPL, GCL and RNFL layers. Given that ganglion cells die initially from their synapses (IPL) and cell bodies (GCL), thinning of the ganglion cell complex (GCC) as detected by SD OCT may prove to be an earlier detector of glaucomatous damage than simple RNFL thickness around the optic nerve head.

GCC scans

Approximately 50 per cent of the total retinal ganglion cells synapse in the central 5 mm of the macula.[4] All commercially available OCTs perform GCC scans that are centred on the fovea to a diameter of between 6 mm and 9 mm, depending on the instrument and software settings. The results can be displayed as an absolute GCC thickness, as well as a probability map compared to the OCT's normative database (Figure 3). Depending on the OCT used, average GCC thickness is approximately 95 to 100 microns. Progression analysis software allows comparison of baseline and follow-up scans to determine if there has been any progressive thinning of the GCC.

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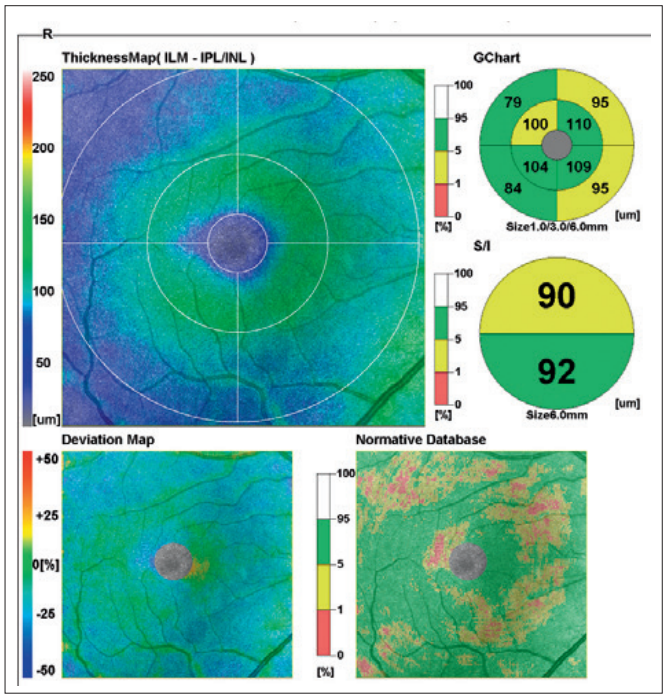
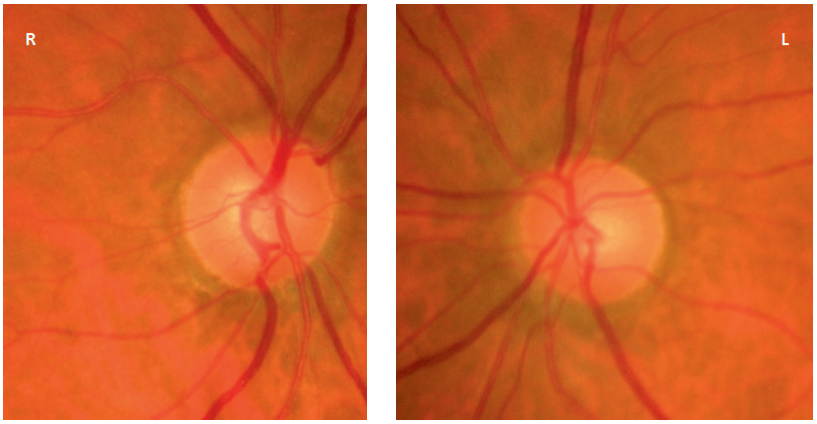
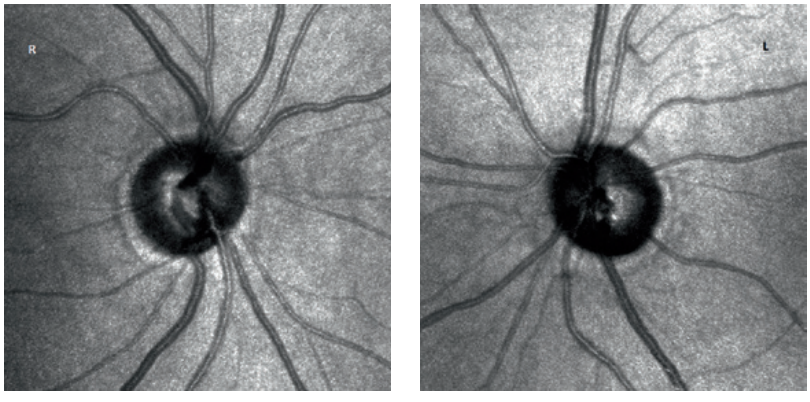


▲ Figure 3. R eye GCC chart (Nidek RS3000). In this instrument the macular region is divided into eight sectors around the fovea which respect the horizontal raphe. There is never a thickness reading centrally as the fovea does not contain any ganglion cells.



▲ Figure 4. Disc photos of patient MP; note the subtle loss of the ISNT rule inferiorly in the R eye



▲ Figure 5. Scanning laser ophthalmoscope disc images (Nidek RS 3000)

The ganglion cell complex and glaucoma

From page 29

CASE REPORT

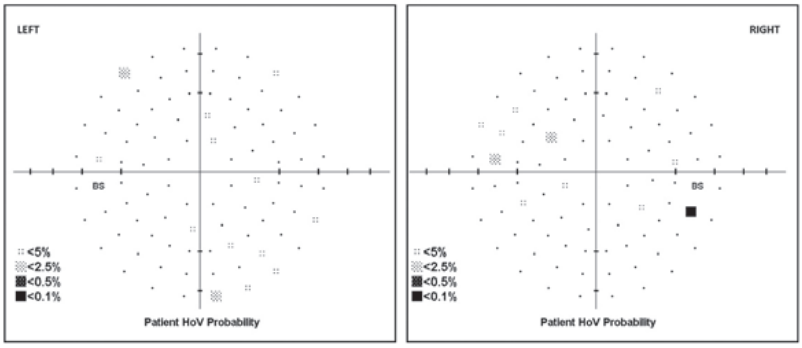
MP is a 53-year-old white female followed as a glaucoma suspect since 2004 due to ocular hypertension. Her pertinent clinical findings were:

IOP: R 23-26, L 22-26 mmHg.
Pachymetry: R 561, L 555 microns.
Gonioscopy: open to posterior trabecular meshwork OU.
Slitlamp: no pigment dispersion or pseudoexfoliation. General health: no medication, no drug allergies. Family history: no glaucoma.

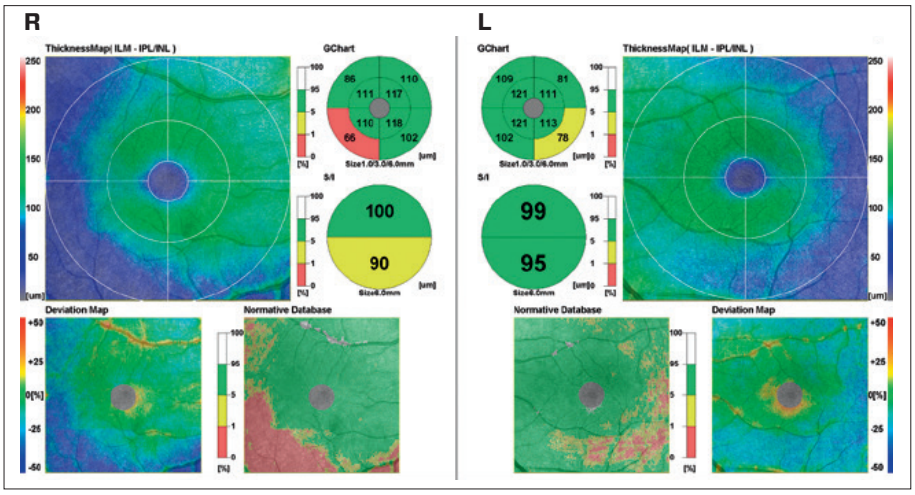
Optic nerve head assessment (Figure 4) showed a subtle loss of the ISNT rule inferiorly in the R eye. This was more evident in the OCT confocal scanning laser ophthalmoscope image (Figure 5) due to the difference in laser light absorption by the neuroretinal rim tissue compared to the more reflective lamina cribrosa. Threshold visual fields were reliable and did not show any clusters of loss or glaucomatous defects in either eye (Figure 6).

GCC scans performed in February 2011 showed a significant reduction in ganglion cell thickness in the inferotemporal sector of the R eye ($p < 0.01$) and borderline thinning in the same sector of the L ($p < 0.05$) (Figure 7). RNFL scans were normal in both eyes. A decision was made to repeat the GCC scans in six months to check for any progressive thinning.

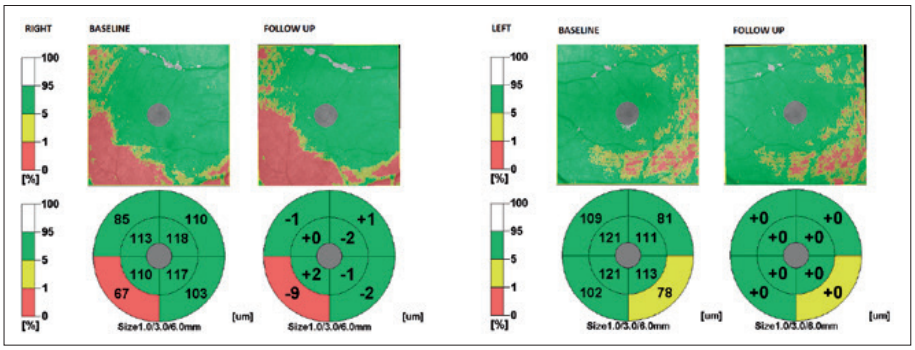
On review in October 2011, follow-up GCC scans were performed and compared to baseline. The defective R inferotemporal sector thinned by a further nine microns, while the equivalent suspicious sector in the L eye remained unchanged (Figure 8). A change of five or more microns is considered significant as it is greater than the test-retest variability of the OCT instrument.[5]



▲ Figure 6. Threshold visual fields (Medmont M700)



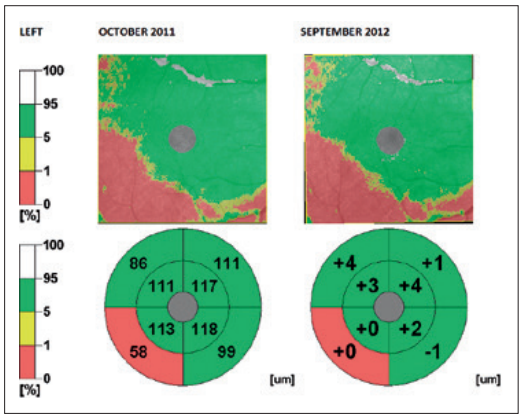
▲ Figure 7. Baseline GCC scan showing R > L thinning of the inferotemporal sectors



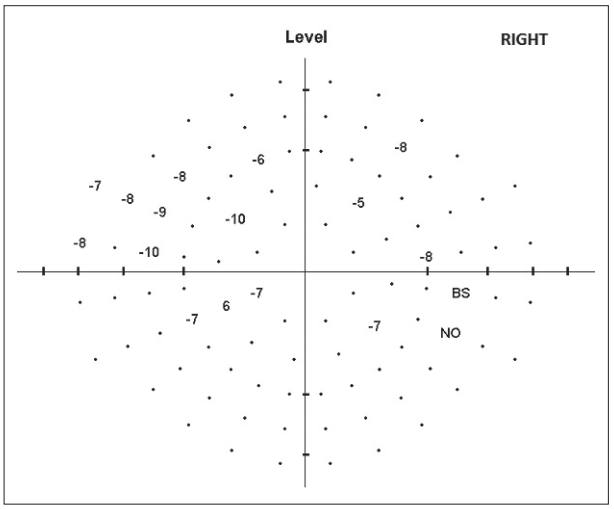
▲ Figure 8. GCC progression analysis shows a loss of nine microns in ganglion cell thickness in the R inferotemporal sector between February 2011 and October 2011 but no changes in the L eye

Due to the progressive nature of the GCC loss in the R eye, the patient was diagnosed with R preperimetric open angle glaucoma and commenced on gt latanoprost nocte in both eyes with a target IOP of 18 mmHg. The patient was compliant and responded to therapy, and target pressure was readily achieved. A post-treatment follow-up GCC scan was taken in September 2012 and compared to the pretreatment scan of October 2011. This now showed stability in the damaged R eye inferotemporal sector and no further GCC thinning (Figure 9).

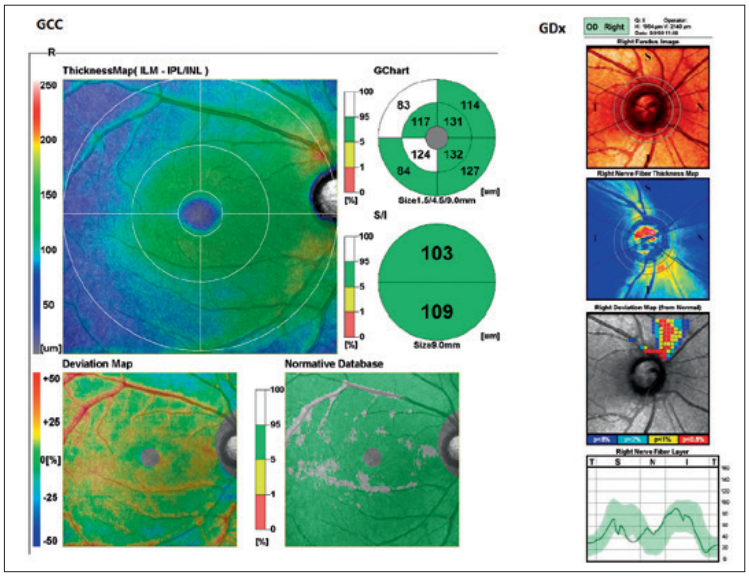
An inferotemporal loss of GCC would eventually be expected to result in a superior nasal visual field defect, that is, a superior nasal step. Further examination of the patient's initial visual field map did confirm a cluster



▲ Figure 9. GCC progression analysis after commencement of glaucoma treatment in the R eye. The damaged inferotemporal sector had stabilised due to the lower IOP and there was no further ganglion cell loss.



▲ Figure 10. A cluster of decreased sensitivity (-7 to -10 dB) in the R superior nasal step area of the visual field corresponding to the damaged R inferotemporal sector on GCC analysis



▲ Figure 11. A superonasal defect mapped by GDx scanning laser polarimetry remained undetected on the GCC scan. GCC analysis only scans the macular region temporal to the optic nerve head.

of mildly reduced sensitivity in the superior nasal step area of the R eye, albeit not to a level reaching statistical significance (Figure 10). In this instance, the GCC scan was able to detect glaucomatous damage prior to obvious changes in disc cupping and visual fields that may have been overlooked clinically; left untreated, further erosion of the inferior disc rim tissue and development of a deep superior nasal step visual field defect would have been the likely outcome.

Limitations of the GCC

All ophthalmic instruments have limitation and GCC is no exception. Commercially available SD OCTs that measure GCC can only scan and statistically analyse the macular region; therefore, no information is provided regarding damage to areas nasal to the disc. Figure 11 shows a patient with a superior nasal RNFL defect detected on GDx analysis but not seen on GCC because damage fell outside of the scanned area. Macular pathology that causes abnormal thickening of the inner retina such as macular oedema or retinal fibrosis will interfere with GCC measurements. This prevents accurate comparison with the normative database, as well as interfering with detection of change over time. Figure 12 shows an epiretinal membrane causing above-average thickening of the GCC.

At present there are about 10 different manufacturers of SD OCTs, and each instrument segments the retinal layers and measures the ganglion cells with differing accuracy and repeatability.[6] The GCC scan area varies from a 6 mm (six segment) circle centred on the fovea (Cirrus) to a much larger (in area) 9 mm square (eight segment) that reaches to the disc (Nidek). The definition of the GCC also varies between manufacturers: most consider the GCC to be made up of the IPL + GCL + NFL (for example, Optovue; Nidek) while Carl Zeiss Meditec uses only IPL + GCL and ignores the NFL, and Topcon gives three different maps with varying combinations of IPL/GCL/NFL.

Due to the newness of the technique and lack of standardisation between OCT units, it is difficult to compare GCC instruments to each other, or

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The ganglion cell complex and glaucoma

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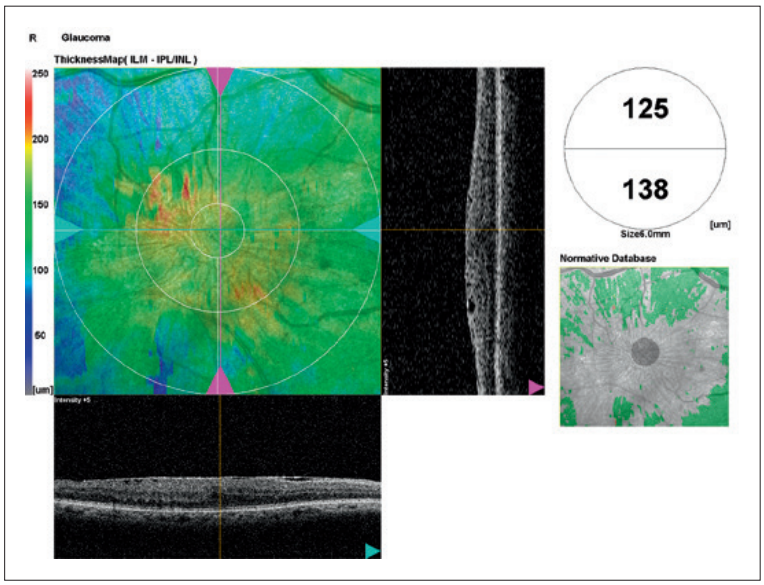
to existing glaucoma instruments in terms of sensitivity and specificity for glaucoma detection and diagnosis.[7] GCC scans are more repeatable and have less inter-scan variability than RNFL scans, but for the Cirrus OCT do not appear to detect glaucoma any earlier than RNFL scans.[8] Future research will help elucidate the particular combination of instrument/scan layer/scan area that is most sensitive and specific for glaucoma diagnosis.

Conclusion

There is no single test or instrument or clinical finding that can make a definitive diagnosis of glaucoma. GCC analysis is an exciting new technique that provides an extra piece of data in the glaucoma puzzle. It appears to detect ganglion cell death via loss of synapses and loss of cell bodies at an earlier stage than existing methods that only look at nerve fibre (axonal) loss. Progressive loss of GCC has been helpful in making the decision to treat ocular hypertensives and patients with preperimetric glaucoma prior to the development of frank visual field defects.



▲ Figure 12. An epiretinal membrane causing abnormal thickening of the GCC. This thickening will mask any glaucomatous ganglion cell loss.

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Mutant myocilin possible root cause of increased eye pressure

RESEARCHERS at the Georgia Institute of Technology in Atlanta, USA have identified molecules with the potential to block the accumulation of a toxic eye protein that can lead to early onset of glaucoma. In their study, the researchers implicated a mutant form of a protein called myocilin as a possible root cause of increased eye pressure. Mutant myocilin is toxic to the cells in the part of the eye that regulates pressure. These genetically-inherited mutants of myocilin clump together in the front of the eye, preventing fluid flow out of the eye, which then raises eye pressure—a cascade of events that can lead to early onset-glaucoma. The researchers are now focusing on mapping the structure of myocilin to learn more about what myocilin does.

ACS Chemical Biology, November 2013

Association of risk factors and glaucomatous damage

Both IOP and perfusion parameters appear to contribute independently—at least in part—to morphological and functional glaucomatous damage, according to a study published in the *Journal of Glaucoma*. Investigators analysed the association between the extent of glaucomatous damage and presumed risk factors for the disease in 50 patients with untreated primary open-angle glaucoma. The investigators found mean retinal nerve fibre layer thickness to be significantly associated (P<.05) with IOP, retinal arterial diameter, and choroidal blood flow. They observed that the visual field mean defect was associated with ocular perfusion pressure, laser Doppler flowmetry volume, and IOP variability.

J Glaucoma, August 2013

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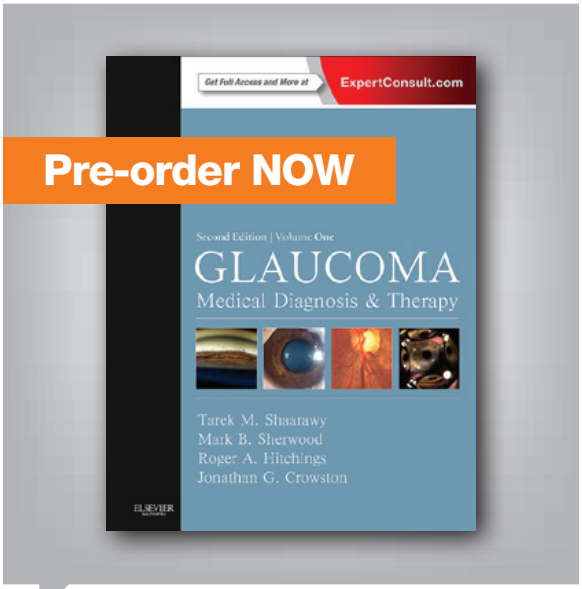

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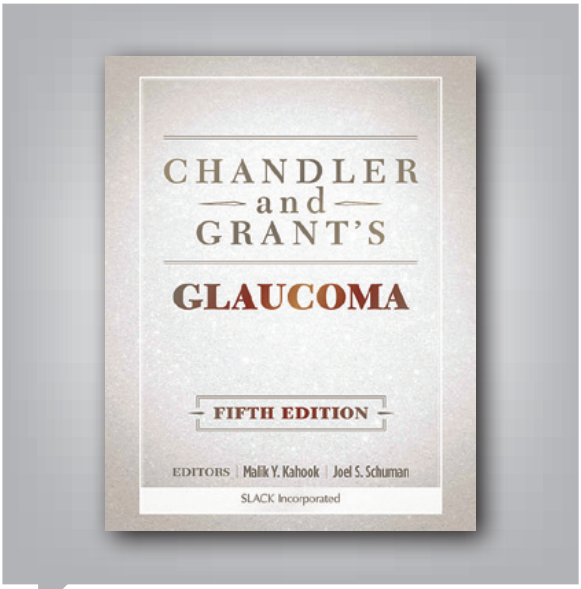

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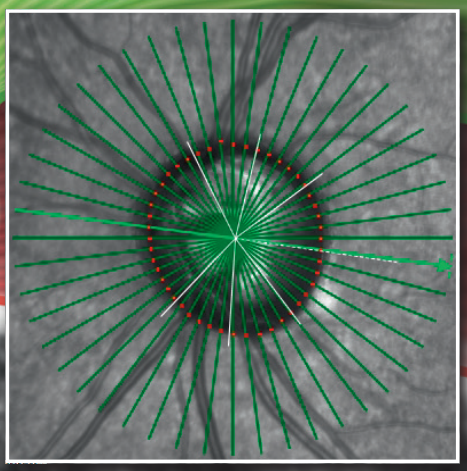

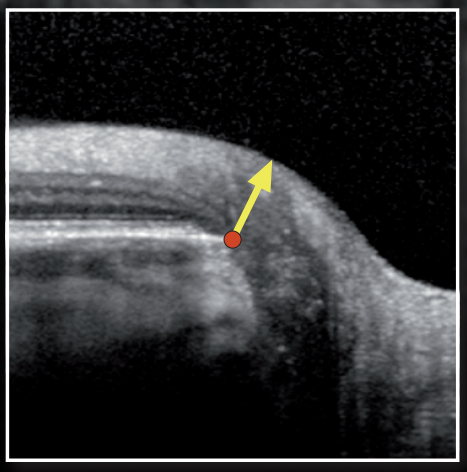

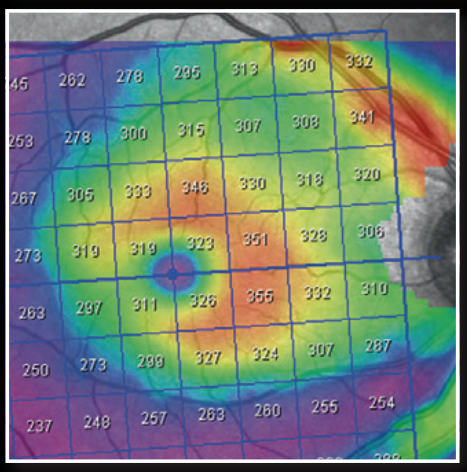

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