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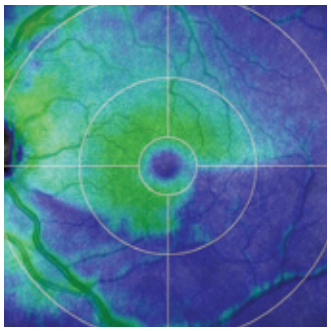

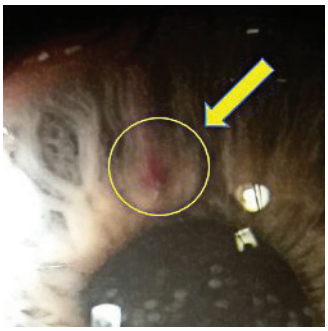

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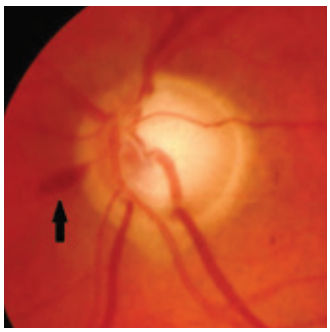

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BSc(Pharm) BAppSc(Optom)
PGCertOcTher NEWENCO FAAO

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(OCT) image, showing a macular map with visual field overlay.
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Optometry Australia
ABN 17 004 622 431

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

j.megahan@optometry.org.au
www.optometry.org.au

Glaucoma without cupping

Dr Adrian Bruce

BScOptom PhD FAAO FACO

Australian College of Optometry and The University of Melbourne

Lisa Lombardi

BOptom PGDipAdvClinOptom

Australian College of Optometry

Consider the optic disc size, not just the cup-to-disc ratio

OPTIC NERVE HEAD cupping and more specifically advancing cupping are widely accepted as one of the key signs of glaucoma. The condition is often known as glaucomatous optic neuropathy (GON), on the principle that the optic nerve is the fundamental site of the disease. With this approach in mind, clinicians may not consider glaucoma if there is a smaller degree of cupping, for example, a cup-disc ratio below 0.5.

Because structural loss usually precedes visual field loss,[1,2] in the absence of obvious cupping the possibility of glaucoma may be discounted. There are many factors to consider when assessing for glaucoma, but to disregard the need for further investigations based on a 'small' cup-to-disc ratio could result in misdiagnosis.

In a retrospective analysis, Sherman and colleagues presented several cases of glaucoma in the absence of significant cupping.[3] They demonstrated how new technologies at the time such as the Heidelberg Retinal Tomograph and GDx were being used in the diagnosis of these cases of glaucoma without cupping.

In this report, we present a case of glaucoma without cupping, this time using optical coherence tomography (OCT) to assist with diagnosis.

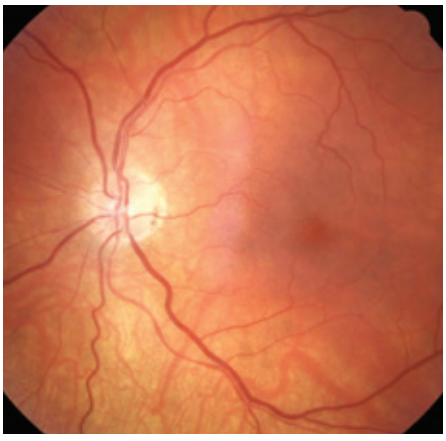
CASE REPORT

A 63-year-old Caucasian male attended the general clinic of the Australian College of Optometry for an annual glaucoma review. He had a family ocular history of glaucoma; his father and aunt had been diagnosed and treated for the disease.

The patient enjoyed excellent unaided vision, with R 6/6, L 6/6. Gonioscopy showed angles to be open to scleral spur in both eyes. There was no pseudoexfoliation syndrome or pigment dispersion syndrome. Cup-to-disc ratios were R 0.25, L 0.3 and the disc diameter was small, estimated at about 1.4 mm, although the neuro-retinal rims were seen as full.

The intraocular pressure (IOP) was R 20 mmHg L 20 mmHg and central corneal thickness (CCT) measured R 534 µm and L 539 µm. In previous years, his IOP had been in the range of 19-22 mmHg. The borderline IOP and the family history had led to the ongoing review (Figure 1).

An OCT examination was performed to assess both the retinal nerve fibre layer (RNFL) at the optic discs and the inner retinal layers (ganglion cell and so on)



▲ Figure 1. Ocular fundus photograph

at the maculae. The Nidek OCT Macula Map showed normal findings in the right eye and a distinct inferior arcuate defect on the normative database map in the left eye (Figure 2). The left eye analysis of the macular inner retinal layers (GChart) highlighted the superior-inferior hemifield asymmetry.

The Nidek OCT Disc Map of the RNFL was normal in the right eye, but for the left eye flagged thinning of the inferior-temporal quadrant (Figure 3).

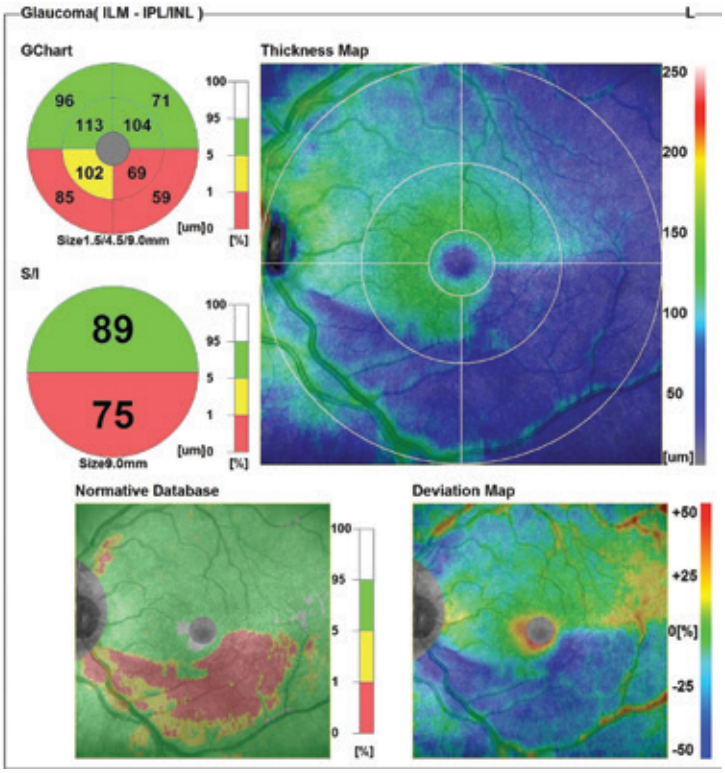
Visual field assessment using the Medmont Central Fast Threshold Test showed a left, superior nasal defect in the perimacular area (Figure 4). This defect was repeatable, with reliable indices. The field defect corresponded with the Nidek OCT macula scan findings of an inferior perimacular defect in the ganglion cell layer as well as the disc map defect in the inferior-temporal RNFL quadrants.

As a result of these findings, the patient was referred to an ophthalmologist who confirmed the diagnosis and commenced treatment for primary open angle glaucoma.

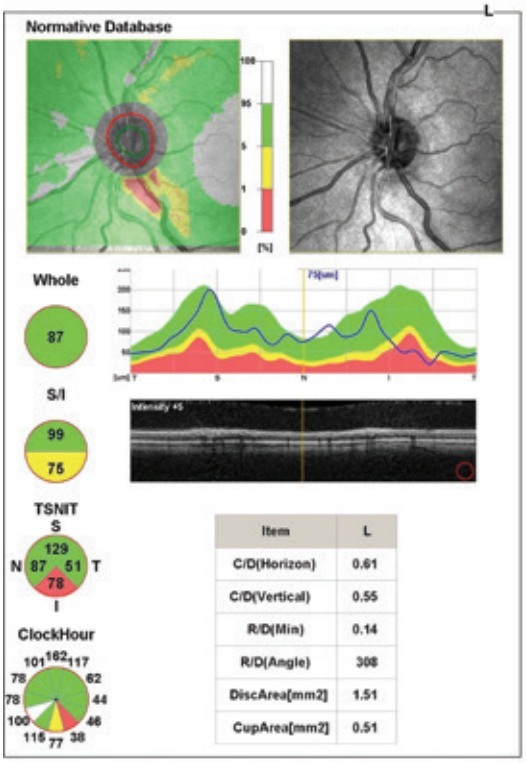
Optic disc size

NHMRC guidelines give the average vertical disc diameter as 1.6 to 2.0 mm.[4] The disc size can be measured clinically using a fundus lens, with low powered lenses (like a Volk 60 D) being the most accurate.[5] Alternatively, most OCT RNFL analyses give an estimate of the disc area. The OCT scan in this case gave the disc areas as R 1.30 mm^2 and L 1.21 mm^2.

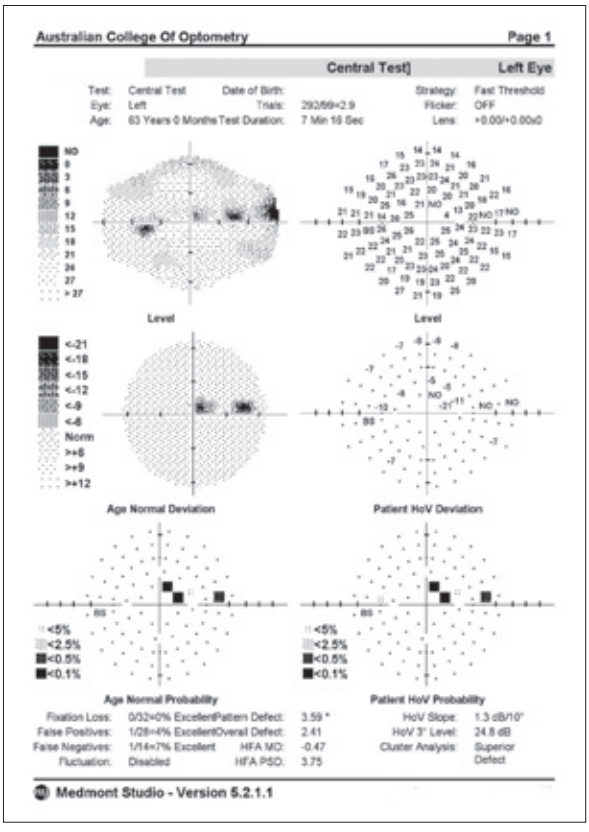
Optic disc area may be compared to the disc diameter most accurately via an ellipse formula, although a circle formula is a simple approximation (area = πr^2, where r = radius). When calculated using the NHMRC's guidelines for disc diameter,[4] the average optic disc is predicted to be 2.0 mm^2 to 3.1 mm^2. This patient's optic disc areas were significantly less.



▲ Figure 2. Nidek OCT Macula Map: left eye showing inferior hemifield defect with an arcuate defect of the macula ganglion cell layer



▲ Figure 3. Nidek OCT disc map flagging the left inferior and temporal RNFL quadrants



▲ Figure 4. Medmont Central Test left visual field, with corresponding superior nasal perimacular defect

This case demonstrates the importance of considering the optic disc size in conjunction with the cup-disc ratio. Clinically, it is tempting to link smaller cupping with a low risk for glaucoma. Just as the corneal thickness provides context for interpretation of the IOP measurement, the optic disc size does the same for the cup-disc ratio. The consequence of not allowing for disc size could be a delay in diagnosis, until more significant optic nerve damage or functional loss has occurred. ▲

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Drance haemorrhages common in glaucoma—and other conditions

Dr Leonid Skorin Jr

OD DO MS FAAO FAOCO

Mayo Clinic Health System, Minnesota USA

Kathryn Dailey

BS

Pacific University College of Optometry, Oregon USA

DRANCE HAEMORRHAGES are linear haemorrhages oriented perpendicular to the optic disc margin and within the retinal nerve fibre layer. Also commonly known as disc haemorrhages, Drance haemorrhages have become synonymous with glaucoma due to their high prevalence in this population and their association with glaucomatous progression. Despite this, they are not unique to glaucoma.

History

Disc haemorrhages became common knowledge in the ophthalmic community due to extensive studies and reports by ophthalmologist Stephen Drance. In his key lecture at the World Glaucoma Congress in 2013,[1] Dr Drance reported that disc haemorrhages were first described in the Danish literature in 1889 but were largely ignored until his investigations beginning in the mid-1960s. Drance's first paper on disc haemorrhages was rejected by an editor who wanted biopsy specimens to determine their origin. Another journal published the paper and Drance has since produced more than 300 contributions to the glaucoma literature.

Aetiology, prevalence and detection

The exact pathophysiology of Drance haemorrhages remains unknown despite extensive research. Two main hypotheses for their origins exist: mechanical and vascular.[2,3] The mechanical hypothesis states that structural changes to the optic nerve put stress on the surrounding blood vessels and eventually cause bleeding. The vascular theory states that poor structural integrity of the blood vessels results in blood leakage and subsequent damage to the optic nerve fibres. Because these haemorrhages are seen in glaucomatous and non-glaucomatous eyes, multiple factors may contribute to their development.

Factors observed to have a possible association with Drance haemorrhage incidence include increased age, diabetes, large vertical cup-to-disc ratio, smoking, female sex, increased intraocular pressure, increased systolic blood pressure, pseudoexfoliation and aspirin use.[2,4]

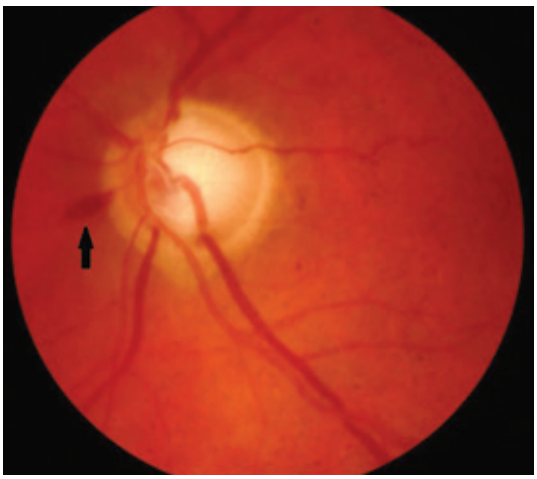
The reported prevalence of Drance haemorrhages varies in the general population from 0.6 per cent to 1.4 per cent.[4] Based on many studies, it is clear that the prevalence is greater in patients with ocular hypertension (OH) and all types of glaucoma.[3] Some research supports the greatest prevalence of Drance haemorrhage in normal-tension glaucoma (NTG), with one study reporting an incidence of haemorrhages in up to 25 per cent of patients.[4]

Variability in the reported prevalence of Drance haemorrhages may be secondary to difficulty in detecting them. No current imaging technology has the capability of detecting disc haemorrhages and they are easily missed on fundus examination.[5] The most consistent method of detecting these haemorrhages is with fundus photography.

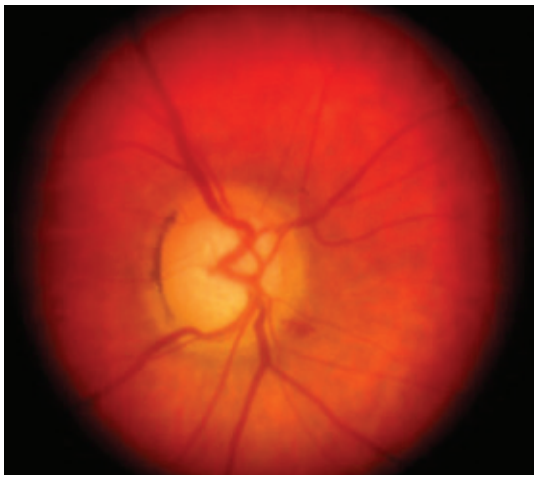
The Ocular Hypertension Treatment Study (OHTS) reported that four times as many Drance haemorrhages were discovered with photography than on standard disc evaluations.[6] It is suggested that to increase detection sensitivity, the practitioner should assess the temporal aspect of the disc closely, especially the inferior temporal sector where two-thirds of these haemorrhages occur.

Drance haemorrhages and glaucoma

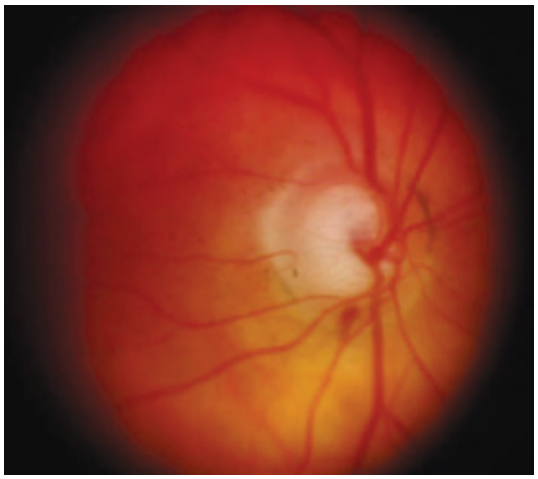
Detection of Drance haemorrhages is paramount for effective glaucoma management as they can be a harbinger of glaucomatous progression. Numerous studies have shown that in patients with glaucoma and Drance



▲ Figure 1. Drance haemorrhage on the inferior nasal aspect of an optic nerve with enlarged vertical cupping from glaucoma



▲ Figure 2. Inferior nasal Drance haemorrhage demonstrating the subtle presentation that often results in poor detection on fundus examination



▲ Figure 3. Drance haemorrhage on the inferior margin of an optic nerve in a patient with NTG

haemorrhages, there is an increased risk of optic nerve cupping, atrophy of the nerve fibre layer and visual field loss progression.[4,7,8]

The link between disc haemorrhages and glaucoma progression has been documented to be strongest for NTG. Some studies, such as the one completed by Rasker and colleagues, also report an association between Drance haemorrhages and visual field progression in OH and primary open angle glaucoma (POAG).[7,8] In addition, the OHTS study reported that the presence of disc haemorrhages significantly increased the risk of progression to POAG from OH over an eight-year period.[6]

Recurrent disc haemorrhages are reported in 60 to 70 per cent of patients. The haemorrhage reoccurs in the same optic disc quadrant as the original haemorrhage 75 per cent of the time. The Collaborative Normal Tension Glaucoma Study and others have reported greater progression in patients with higher frequency of Drance haemorrhages.[3]

It is well-documented that the observed location of a Drance haemorrhage often corresponds with areas of optic nerve notching and visual field progression. There is some dispute about whether the changes in the nerve fibres occur prior to or following the appearance of the haemorrhage.[5] What is clear is that in glaucoma suspects or patients diagnosed with glaucoma, the presence of a Drance haemorrhage indicates disease progression and the need to initiate or increase medical therapy.

Other associations

Despite the strong association of Drance haemorrhages with glaucoma, it is important to consider that a reported 70 per cent of these haemorrhages occur in non-glaucomatous eyes.[4] Posterior vitreous detachments, small vascular insults from systemic diabetes mellitus or hypertension, optic disc drusen, ischaemic optic neuropathy, leukaemia, and branch or central retinal vein occlusions can all result in disc haemorrhages.[2,3,5] Presence of a disc haemorrhage in a patient previously undiagnosed with glaucoma requires careful disc evaluation for signs of glaucoma and consideration of alternative causes to prevent unnecessary glaucoma treatment.

Conclusion

Extensive research is still required to determine how Drance haemorrhages occur, why they are more common in some types of glaucoma and how they are linked to progression. Taking regular fundus photographs of glaucoma patients can help detect Drance haemorrhages and direct treatment.

In glaucoma suspects or those being treated for any type of glaucoma, presence of a Drance haemorrhage should initiate a change in medical therapy. In addition, patients with recurrent Drance haemorrhages should be treated even more aggressively and followed closely for glaucomatous changes. When medical treatments are no longer effective, surgical intervention may be required. In patients not diagnosed with glaucoma, assess for glaucoma risk factors and other ocular causes. Consider that Drance haemorrhage presence in this population may be secondary to vascular disease. ▲

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One 'other' pressure in glaucoma: intracranial pressure

Dr Da Zhao
BMed China MVisSci

Dr Christine Tram Oanh Nguyen
BScOptom PhD

Dr Zheng He
BMed China PhD

Professor Algis J Vingrys
BScOptom PGCertOcTher PhD FARVO FAAO

Associate Professor Bang Bui
BScOptom MOptom PGCertOcTher PhD

Department of Optometry and Vision Sciences, The University of Melbourne

IT IS WIDELY ACCEPTED that glaucoma is associated with elevated intraocular pressure (IOP) elevation. There are some patients who develop glaucoma without IOP elevation (normal tension glaucoma [NTG]) and in some patients, vision loss keeps progressing despite successful IOP reduction. Recent studies suggest that many non-IOP factors can also have important roles in glaucoma, such as diet,[1] diabetes,[2] blood pressure[3] and intracranial pressure.[4,5]

The optic nerve head is thought to be the site of injury to the optic nerve axons. It is biomechanically the most susceptible part of the eye to stress because it is the thinnest part of a pressurised chamber; therefore, it is prone to displacement when subjected to changes in the pressure gradient across the lamina cribrosa.

Two key forces exert their effects at the optic nerve head: intraocular pressure from inside the eye and intracranial pressure (ICP) from the retro-laminar subarachnoid space.[6] Elevated IOP has been well-established to cause backward bowing of the lamina cribrosa, which is consistent with the increased cupping seeing in glaucoma.[7] Conversely an increase in retro-laminar pressure will cause the nerve to move forward.

For example, intracranial hypertension can manifest in the eye as papilloedema, which is associated with a forward displacement of the optic nerve tissue. This is because cerebrospinal fluid fills the subarachnoid space that surrounds the optic nerve all the way up to the sclera (Figure 1A). As such, the balance between IOP and ICP can affect the ganglion cells that exit the eye at the optic nerve head.

The balance between IOP and ICP creates a pressure gradient across the lamina cribrosa known as trans-laminar pressure (TLP = IOP - ICP). It stands to reason that a higher ICP should help to counteract the detrimental effects of IOP elevation on the optic nerve.

A recent study by our group shows that this is the case.[5] In a rodent model, we demonstrate that progressive deformation of the optic nerve head and peripapillary retinal surface can be induced by increasing IOP. The effect of IOP elevation was made worse in animals that had low ICP and conversely, raising ICP prevented much of the detrimental effects of IOP elevation. This is in agreement with studies conducted in canine eyes, where significant posterior movement of the optic disc surface has been found with IOP elevation and anterior displacement with ICP increase.[8]

These structural changes to the optic nerve affect retinal function. Using the electroretinogram we show that loss of the ganglion cell response to light caused by IOP elevation could be modified by the ICP level (Figure 1). A higher ICP was protective against IOP elevation, whereas the converse was true for lower ICP levels.

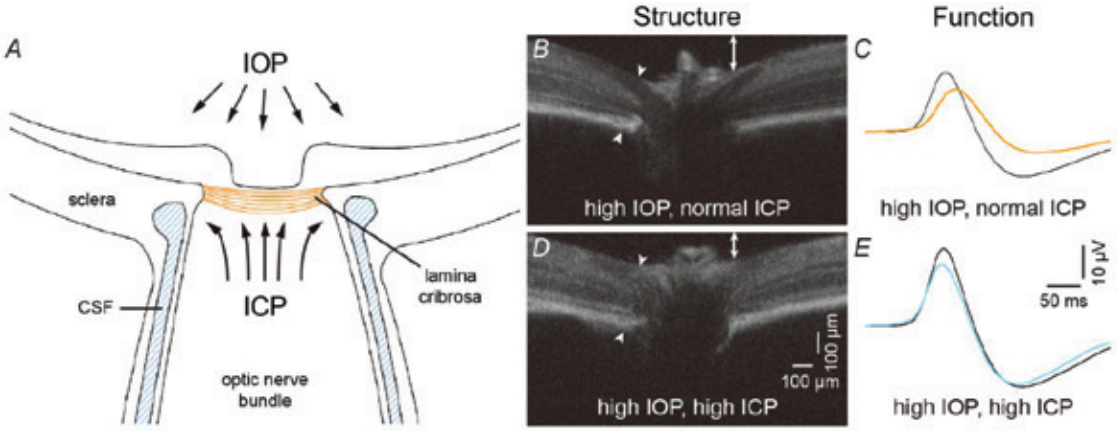
Interestingly, our study shows that small changes to intracranial pressure can produce more substantial effects on the optic nerve structure and function than do equivalent changes in intraocular pressure. For example, the total complete loss of retinal ganglion cell function caused by IOP elevation of 80 mmHg (from 10 to 90 mmHg) could be entirely ameliorated by elevating ICP by 25 mmHg (from 5 to 30 mmHg, normal ICP ~ 5 mmHg). While the findings of our study need to be interpreted with caution, they highlight the potential that small changes in ICP might significantly influence glaucoma risk.

There are both laboratory and clinical studies that support a potential role for ICP in glaucoma. Yang and colleagues[4] placed lumbar-peritoneal shunts into non-human primates to chronically drain a small amount of CSF and lower ICP. After 12 months, the authors reported reductions in retinal nerve fibre layer thickness, neuroretinal rim area and volume, as well as increased cup/disc ratio.

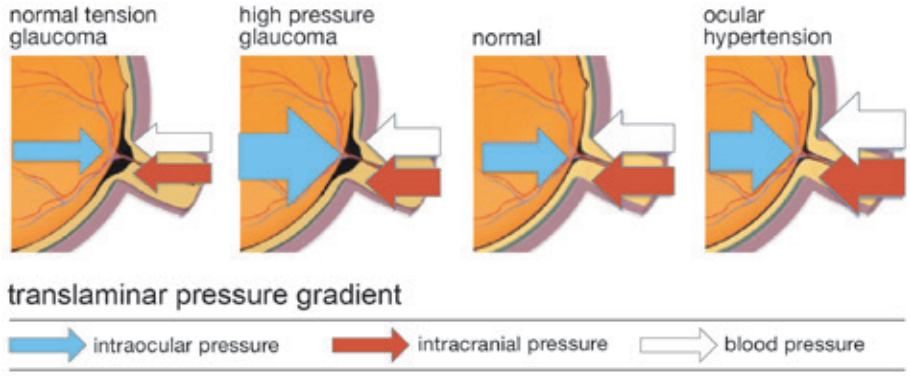
These results suggest that even with normal IOP, one can get ganglion cell loss, as low ICP produces a higher trans-laminar pressure gradient. These findings raise the possibility that injury in both normal tension glaucoma and primary open angle glaucoma arises from a higher trans-laminar pressure. Similarly, the absence of injury with apparent ocular hypertension is due to a lower trans-laminar pressure. These concepts are shown in Figure 2.

Consistent with this above contention, several studies report that ICP is lower in those with NTG and POAG compared to age-matched controls.[9,10,11] These authors found that the lower ICP was, the more severe the visual field loss tended to be. Also consistent with a critical role for trans-laminar pressure is the finding that those with ocular hypertension (without visual field loss) tended to have higher ICP.[12]

Interestingly, it has been found that ICP decreases by about 3 mmHg between the fourth and ninth decades of life.[13] A 3 mmHg higher trans-laminar pressure gradient may be enough to increase the risk of glaucoma.



▲ Figure 1. Intracranial pressure can counteract the effect of IOP on optic nerve structure and function. A. Intraocular and intracranial pressure are forces that oppose each other across the lamina cribrosa. Using optical coherence tomography, we show that there was more backward bowing of the optic nerve surface (arrow lines) and retinal compression (arrowheads) with IOP elevation when ICP was normal (B. ICP 5 mmHg) compared with a high ICP (D. 30 mmHg). Using the electroretinogram we show that high ICP prevents ganglion cell dysfunction caused by elevated IOP. Black traces indicate baseline waveforms and coloured traces indicate waveforms when IOP was 70 mmHg. The response is more affected when ICP was normal (C, orange trace) and less affected when ICP was high (E. blue trace). Adapted from Zhao and colleagues[5]



▲ Figure 2. Pressures that can influence the health of the optic nerve include IOP, which is opposed by both intracranial pressure and blood pressure. Growing evidence suggests that combinations of these pressures and the subsequent translaminar pressure gradient may help in our understanding of glaucoma.

While it is not clear how the findings of studies such as ours will impact clinical practice, it is critical that we first attempt to fully understand the risk factors for glaucoma. If simple non-invasive approaches for ICP measurement become available, perhaps we will have a much clearer picture of an individual's risk for glaucoma development and progression.

In this regard, it is worth noting that formulae are available that allow us to estimate ICP, based on age, blood pressure and body mass index.[14] Further studies are needed to allow us to fully understand how to implement these ideas in clinical practice. ▲

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Pressure-cooked chicken and red hot chilli eggs

Dr Ehud Zamir

MD FRANZCO

McKinnon Eye Clinic
McKinnon VIC

FOR THE PURPOSE of this review we will assume that eggs come from chickens and that chickens come from the supermarket.

CASE REPORT 1

Let us start with a story

A middle-aged man with a lifelong hypermetropia of about +5.0 walks into his usual optometrist's practice complaining of acute discomfort and visual symptoms in one eye. The eye is red and inflamed, and the pressure is over 50. There are cells floating in the anterior chamber.

A diagnosis of hypertensive uveitis (or uveitic glaucoma) is made and the patient is treated with topical steroids and atropine. While the redness and discomfort improve, the pressure two weeks later is still above 50, when he is noted to have shallow anterior chambers and full-on angle closure glaucoma in his symptomatic eye. The other eye has slit angles with imminent angle closure.

Both eyes then undergo laser iridotomies and are just fine the next morning. The patient goes on to have bilateral lens extraction and intraocular lenses for resolution of his angle closure glaucoma. In hindsight, his first presentation was merely acute, primary, pupillary block glaucoma, diagnosed as uveitis due to the presence of anterior chamber cells, which is one of the common features of acute angle closure glaucoma.

This case demonstrates that the combination of uveitis and high pressure can be tricky. We expect the pressure to drop in acute anterior uveitis, due to dysfunction of the ciliary body and increased uveoscleral outflow. However, when the pressure is high in this context, there could be many different reasons for it, all requiring different diagnostic and therapeutic steps. The clinician has to stop, think and decide:

1. Which is the 'chicken' and which is the 'egg' (uveitis vs high pressure)?
2. If indeed uveitis is the chicken, why is it causing high pressure?
3. If indeed uveitis is the chicken, is it really uveitis, or is it another problem that looks like uveitis? For example: acute glaucoma, pigment dispersion syndrome, lymphoma or haemorrhage.

Diagnostic algorithm

It is conceptually easier to approach this diagnostic junction/tangle from the glaucoma side. This is because one can reliably walk down a concise algorithm in diagnosing acutely elevated intraocular pressure and reach a diagnosis. It is a mechanistic process with a more definite and simpler route to the diagnosis than the elusive and complex uveitis.

Understanding the mechanism of increased pressure can help us diagnose the uveitis correctly, too. Therefore, I will outline the main junctions in this algorithm here, and provide some detail on each of them, using questions that we should ask ourselves when approaching this problem.

The pressure is high and there are signs of uveitis

Is the angle open or closed?

This question, if it had been asked, would have averted the misdiagnosis described above. It is difficult to miss angle closure if you think about it. It is much easier to miss if you don't.

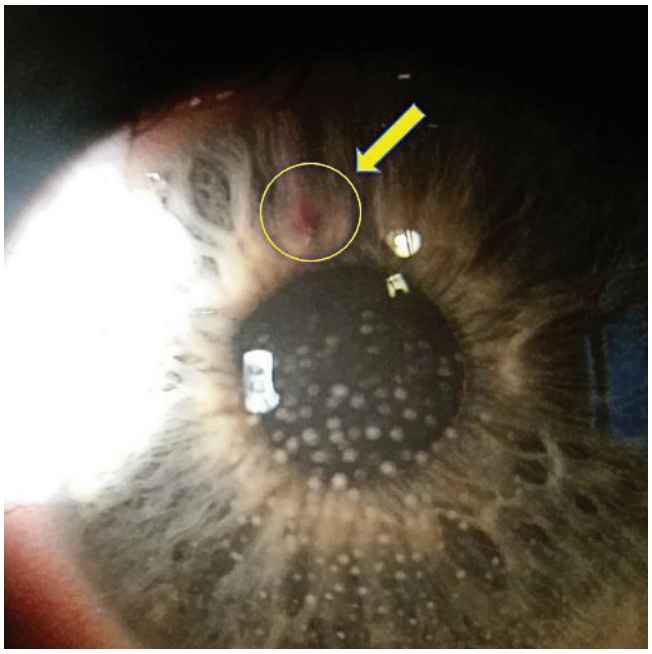
Open angle (more common)

This scenario is more common than hypertensive uveitis with a closed angle. Possibilities include:

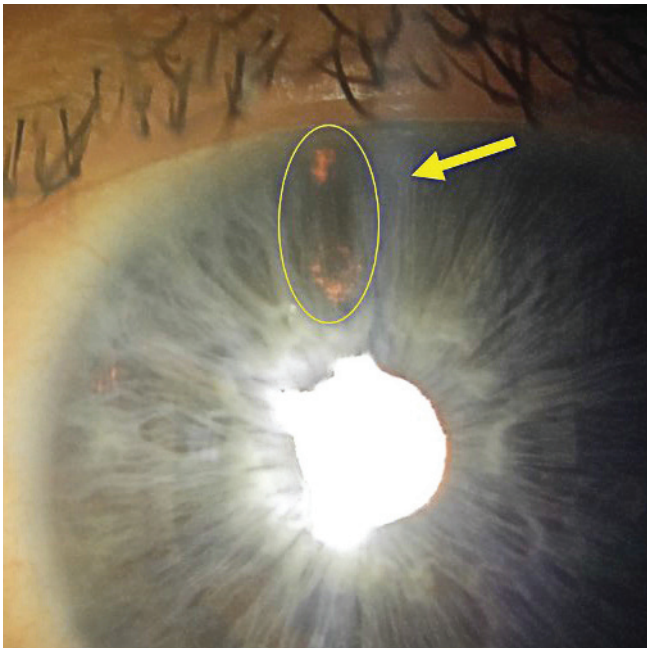
1. Trabeculitis (inflammation of the trabecular meshwork) usually seen in:
a. Viral anterior uveitis (most often HSV/VZV/CMV)
b. Posner Schlossman syndrome
c. Infectious posterior uveitis (toxoplasmosis, herpetic retinitis, endophthalmitis)
d. Autoimmune disease (sacroidosis)

Trabeculitis usually improves quickly with intensive topical steroid therapy. This is a helpful diagnostic feature, as patients whose intraocular pressure drops dramatically overnight with topical steroids alone (without anti-glaucoma therapy) probably have trabeculitis.

2. Steroid response, in patients who have already had previous attacks and are chronically treated with topical steroids.
3. Fuchs' uveitis, mistakenly diagnosed as acute because of new symptoms.
4. Hyphaema mistaken for uveitis. This can happen especially with spontaneous, non-traumatic hyphaemas.
5. Brimonidine-induced uveitis[1] tends to paradoxically worsen the glaucoma control, and present with small keratic precipitates and (only sometimes) a red eye, days to years after commencing treatment with brimonidine.
6. Phacolytic glaucoma should be considered if there is a dense, hypermature cataract with a hypopyon and high pressure (beware of endophthalmitis).
7. Pigment dispersion syndrome/ glaucoma may be mistaken for uveitis, due to the presence of pigmented cells in the aqueous.
8. Intraocular lymphoma, which in this setting presents with multiple keratic precipitates and debris blocking the trabecular meshwork, usually with vitritis and/or signs of



▲ Figure 1. Hypertensive acute anterior uveitis with mutton fat keratic precipitates. Note the area of iris hyperaemia (arrow) indicating herpetic iritis. Empirical treatment was commenced with oral antivirals and topical steroids.



▲ Figure 2. Same eye, two months later. Note resolution of uveitis, and appearance of typical iris atrophy and transillumination in the same area, confirming the original suspicion. Slitlamp photographs taken with a mobile phone camera.

lymphoma in the retina and choroid.
9. Anterior uveal melanoma infiltrating the angle

Closed angle (less common)

Once we established that the angle is closed, we need to find out the mechanism of angle closure. Possibilities include:

1. Pupil block
a. Posterior synechiae, causing iris bombe
b. Fibrin 'plug' blocking the pupil
c. Primary angle closure glaucoma with a mid-dilated, non-reactive pupil and bilaterally narrow angles, as the case above demonstrated, where the 'egg' was confused with a 'chicken'.

2. Forward pushing of the iris from behind:
a. Choroidal effusions, as may happen in some types of choroiditis or posterior scleritis
b. Uveal tumours such as malignant melanoma
c. Malignancy of the iris causing diffuse iris thickening, most commonly lymphoma.
3. Forward pulling of the iris from the front:
a. Anterior synechiae in chronic uveitis
b. Rubeosis of the iris from any cause.

CASE REPORT 2

Now that we have a list of possibilities, divided into mechanistic headings, let us look at another patient story.

A middle-aged man was seen by his optometrist for a painful loss of vision in one eye. The optometrist noted signs of severe anterior uveitis, deep anterior chamber and a high intraocular pressure of 40. A diagnosis of Posner Schlossman syndrome was made and the patient received a combination of topical dexamethasone, brimonidine and timolol, with partial reduction in the pressure and improvement of the uveitis.

The patient then complained of worsening vision three weeks later. Examination included pupil dilation this time, revealing a large toxoplasma retinitis lesion with a secondary macula off retinal detachment.

This case demonstrates an important principle: anterior uveitis is a diagnosis of exclusion; it can be called that only if we know for a fact the patient does not have posterior uveitis. If the fundus is not visualised (no attempt made/ hazy view), one cannot be sure that the source of this 'anterior' uveitis is not posterior infectious uveitis requiring urgent and specific treatment.

This treatment may need to be antiparasitic or antiviral therapy, either systemically or intraocularly, and in the case of endophthalmitis, vitrectomy, intraocular antibiotic treatment and systemic treatment of sepsis.

One of the most common scenarios is unilateral, hypertensive, truly anterior uveitis with mutton fat keratic precipitates. In this scenario, the most common culprit is a herpetic infection. One has to think about this possibility and look for supportive evidence.

1. Is there a vesicular (blistery) rash on the patient's upper lid, forehead, brow, or scalp to indicate zoster?

Continued page 10

Pressure-cooked chicken and red hot chilli eggs

From page 9

2. Is there evidence of past or present herpetic keratitis?
3. Is there focal iris hyperaemia or swelling?
4. Is there iris atrophy and transillumination in a typical herpetic pattern?

If one or more of these features is present, I usually treat the patient with a combination of topical steroids and topical or even oral anti-herpetic therapy, in an attempt to reduce the risk of long-term complications of iris atrophy, atonic pupil et cetera. If I think it may be herpetic but cannot be sure, I sometimes perform a tap of the anterior chamber and send the aqueous for viral DNA testing.

Summary

Hypertensive uveitis is a tricky and potentially dangerous presentation. High intraocular pressure makes the aetiology of uveitis more likely to be infectious or even cancerous. The following key questions must be considered in such patients.

1. Which is the chicken (the cause) and which is the egg (the result): glaucoma vs uveitis.
2. Is the angle open or closed?
3. Could this be an intraocular infection?
4. Could this be something else, not uveitis (cancer, phacolysis or a bleed)?

Remember that the differential diagnosis is very wide and includes a few serious pitfalls of conditions that can blind or kill the patient if not diagnosed correctly and treated appropriately. ▲

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Detect glaucomatous

Dr Rim Makhlouf

OD FAAO

Nova Southeastern University College of Optometry, Florida USA

THE IRREVERSIBLE nature of glaucoma makes prompt detection of progression crucial in order to preserve vision and prevent blindness.

Traditional ways of detecting glaucomatous progression include longitudinal stereoscopic analysis of the optic nerve, either ophthalmoscopically or by photography, as well as serial automated threshold perimetry.

The former method requires a trained eye to detect subtle morphologic changes in addition to the presence of observer-related subjectivity; the latter method can be difficult to use because patients are often poor visual-field-takers.

With poor visual-field takers, it may be especially challenging to distinguish between true glaucomatous changes and fluctuations that are due to inter-visit measurement variability or poor performance.

It is well established that evidence of structural changes may occur before any evidence of functional change is detected with automated perimetry.[1,2] Therefore, assessment of structural parameters is crucial in determining glaucoma progression.

Optical coherence tomography (OCT) is an imaging technology that allows an *in vivo* cross-sectional view of the retina and optic nerve. It has emerged as a powerful tool in diagnosing and monitoring progression in glaucoma by measuring the thickness of the retinal nerve fibre layer (RNFL).

Time domain OCT

Two main generations of OCT are commercially available. Time domain OCT (TD-OCT) is the original version and measures progression based on event analysis. This type of analysis identifies progression when the amount of change in RNFL thickness from baseline exceeds a pre-established threshold considered to be indicative of true progression. Any amount of change below this threshold is assumed to be due to natural age-related loss and/or measurement variability.[3] The disadvantages of this technique are the reduction of sensitivity if the threshold is set too low, or conversely, the reduction of specificity if the threshold is set too high.

Spectral domain OCT

Fortunately, technological advances have led to a new generation of OCT, spectral domain OCT (SD-OCT), which offers higher scanning rates and improved resolution, potentially decreasing the variability in RNFL thickness measurements.[3] This allows the use of a trend-based approach for detecting progression by monitoring the behaviour of RNFL thickness over time, thus providing a rate of progression. This method is less sensitive to measurement variability because it is filtered out by the overall rate of change.[3]

It is important to note that there is often a poor agreement between functional and structural tests in the evaluation of glaucoma progression.[4] Studies have shown that functional and structural tests may have different levels of sensitivity in detecting progression, depending on the stage of the disease.

In fact, in early glaucoma, progression by RNFL thickness is more noticeable than progression by visual field, whereas in advanced glaucoma, progression by visual field when expressed on a decibel scale is more noticeable than progression by RNFL thickness.[4,5,6,7] Therefore, it may be less beneficial to use the OCT to detect progression in advanced glaucoma.

progression using OCT

Another reason is the 'floor' effect by which it becomes hard for the OCT to detect significant change and distinguish between true glaucomatous changes and measurement noise when the RNFL has become too thin.[8]

Ganglion cell complex

Another recent development is the use of SD-OCT to measure ganglion cell complex (GCC) thickness in order to detect glaucoma progression. As mentioned earlier, glaucoma involves loss of retinal ganglion cells. A retinal ganglion cell, like any other neuron, has a cell body, an axon and dendrites. The ganglion layer, RNFL and inner plexiform layer, respectively, represent the cell bodies, axons and dendrites of the retinal ganglion cells. Therefore, the GCC is the combination of all three of these layers.

The GCC thickness is measured at the level of the macula because retinal ganglion cell density is high in that area. As glaucoma progresses and ganglion cells continue to die, the GCC thickness decreases; therefore, progression is identified based on a trend analysis of GCC thickness over time. A recent study published by Bresciani-Battilana and colleagues found a strong correlation between GCC and RNFL parameters, suggesting that GCC is an additional structural parameter that can be used in the management of glaucoma.[9]

Because GCC is measured at the macula, it is important to rule out the presence of concurrent macular conditions that may affect results when taking GCC into consideration for glaucoma management.

Detecting progression remains one of the biggest challenges in glaucoma management even with the advent of recent technologies. OCT is a powerful tool in detecting structural changes but should not be used alone. It is important to look at both structure and function, due to the limited agreement between the two in regards to detection of progression. ▲

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9. Bresciani-Battilana E et al. Correlation between the ganglion cell complex and structural measures of the optic disc and retinal nerve fiber layer in glaucoma. *Int Ophthalmol* 2014; 35: 5: 645-650.

RNFL assessments aid early disease detection

CHANGES IN OCT measurements of the retinal nerve fibre layer are detectable many years before visual field defects are detected on standard automated perimetry.

This is the finding of a study that observed 75 eyes of 75 patients suspected of having glaucoma. The patients had normal standard automated perimetry (SAP) at baseline and demonstrated repeatable (three consecutive) abnormal tests during a median follow-up of 6.3 years. A control group of 75 eyes of 75 healthy subjects matched by age and number of OCT tests during follow-up was included.

The retinal nerve fibre layer (RNFL) thickness measurements were obtained at the time of development of the earliest SAP defect (time 0) and also at times –1, –2, –3 and so forth, corresponding to one year, two years, three years and so on, before the development of field loss.

The OCT measurements at corresponding intervals were analysed for controls. Time-dependent receiver operating characteristic (ROC) curves were used to evaluate diagnostic accuracy of OCT.

At 95 per cent specificity, up to 35 per cent of eyes had abnormal average RNFL thickness four years before development of visual field loss and 19 per cent of eyes had abnormal results eight years before field loss.

The authors concluded that assessment of RNFL thickness with OCT enabled the detection of glaucomatous damage before the appearance of visual field defects on SAP. 'In many subjects, significantly large lead times were seen when applying OCT as an ancillary diagnostic tool,' they wrote.

Ophthalmology 2015; 122: 10: 2002-2009

Progressing glaucoma despite optimal medical therapy

Dr Jose Estevez

BMedSci (VisionSci) MOptom

South Australian Health & Medical Research Institute, Adelaide SA

CASE REPORT

OPEN ANGLE glaucoma is classified as 'primary' if the cause of elevated IOP is unknown and the anterior chamber angles (ACA) are open. The diagnosis of primary open angle glaucoma (POAG) revolves around structural (optic nerve head) and functional (visual field) parameters. These two tests are the most important for detection, follow-up and management over time. Having the ability to detect subtle changes or signs of progression of the disease is key to confirming the diagnosis.

It is clear from many studies that IOP is a major risk factor for POAG.[1,2] The cut-off for 'normal' IOP is 21 mmHg; this arbitrary number originated from a study that showed it represented the 95 per cent confidence limit for normal people. However, this assumes the distribution of IOP in populations is normal but in fact, it is skewed to the right.[3] This right skew increases with age and varies with race. Therefore, there is a proportion of people with IOP exceeding 21 mmHg who do not have glaucoma and many will be diagnosed with ocular hypertension (OH).

The Ocular Hypertension Treatment Study (OHTS) indicated that the risk of POAG conversion for an OH patient was 9.5 per cent over five years, with the risk increasing if IOP is greater than 24 mmHg.[4] Other significant risk factors identified in landmark studies include genetic predisposition (such as first-degree relative with POAG or mutated myocilin gene), race, disc haemorrhages and thinner central corneal thickness (CCT).[4-6] Myopia, diabetes, systemic hypertension and vascular insufficiencies have also been suggested as relevant risk factors but not consistently shown.[7]

This case highlights glaucoma diagnosis, management and progression despite pressure-lowering therapy.

An 82-year-old male presented for a glaucoma review. His medical therapy for glaucoma had been changed to Ganfort (bimataprost 0.03%/timolol 0.5%).

Ocular history

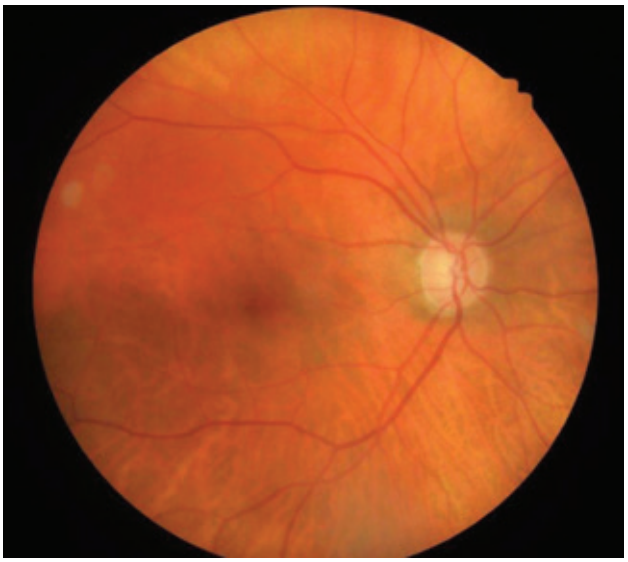
Diagnosed with POAG in 2012 due to:

- Elevated IOP (R 27 L 28 mmHg by Goldmann)
- Open angle on gonioscopy (ciliary body band visible 360 degrees)
- Thinning of the NRR (R 0.6 with inferior rim thinning L 0.8 with concentric thinning (Figures 1 and 2)
- Thinner than average corneas (R 506 L 521 microns)
- Corresponding VF defects
- RNFL thickness as significantly low on OCT (Figure 3).

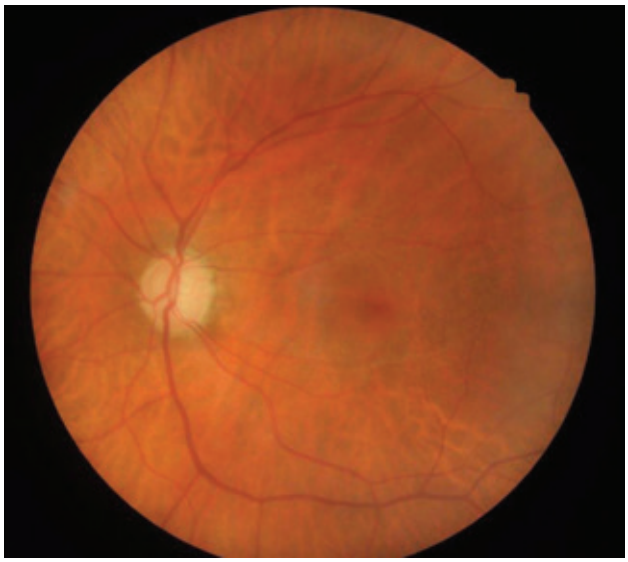
Began medical therapy with Xalatan 0.005% nocte. Target pressure set at 18 mmHg in both eyes.

Progression noted in 2013

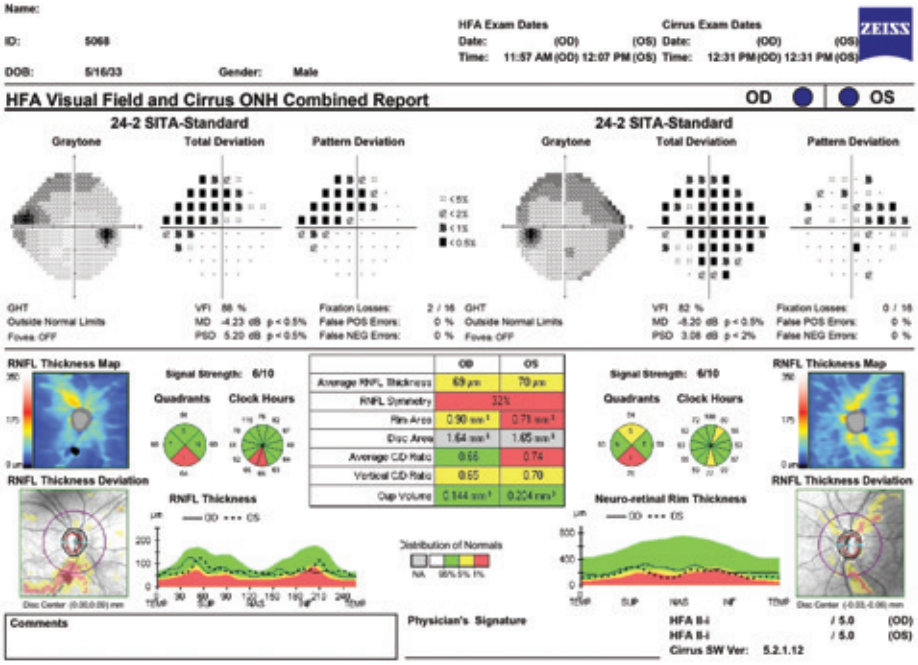
- IOP R 19 L 20 mmHg, target not met
- Visual field progression, particularly in the RE where the MD has dropped from -4.23 to -8.25 and the PSD from 5.20 to 9.70



▲ Figure 1. Colour fundus photograph of the RE captured in 2012



▲ Figure 2. Colour fundus photograph of the LE captured in 2012



▲ Figure 3. Visual field and OCT combined report in 2012

- Switched to Xalacom 0.005%/0.5% nocte; aim for 20 per cent reduction
- OCT also shows progression with a drop in average thickness in the LE from 70 microns down to 63 microns (Figure 4)
- IOL implant LE
- Review in eight weeks

Further progression in 2015

- IOP of 12 mmHg in both eyes
- C/D RE 0.7 with inferior rim thinning and associated infero-temporal disc haemorrhage LE 0.8 with concentric rim thinning
- Rapidly progressing glaucoma in RE (Figure 5) and relatively stable glaucoma in the LE (Figure 6)
- Acceptable IOP currently but clearly not low enough, therefore begin Ganfort 0.03%/0.5% nocte
- Set target pressure of < 12 mmHg in both eyes at all occasions
- Review 3/12
- May need surgical intervention in the near future

Diagnosis

The clinical diagnosis of POAG for this 82-year-old Caucasian male was made in 2012, after having had elevated IOP of ~27 mmHg since at least 2009. The raised IOP together with thinning of the NRR led to the diagnosis of POAG. Importantly, the patient had characteristic and corresponding VF defects. The ACAs were open on gonioscopy, and the patient had significant risk factors such as older age and thinner than average CCT. No signs of secondary glaucomas were present such as pigment dispersion, pseudo-exfoliation, uveitis and rubeosis irides or other optic neuropathies such as anterior ischaemic optic neuropathy.

Discussion

Key concepts in management of POAG

Early diagnosis is always preferred, even if some disease progression may have already occurred, as in this case. A major long-term issue is compliance with medication and adherence to treatment. Therefore, it is important to educate patients and simplify drop regimens.[8]

A treatment plan is necessary and includes a target pressure. In the current case report, the initial target pressure was set at 18 mmHg (down 33 per cent), which is an appropriate reduction for early-to-moderate POAG.[9] This is the IOP that is judged to have the best probability of limiting disease progression. However, before a target pressure can be decided, the clinician must have a clear idea of the baseline pressure.

Phasing IOP measurements may be useful to factor in IOP fluctuations throughout the day.[10] If disease progression is noted, as occurred 2013, controlled-trials recommend a further 20 per cent reduction in IOP.[11] Finally, the target IOP also depends on the level of damage already present, with advanced glaucomatous loss requiring more aggressive pressure lowering.[12]

Two or more VF tests should be performed in the first year of diagnosis. The aim of these repeated visual fields is to set high-quality baselines to allow comparison over time and detect early signs of progression. The clinician should identify a moment when progression has occurred either by event analysis or trend analysis.

Trend analysis quantifies the rate of loss on a VF index (VFI) in individual sectors or points. Linear regression is used to visualise and predict visual loss. In the current case, the VFI showed a downward trend (-5.6 dB/year) in the RE, indicating progression and vision loss (Figure 5). In the LE of this patient, the VF showed a relatively stable line but with variability.

Medical therapy

The NHMRC Glaucoma guidelines recommend the initial treatment of patients with early-moderate POAG to be with topical IOP-lowering

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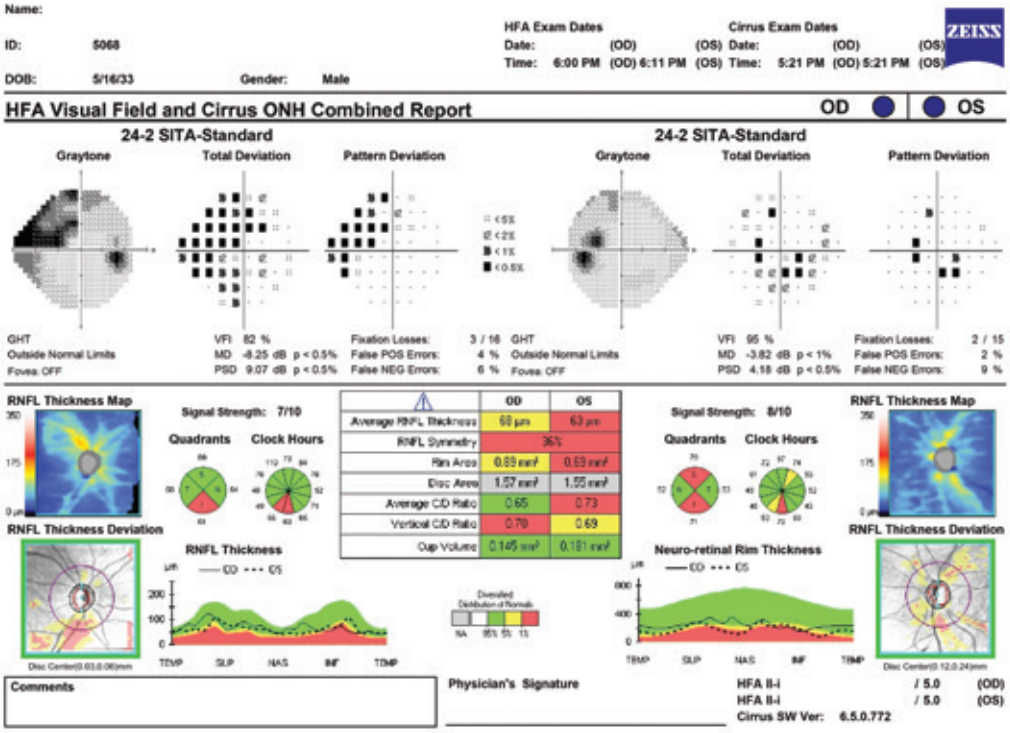

▲ Figure 4. Visual field and OCT combined report in 2013

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agents because that is the simplest and safest choice. Exceptions include pregnant/lactating women, known medication intolerances or suspected poor compliance.[9] Medications with the least amount of side-effects, administration, lowest effective concentration and most convenient delivery system should be chosen.

Best first line therapy for POAG

It is recommended to start with monotherapy to reach target therapy. Latanaprost 0.005% is commonly chosen because it has once-daily dosage, average IOP lowering of ~25-35 per cent, minimal systemic contraindications and few local side-effects. It increases uveoscleral outflow.

Importantly, relative contraindications to Latanaprost include macular oedema and history of herpetic keratitis.[13] Side-effects to monitor include conjunctival hyperaemia, reactivation of herpetic disease, uveitis (controversial), macular oedema, peri-orbital fat atrophy (long-term use) and peri-ocular skin hyperpigmentation (reversible) and iris hyperpigmentation.[9,11] Systemic side-effects are rare. Our patient was reviewed in March 2012 after the diagnosis to assess whether the target IOP was met, which was plenty of time as prostaglandins can take three to five weeks for maximal effect.[9]

Other prostaglandins are also a reasonable choice. Bimataprost 0.03% has been found to give the largest IOP reduction (33 per cent), followed by latanaprost (31 per cent) and then travaprost (27 per cent) in a meta-analysis of controlled trials.[14] This added benefit of 1-3 mmHg must be weighted against the higher incidence of conjunctival hyperaemia, although no patients withdrew from treatment because of this in a 12-week trial.[15] Therefore, it is reasonable to switch between prostaglandin analogues, if the first one does not meet the target pressure.

It is also reasonable to start with the beta-blocker timolol 0.5% bid, if there are no systemic contraindications. However, given its potential systemic side-effects, twice-daily dosing and potentially lower IOP lowering, it is often reserved as a combination agent or second line therapy.

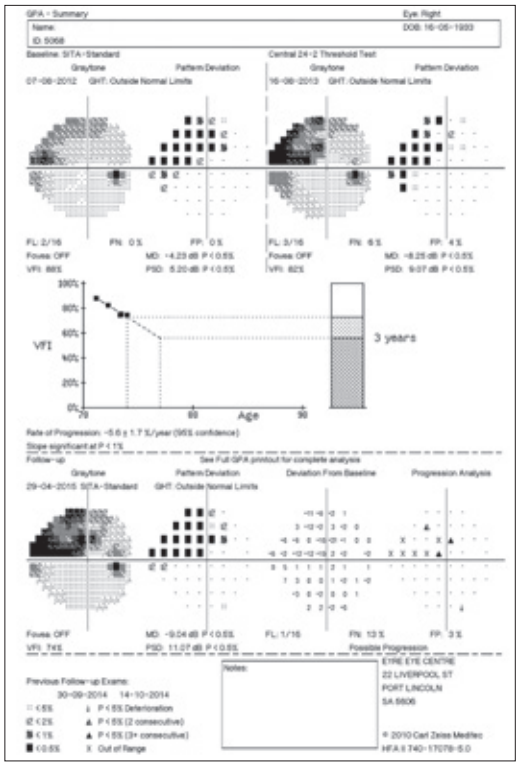
What happens if progression is identified or target pressure not met?

Once progression is noted, a lower target pressure is needed. The patient was switched to the combination drop Xalacom (xalatan 0.005%/timolol 0.5%). At this point it is important to consider the safety profile of both drugs. Xalatan has been discussed above. Timolol, a non-selective beta-blocker, suppresses the production of aqueous at the ciliary body.

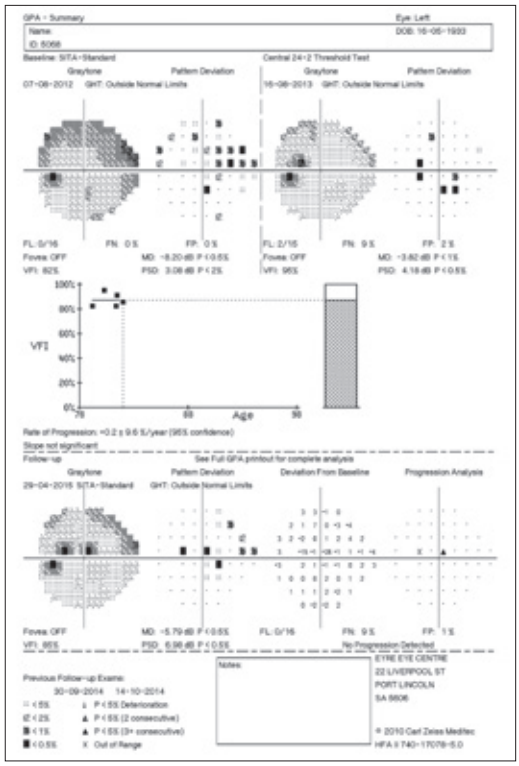
Importantly, all patients beginning therapy with a beta-blocker must be questioned about their systemic health, with particular emphasis on cardiorespiratory health. Once treatment is deemed safe and initiated, the clinician should enquire with the patient about symptoms such as coughing, dizziness, difficulty breathing and mood disturbances.

A beta-blocker reduces IOP by 20-25 per cent with a quicker onset of action (30 minutes), effects last 12 hours and maximal effect is at two to four weeks. However, 20 per cent of the population are non-responders to beta-blockers, and tachyphylaxis occurs in up to 50 per cent of the population after two years.[9] Finally, beta-blockers are found to lower the IOP poorly during sleep as aqueous production is lowest during sleep.

At the point where the patient is rapidly progressing in the RE, additional IOP lowering is needed.



▲ Figure 5. Guided progression analysis of the RE from 2012 to 2015



▲ Figure 6. Guided progression analysis of the LE from 2012 to 2015

Ganfort (bimataprost 0.03%/timolol 0.5%) has been shown in clinical studies to be one of the strongest combination drops available with the lowest diurnal variation.[16] Given the rapid progressive nature, it would have been reasonable to refer the patient for laser and/or incisional surgery.[17] Fortunately, Ganfort managed to meet the target pressure (12 mmHg) and provide stabilisation of the disease.

What happens if the patient continues to progress and/or wants to delay surgery?

In the event of the patient still progressing and surgery is wanted to be delayed, a third-line treatment can be initiated, with a CAI (brinzolamide 1%) or an alpha2-agonist (brimonidine 0.2%). However, polypharmacy severely reduces the risks of non-compliance, reduces efficacy through wash-out of earlier medications with later medications, and increases exposure of preservatives.[11] Both of these agents require dosing two to three times daily. Thus, surgical intervention must be seriously considered once a third drop is being taken into account. A link to neuroprotection with alpha-agonists has been identified in one trial but is not certain due to a high-drop-out rate in the brimonidine arm.[18]

Prognosis for our patient with POAG

It is certain from treatment/no treatment trials that long-term IOP reduction can slow glaucoma progression.[5,6] The decision to treat must take into account the risk of visual disability, binocular function, age, severity of disease in both eyes and any comorbidity (ocular or systemic). The baseline IOP is important, as is the presence of other risk factors.[19] It seems that this patient may be on his way to surgical intervention, as he appears to have aggressive disease. Close monitoring is needed. ▲

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Contraindications	Systemic side-effects	Local side-effects
asthma	bradycardia, arrhythmia, congestive heart failure, hypotension/nocturnal hypotension	allergic blepharoconjunctivitis
history of COPD	bronchospasm and airways obstruction	ocular surface disease or SPK
sinus bradycardia	masking of hypoglycaemia	corneal anaesthesia
heart block/cardiac failure	confusion	conjunctival hyperaemia
peripheral vascular disease (Raynaud's)	sexual dysfunction reduced exercise intolerance	

▲ Table 1. Other important contraindications and side-effects of beta-blockers[10-12]

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Progressing glaucoma despite optimal medical therapy From page 15

Contraindications	Systemic side-effects	Local side-effects
sulfa hypersensitivity	angioedema	blurred vision/transient myopia
low endothelial cell count/ Fuchs dystrophy and corneal grafts	fatigue/dizziness	endothelium cell decompensation
severe renal or liver disease	idiosyncratic bone marrow suppression (possible)	corneal anaesthesia
	paraesthesia	conjunctival hyperaemia
	anaphylaxis/SJS/urticaria	

▲ Table 2. Important contraindications and side-effects of CAIs[10-12]

Side-effects of alpha-agonists include:

Contraindications	Systemic side-effects	Local side-effects
avoid in children all together due to fatal respiratory arrest	systemic hypotension	limited mydriasis
monoamine oxidase use for depression or similar CNS depressants	fatigue/depression	allergic blepharo-conjunctivitis
very low body weight	CNS depression	contact dermatitis
severe cardiovascular disease	hypothermia	delayed hypersensitivity
vascular insufficiency can be potentiated	bradycardia	conjunctival hyperaemia granulomatous anterior uveitis (rare)

▲ Table 3. List of important systemic side-effects of alpha-agonists, which occur in five to 10 per cent of users. [10-12]

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Evidence for

Dr Mariem Abdou

OD FAAO

Nova Southeastern University College of Optometry, Florida USA

GLAUCOMA is an optic neuropathy characterised as damage to the optic nerve with loss of the ganglion cells and nerve fibre layer, resulting in permanent vision loss.[1,2] It is the second leading cause of blindness worldwide,[3] with nearly 70 million individuals suffering from glaucoma.[4] Risk factors include age, ethnicity, family history and elevated intraocular pressure (IOP).

Glaucoma was historically and incorrectly defined as increased IOP, which is considered higher than 21 mmHg. We now understand that elevated IOP is not the hallmark feature of glaucoma because pressures below 21 mmHg result in glaucoma in a number of cases, and pressures above 21 mmHg do not always lead to glaucoma.[4] About 33-50 per cent of patients with glaucomatous damage have a normal IOP measured at the first visit.[1] However, being the only modifiable element in this disease, the only known management protocol for glaucoma is to adjust the intraocular pressures to an appropriate target level via medicinal, laser or surgical techniques in order to reduce progression of the disease.[2,4] Several randomised, controlled large-scale studies have confirmed the efficacy of lowering IOP for the treatment of glaucoma.[5]

The Early Manifest Glaucoma Trial saw that an increase in intraocular pressures by even 1 mmHg portended an 11 per cent risk of disease progression; therefore, it is

continuous IOP monitoring

critical to obtain completely accurate measurements of IOP at each visit.[4]

Goldmann applanation tonometry

Unlike other medical devices, Goldmann applanation tonometry (GAT) was developed and has remained unchanged for more than a century. It measures the IOP at the flattened, central region of the cornea using the Imbert-Fick Law. We know this is not ideal and factors such as corneal thickness, scleral rigidity, and biomechanical properties including tear film and other substances can affect the IOP reading performed via GAT.[2,3,4]

According to the Ocular Hypertension Treatment Study, corneal thickness should be taken into consideration as an independent risk factor for progression of ocular hypertension to glaucoma. This study suggests that when the corneal thickness is high, the IOP is likely to be overestimated, whereas a thinner corneal thickness indicates an underestimation of the IOP measurement. Subjects in this study with the thinnest central corneal thickness were three times more likely to develop glaucoma than the subjects with a thicker central corneal thickness.[6]

IOP variability

In addition to these factors, intraocular pressures follow a variable circadian rhythm. IOP fluctuations in a normal individual can be up to 4-5 mmHg, whereas glaucoma patients tend to have much higher fluctuations.[2,3,4] Fluctuations in IOP can be due to a number of factors including body position and time of day or night.[1] Therefore, a single measurement of IOP does not provide enough data to diagnose or treat a patient because it excludes potential peaks and fluctuation of the IOP.[7]

Studies that measure IOP over a 24-hour period have shown that measurements taken during regular office hours are not true representations of the IOP because two-thirds of the measurements were greatest during nocturnal periods when the individual was in the supine position[4] and generally peak in the early morning.[7] Nighttime IOP can be measured only if a patient is hospitalised or in a sleep laboratory, but this can be costly and cause stress-related artifacts in the measurements so it is not done routinely.[2]

Diurnal tension curve

Intraocular pressures are frequently obtained during regular business hours to develop a diurnal tension curve (DTC). The DTC is collected via four to five IOP measurements, two hours apart, to acquire as much variability in the IOP at different times of the day as is practical. Although serial IOP measurements in-office still remain the most efficient way to identify peaks in pressures and guide treatment decisions,[6] the DTC can serve only as a summary of the IOP pattern because a complete 24-hour analysis is needed to reveal higher peaks and larger variations in IOP.[3]

Studies have demonstrated that the diurnal pattern of the IOP tends to be repeatable in untreated glaucoma patients. According to Katavisto, 80 per cent of glaucoma patients displayed consistency in their diurnal curve, yet Wilensky found this to be true in only 28 per cent of ocular hypertensive patients and 34 per cent of open angle glaucoma patients.[8]

Realini found that the diurnal IOP is highly variable and not repeatable day-to-day or several weeks apart, thus limiting the information gained from in-office studies.[9,10] In studies comparing the DTC over time for ocular hypertensive patients who have developed glaucoma versus ocular hypertensive patients who did not progress, the subjects who converted to glaucoma had IOP patterns similar to those of glaucomatous eyes when compared to the controls.[7] Additional studies reveal that treatment may regulate the IOP pattern in glaucoma so that there is less fluctuation.[8]

Contact lens sensor measurements

The likely highly variable diurnal IOP curve and long-term inconsistency of the IOP variation make in-office measurement a 'snap-shot' only of what is happening to a particular patient on a given day. Perhaps more information can be gained by 'continuous measurement of IOP', similar to a Holter monitor used to gauge heart electrical activity throughout the day.

The SENSIMED Triggerfish is a contact lens sensor (CLS) for 24-hour monitoring of IOP in clinical studies. CLS measurements may be of practical use for detection of sleep-induced IOP changes as well as being able to obtain a true understanding of IOP circadian variations in both short- and long-term situations.[11] Unfortunately, this devise is not currently clinically available but may be a future option to give a more complete assessment of IOP.

Although there are shortcomings by measuring IOP with the GAT technique and only during regular clinic hours, this still remains the standard in managing glaucoma patients today. Due to the diurnal variability of IOP, multiple measurements should be obtained during different clinic hours to obtain an understanding of diurnal tension curve in the least cumbersome manner. With these data, an appropriate target level and response to treatment can be better evaluated in an effort to delay or prevent the progression of glaucoma. ▲

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Corneal hysteresis: a risk factor in glaucoma

Dr Jessica Steen

OD FAAO

Nova Southeastern University
College of Optometry, Florida USA

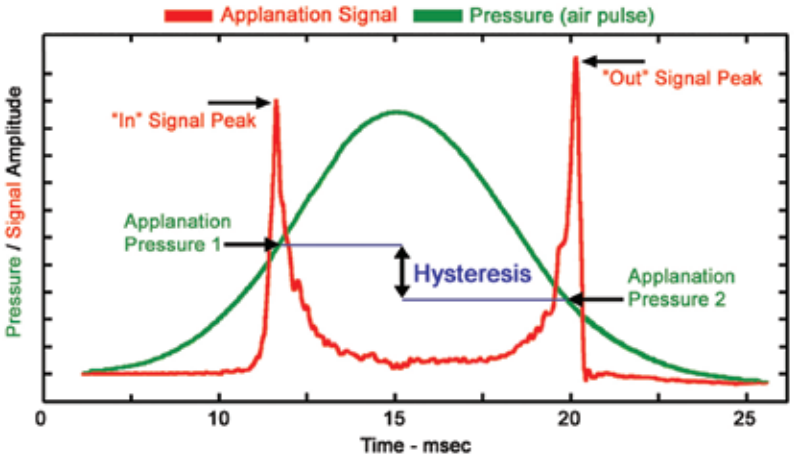
GLAUCOMA RISK assessment and identification of patients who may benefit from intraocular pressure (IOP) lowering therapy is a complex process. Well-established risk factors for glaucoma include IOP, age, central corneal thickness (CCT), family history and ethnicity, which help guide our treatment plan and evaluate general risk assessment of the development and progression of glaucoma.

Corneal hysteresis (CH), a corneal biomechanical property easily measured non-invasively in-office, is a relatively new parameter that may provide additional information to aid in clinical decision-making.

Hysteresis is an inherent biomechanical property of the cornea, which measures the cornea's ability to dampen a force when applied. Although CCT plays a role, CH may be a better indicator of how the cornea, as well as other ocular tissues, possibly including the lamina cribrosa, respond to short- and long-term pressure fluctuations.[1] CH is a measure of tissue function, rather than just a structural parameter like CCT.

Measuring hysteresis

The Ocular Response Analyzer (ORA-Reichert Ophthalmic Instruments, Buffalo, NY, USA) is the only device used to measure CH. An air impulse applies a force to the cornea in a similar fashion to a non-contact tonometer. Corneal applanation is measured at two moments in time: at an 'inward' bending and an 'outward' bending point over a total period of 20 milliseconds. The difference between the two endpoints, the inward and outward applanation pressure, reflects corneal hysteresis, measured in mmHg. The ORA also provides an estimation of objective Goldmann IOP (IOPg) as well as cornea compensated IOP (IOPcc) which incorporates CH into an adjusted IOP value.[2]



▲ Figure 1. Corneal hysteresis (CH) is the difference in the inward and outward pressure values obtained during the dynamic bi-directional applanation process employed by the Ocular Response Analyzer, as a result of viscous damping in the cornea

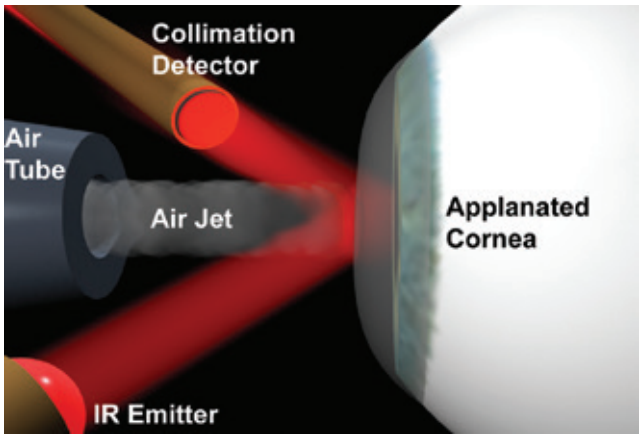
Clinical correlation of CH

Corneal hysteresis is related to cellular and structural properties of the cornea. Independent factors that affect CH include age, CCT, IOP, glaucoma diagnosis and glaucoma severity.[3] In general, lower CCT values correspond to lower CH.[4] With increased age and IOP, CH is also lower.[4] Additionally, as glaucoma severity increases, corneal hysteresis decreases.[3] Corneal hysteresis is stable throughout the day and is unrelated to corneal radius or spherical equivalent.[5] African Americans have the lowest CH (and CCT) compared to Hispanics and Caucasians.[6] Data show that women have a higher CH than men but exhibit no difference between IOPg or IOPcc.[7]

CH has been identified as an independent risk factor in glaucoma progression.[8] It is thought that eyes with a higher CH, or a greater ability to dampen IOP fluctuations, may be less susceptible to the development of glaucoma. In contradistinction, eyes with a low CH, or less ability to dampen such fluctuations in IOP, may increase the risk of glaucomatous optic neuropathy.[3] It has been established that eyes with primary open angle glaucoma, exfoliative glaucoma as well as glaucoma with statistically normal pressure have lower CH than eyes of ocular hypertensives and normal people. These eyes with lower CH seem to progress more quickly than those with higher CH.[3,8,9]

Eyes with low corneal hysteresis at initiation of treatment with topical prostaglandin analogue showed a greater reduction in IOP than those patients with higher baseline CH.[10] Data show that corneal hysteresis may increase following the initiation of topical therapy.[11]

Currently, CH may be somewhat quantifiable as a potential risk factor for the progression of suspects progressing to glaucoma as well as the progression in previously diagnosed glaucoma patients. A normal range of CH has not been well established but seems to range between 8 and 14 mmHg.[6,9,10]



▲ Figure 2. The Ocular Response Analyzer uses a bi-directional applanation process to measure biomechanical properties of the cornea and the intraocular pressure of the eye.

Current challenges

Questions remain regarding the true importance and clinical implications of CH in practice. We know that as IOP is lowered, CH increases. However, it is unknown whether this is a mechanical result, an indicator of possible recovery or true slowing of progression of the glaucomatous disease process. Additionally, due to the lack of longitudinal studies at this period of time, uncertainty remains whether CH is variable over a patient's lifetime in the case of individuals with established glaucoma, which clinically correlates to defining how frequently the test should be administered.

Clinical applications of CH

The combination of CH and CCT in evaluating risk assessment of glaucoma appears to provide more information than using either factor in solitude. As such, CH is not likely to replace CCT as a standard of care in glaucoma risk assessment but will continue to become an adjunct to CCT in glaucoma risk assessment, identifying those patients who may progress more quickly as well as providing an explanation for why some patients have greater IOP lowering with topical prostaglandin therapy than others. Measurement of corneal hysteresis including the adjusted IOP measurement provided by the ORA may be of additional importance in patients following keratorefractive surgery or with corneal pathology.[9]

Understanding CH and the effect that it may have on an individual's variability in disease or disease progression and incorporation of this data into glaucoma risk assessment may allow for earlier diagnosis of glaucoma as well as more appropriate long-term management of our patients with glaucoma. ▲

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Evidence for continuous IOP monitoring

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Progressive visual field loss from optic nerve head drusen

Dr Mark Chiang

MBBS MPhil FRANZCO
Queensland Eye Institute
City Eye Centre Brisbane

VISUAL FIELD LOSS is one of the hallmarks of glaucoma. In general or glaucoma clinics, we often encounter patients with visual field loss that may or may not be progressive. In assessing a patient with visual field loss, it is important to obtain a thorough history, followed by a complete ophthalmic examination, a central nervous system (CNS) examination, as well as other systemic examination as indicated. Investigations are then performed to provide further support or to confirm the diagnosis.

CASE REPORT

A 60-year-old male was referred for symptomatic progressive visual field loss. The patient had been aware of gradual constriction of his peripheral field over several years. There were no other associated symptoms such as headache or transient visual loss. He was otherwise well, without any medical problems. He works as a company executive, which requires extensive driving.

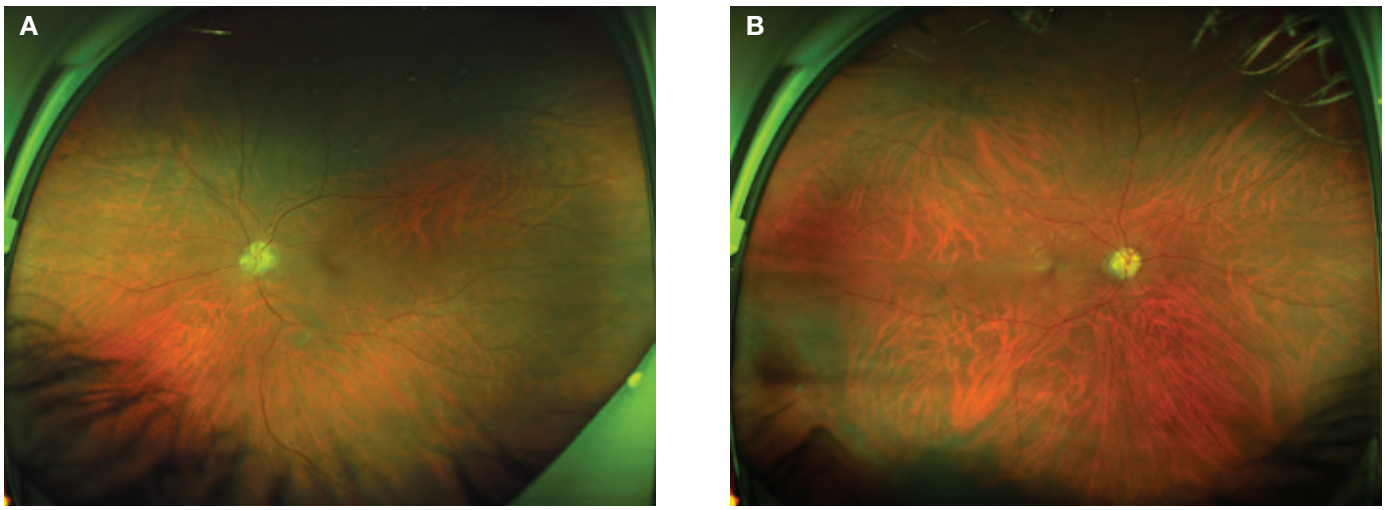
On examination, pupils were equal and reactive and there was no relative afferent pupillary defect. Ishihara colour plates were full in each eye. He had full ductions and versions as well as a normal CNS examination. His BCVAs were 6/6 in each eye. Anterior segment examination was normal and gonioscopy revealed open drainage angles. Presenting IOPs were 19 mmHg in each eye. Dilated fundal examination showed bilateral optic nerve head (ONH) drusen and attenuated retinal vasculature (Figures 1A and 1B).

OCT performed on presentation showed grossly reduced retinal nerve fibre layer (RNFL) thickness in both eyes and illustrated well the readily-visible ONH drusen (Figure 2).

Visual fields were also performed and confirmed the constricted fields (Figures 3A and 3B). Surprisingly, his performance on the binocular Esterman field test fulfilled the requirements for the driving standard.

A diagnosis of bilateral progressive field loss secondary to extensive ONH drusen was made and the patient was commenced on brimonidine bd OU and aspirin 100 mg daily. At the same time, a gadolinium-enhanced MRI of the visual pathway was performed, which did not show any other intracranial lesion that could have caused the patient's field loss.

On review two months later, vision and visual fields remained stable and the IOPs were 17 mmHg in each eye. Latanoprost nocte OU was then added in an attempt to lower further his IOPs. On subsequent reviews over the next 18 months, his vision and fields remained stable with IOPs at around 13 mmHg OU.



▲ Figures 1A and 1B. Optos imaging showing bilateral ONH drusen with attenuated retinal vasculature

About two years after initial presentation, he noticed a fairly rapid worsening of both the BCVA and fields. His BCVAs had reduced to 6/12 OD and 6/9 OS with worsening of visual fields (Figures 4A, 4B, 5A and 5B). Clinical examination did not reveal any additional pathologies such as central artery or vein occlusion, or choroidal neovascular membrane (CNVM) which can be associated with ONH drusen. The patient needed to cease his current employment as he could no longer drive.

Discussion

This case represents the severe end of the spectrum of visual field loss secondary to ONH drusen. The exact aetiology of ONH drusen is not well understood but it is thought to be congenital. Some suggested an abnormal axonal metabolism leading to calcium deposition. Others postulated reduced anterograde and retrograde axoplasmic flow leading to axoplasmic stasis and subsequent mitochondrial calcium deposition.

ONH drusen may be buried or readily visible and can be confused with optic disc swelling. In buried

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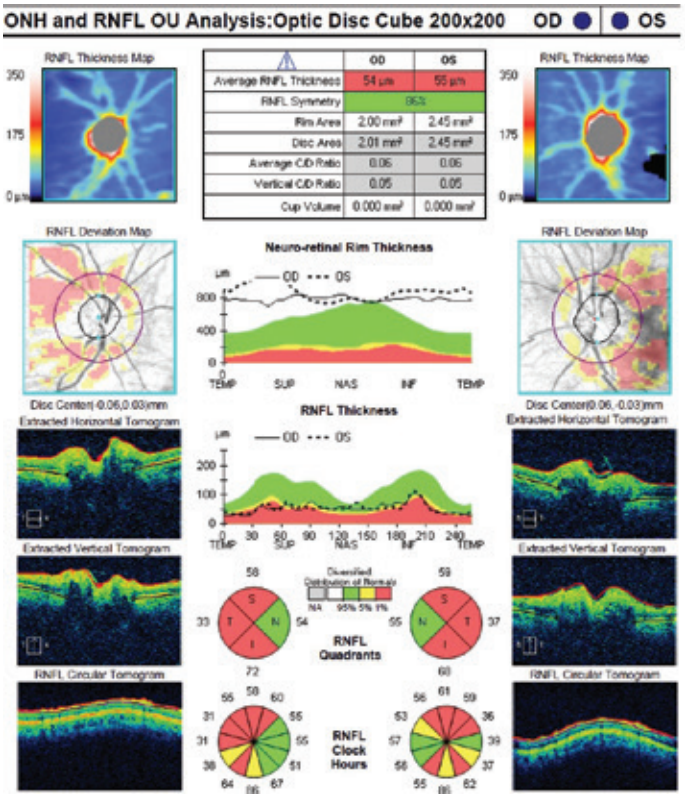
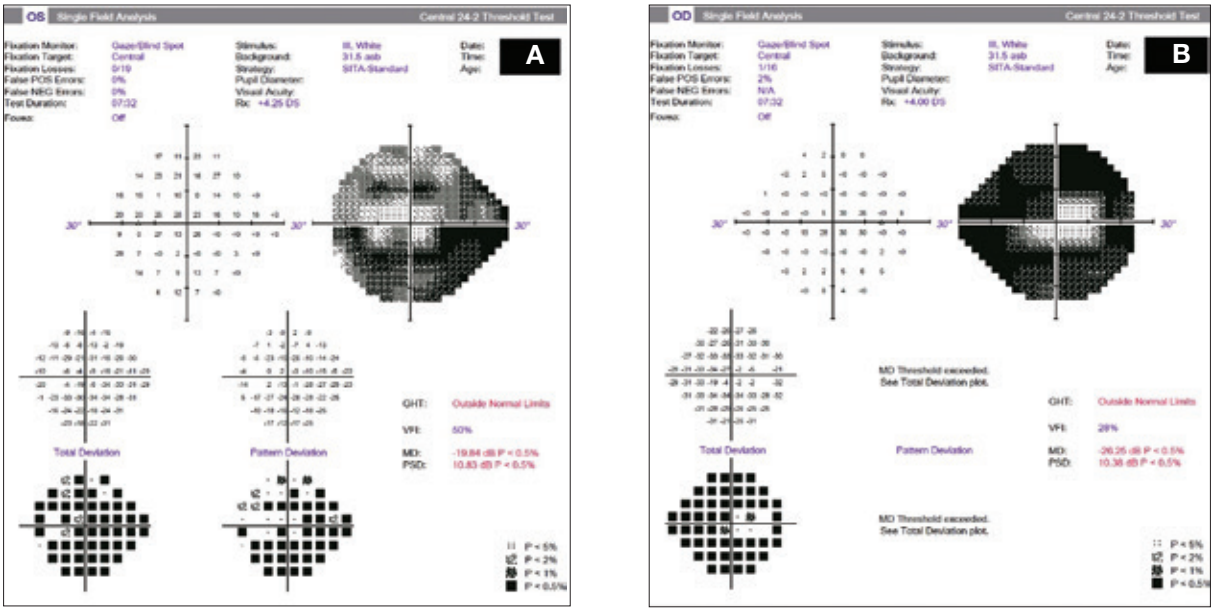
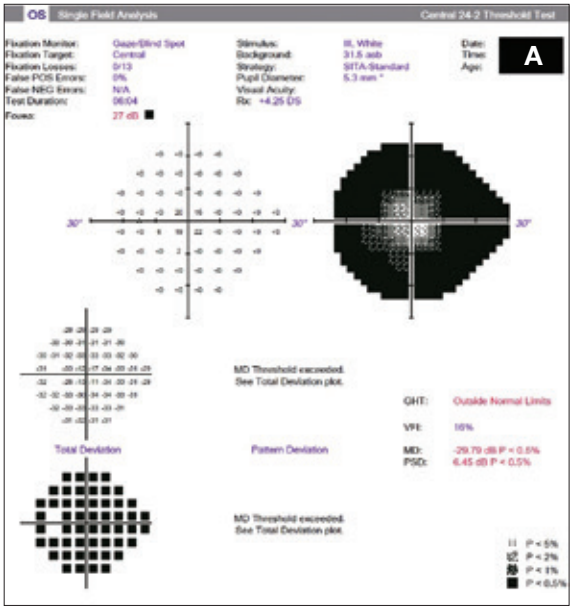
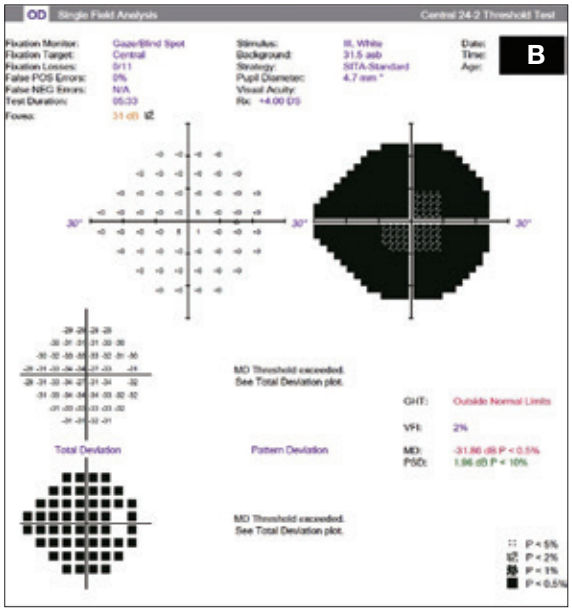


▲ Figure 2. OCT of the ONH and RNFL analysis

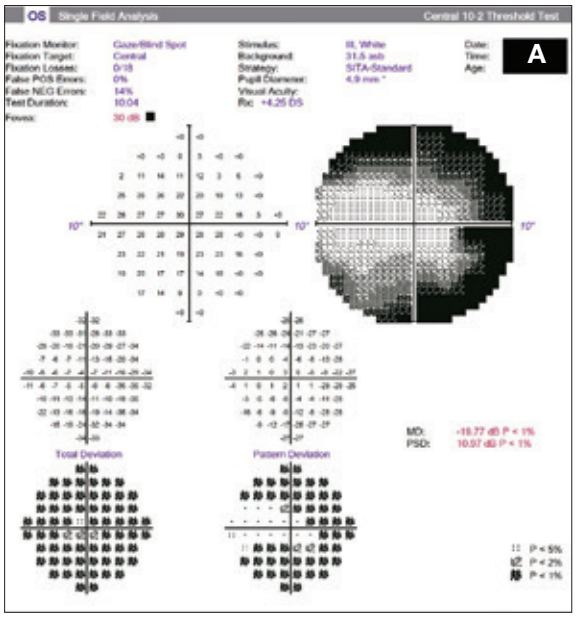


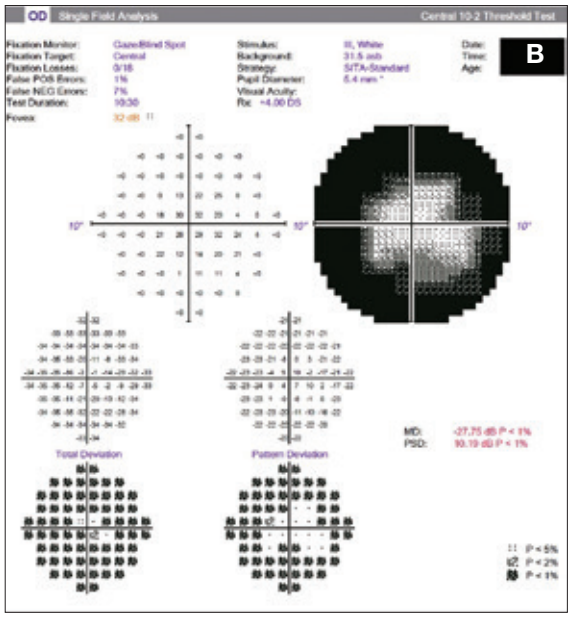
▲ Figures 3A and 3B. Visual fields on presentation





▲ Figures 4A and 4B. Latest 24-2 fields showing significant progression





▲ Figures 5A and 5B. Latest 10-2 visual field with extensive central vision involvement

Progressive visual field loss from optic nerve head drusen

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drusen, investigations such as B-scan ultrasonography, autofluorescence or even CT scans can aid in the visualisation. It is associated with central retinal vein occlusion, central retinal artery occlusion, anterior ischaemic optic neuropathy, choroidal neovascular membranes, and glaucoma. Patients may range from being totally asymptomatic to having transient visual obscurations, or having visual field loss.

While there is no proven treatment for ONH drusen, some patients are treated with IOP-lowering medications to relieve ONH mechanical stress and improve blood flow. Hopefully, with future research, we can better understand this condition and perhaps offer an effective treatment for this infrequent but sometimes debilitating condition. ▲

Selective laser trabeculoplasty therapy

Dr Simon Skalicky

FRANZCO MPhil MMed (Ophthal Sci) MBBS(Hons 1) BSc(Med)

Melbourne Eye Clinic

TO DATE, intraocular pressure (IOP) lowering is the only proven strategy to halt or slow progressive glaucoma yet the decision to commence or augment IOP-lowering treatment is not always easy. It can be difficult to determine if the measured IOP is the true IOP, if the patient is having large IOP fluctuations over the diurnal cycle such as night-time spikes, if the patient really has glaucoma or just suspicious discs, and if the IOP might cause disabling vision loss for the patient.

Weighed against the indication for treatment is the nature of the treatment itself: what it involves, the efficacy and likelihood of success, the cost, the side-effects and contraindications and the burden on daily life. When making decisions regarding glaucoma treatment, it is important to discuss these issues openly with our patients, outlining all the options including no treatment.

Patients with glaucoma are understandably concerned about their risk of future vision loss. Increasingly, they are presenting to optometrists and ophthalmologists better educated, requiring more detailed discussions and consultations, and wanting more autonomy in their management.

With these issues in mind, selective laser trabeculoplasty (SLT) is a useful treatment option to offer our patients. Well tolerated, minimally invasive and generally effective, the laser treatment is often used for patients with ocular hypertension or open angle glaucoma, including primary open angle glaucoma, pseudoexfoliation (PXF) glaucoma, pigment dispersion (PD) glaucoma, steroid-induced glaucoma and normal tension glaucoma.

SLT can be used alone or in combination with topical eye-drops. It is used as initial therapy, as an alternative to eye-drops for patients with local or systemic side-effects to their medication, as an adjunct to drops for established glaucoma patients not meeting their target IOPs, or for patients on maximal tolerated medical therapy to avert or delay filtration surgery.

Selective laser trabeculoplasty

SLT was first described 20 years ago and designed to selectively target pigmented cells in the trabecular meshwork (TM) and spare adjacent cells and tissues from thermal damage.[1] Having largely superseded argon laser trabeculoplasty (ALT), SLT has many inherent advantages over the previous laser technology.

Compared to ALT, the spot size is larger (400 micrometres vs 50 micrometres), allowing the energy to diffuse over a larger area. This prevents harmful focus on any one point in the trabecular meshwork (Figure 1). In addition, the laser duration is much more brief, three nanoseconds (SLT) v 100 milliseconds (ALT).

The longer duration, highly-focused beam of ALT was capable of photocoagulation, resulting in potential structural damage to the trabecular meshwork.

In comparison, the laser application of SLT is too brief and too low in energy to cause significant structural damage (Figure 2A and 2B).[2] SLT and ALT have a similar IOP-lowering efficacy,[3]

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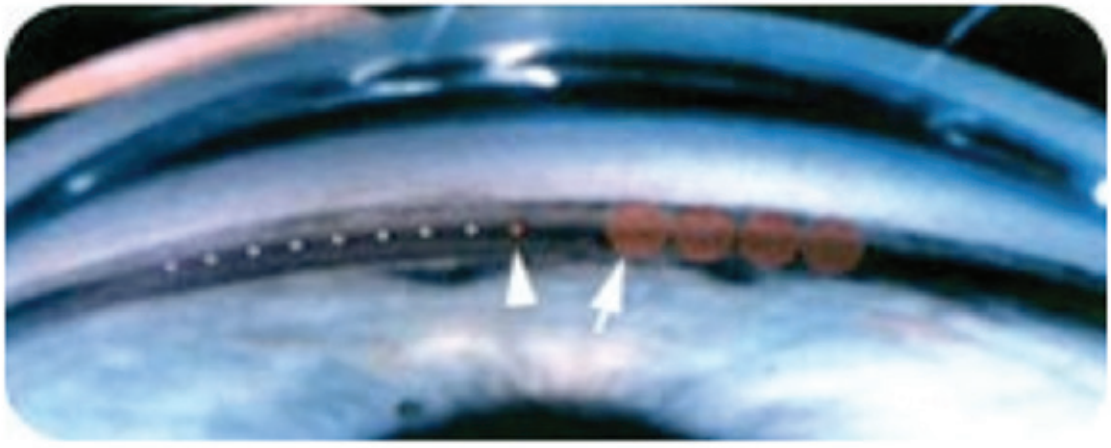

▲ Figure 1. Comparison of 50 micron spot size with ALT (white arrowhead) and 400 micron spot size with SLT (white arrow)

Selective laser trabeculoplasty therapy

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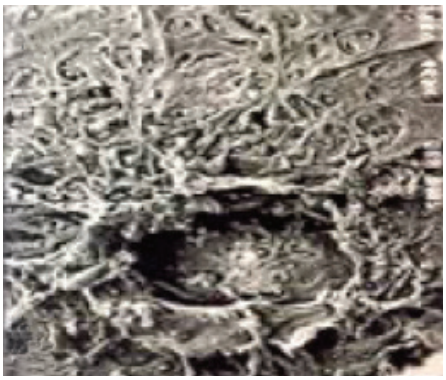
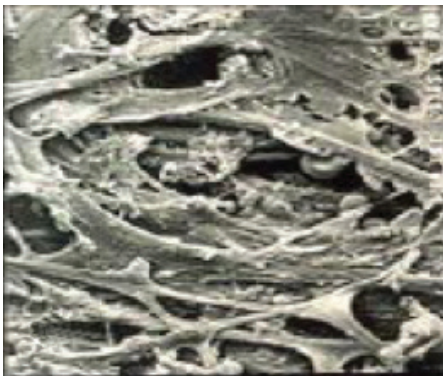


▲ Figure 2A. Electronmicroscopic images of trabecular meshwork following ALT



▲ Figure 2B. Electronmicroscopic images of trabecular meshwork following SLT

indicating that they may lower IOP through similar mechanisms and as a consequence, the coagulative TM damage with ALT may be unnecessary.[4]

Despite many years of research the precise mechanism of SLT is still uncertain. SLT delivers short bursts of low-fluence laser energy to selected melanin-containing cells of the TM without damaging adjacent non-pigmented cells or structures.[5] This induces cellular and biochemical changes in the TM cells, resulting in increased expression of pro-inflammatory cytokines and matrix metalloproteases.[6]

This pro-inflammatory drive results in recruitment of macrophages that phagocytose TM debris[7] and probably causes trabecular cell division to stimulate growth of healthy TM and optimise outflow.[8] Some evidence suggests SLT disrupts the integrity of tight junctions binding endothelial cells lining Schlemm's canal, enhancing transendothelial aqueous outflow.[9]

The laser energy is applied using a gonioscopic mirror as a series of contiguous spots circum-linearly over the TM (Figure 3). Laser energy is generally titrated between 0.6–1.4 mJ to produce fine 'champagne' bubbles on application.

Typical treatment parameters are 50 (or 100) applications over 180 degrees (or 360 degrees). To prevent a transient IOP spike post-SLT that may occur in some patients, apraclonidine 0.5% (Iopidine; Alcon Laboratories, Inc., Fort Worth, TX, USA) is commonly given one hour before treatment.

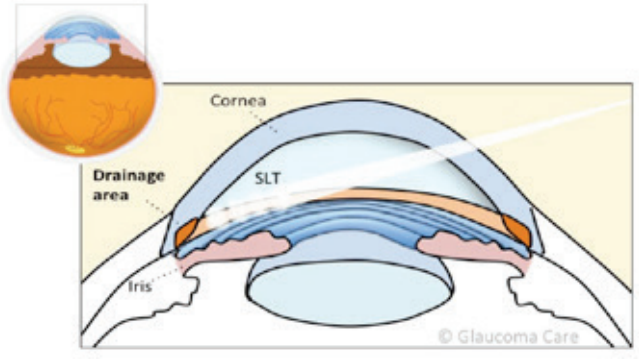
Topical anti-inflammatory drops are generally not administered as the induction of an inflammatory response may be beneficial for the IOP-lowering effect of SLT. Several studies have compared outcomes following 90 degree, 180 degree and 360 degree treatment, and there is a trend suggesting that greater treatment area results in a greater and more reliable IOP reduction, although differences in IOP lowering between 180 degree and 360 degree treatment are not consistently found.[10-13]

SLT has a good success rate when first applied, resulting in an average IOP reduction of 15-30 per cent in most patients; however 15-25 per cent of patients either do not respond or minimally respond to the therapy.[14,15] This efficacy is comparable to monotherapy with topical prostaglandins or beta-blockers.[14]

Four randomised control trials have compared SLT to medical therapy, and 10 randomised control trials have compared SLT to ALT. Meta-analyses of these studies showed that there was no statistically significant difference in treatment success or IOP reduction.[14,16] The strongest predictor of success for SLT is high baseline (pre-treatment) IOP;[17] yet SLT can still be effective for patients with normal tension glaucoma or patients on multiple topical medications. SLT is probably effective in reducing diurnal IOP fluctuation, although how it compares to topical medical therapy in this regard is uncertain.[12]

If successful, the effect of SLT is likely to reduce over time, resulting in an eventual IOP rise. On average the treatment lasts from two to three years but the range of length of treatment response can vary from six months to more than five years.[18] It is critical that this fact is explained to patients who therefore need ongoing monitoring, ideally six-monthly.

The danger of using SLT to reduce IOP is that if the patient has the impression that once treated, the IOP will stay permanently lowered, an asymptomatic rise in IOP as the laser wears off can cause optic nerve damage if not



▲ Figure 3. Application of SLT

monitored. SLT is repeatable, provided it had a significant effect on the first treatment; however, the efficacy of subsequent treatments is less than when first applied.

SLT has few side-effects. Commonly redness, discomfort or photophobia may occur after SLT but these symptoms resolve within a few days without treatment. Rarely, an IOP spike can occur immediately following SLT. This is more common in eyes with PXF, PD glaucoma, 360-degree treatment in one session or otherwise very damaged TM. The incidence of such spikes is significantly lower than following ALT and can be minimised by the pre-treatment use of IOP-lowering topical medication.[14]

Peripheral anterior synechiae can occur rarely following SLT (one to three per cent); likewise the incidence following SLT is less than following ALT.[15] Transient deposits on the corneal endothelium and even occasional interstitial corneal stromal inflammation can occur following SLT, both of which resolve spontaneously.[19] Rarely, SLT treatment can result in reactivation of herpetic corneal disease, and should be used with caution in patients with a history of herpetic keratitis.

Compared to daily eye-drops, SLT avoids the complex issues of treatment adherence[20] and is probably gentler on the surface of the eye than long-term use of preserved topical medications. There is considerable interest in how SLT compares to prostaglandin monotherapy as initial treatment for glaucoma in terms of treatment efficacy, ocular discomfort, quality of life issues, prevention of glaucomatous progression and cost to the patient and society.

Health economic modelling varies considerably in different countries; however, modelling performed in a Canadian health-care settings suggest it is cost-effective compared to topical medical therapy, especially compared to multi-agent therapy.[21]

To compare SLT to topical medication as the initial treatment for glaucoma an international, multicentre RCT (the Glaucoma Initial Treatment Study) based mainly in Australia is underway.[22] At the time of writing this article, results from this study have not yet been published.

Conclusion

Minimally invasive, well-tolerated and generally successful, SLT is an increasingly popular treatment alternative to topical medications for patients with ocular hypertension or open angle glaucoma. It is probably as effective as a single topical medication, and can be used either as a sole treatment or in addition to eye-drops.

SLT does not rely on patients adhering to a daily eye-drop regimen, and averts ocular surface side-effects related to drop toxicity. The common adverse effects related to SLT, redness and discomfort, are transient and self-limiting. SLT is not uniformly effective in all eyes. The IOP-lowering effect of SLT reduces over time; this must be explained clearly to our patients who therefore need ongoing six-monthly monitoring. Although the treatment is repeatable, subsequent treatments are generally not as effective in lowering IOP as the first treatment.

SLT may be cost-effective compared to therapy with topical medication but we await key RCT data to evaluate the health economic impact of SLT treatment for glaucoma. ▲

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Setting target intraocular pressure

IOP lowering is not an end in itself

Dr Jennifer Fan Gaskin

FRANZCO MD

Glaucoma clinician, Royal Victorian Eye and Ear Hospital and Centre for Eye Research Australia

THE CONCEPT of target intraocular pressure (IOP) dates back as least as far as Paul Chandler's lecture series in the 1950s. The notion was reinforced by a post hoc analysis from the Advanced Glaucoma Intervention Study (AGIS) that led to the conclusion that if IOP was kept below 18 mmHg at all visits or at a mean of 12.3 mmHg, then glaucoma progression could be halted (Figure 1).[1]

Soon afterwards, the American Academy of Ophthalmology and other ophthalmic organisations began encouraging clinicians to identify their therapeutic goals and advocated the term 'target IOP', defining it as a range of intraocular pressure adequate to stop progressive pressure-induced injury.[2-4]

There are various methods by which target IOP can be derived. Most glaucoma trials aim for a percentage reduction of 25-30 per cent as such a percentage drop is likely to be statistically significant and exceed the normal fluctuations of IOP.

A percentage reduction also individualises the target somewhat for each patient, rather than arbitrarily setting a target of 8 mmHg for every patient, which would also prevent progression but undoubtedly would lead to overtreatment of a large number of patients.

Alternatively, several complicated formulae have been derived to assist us in setting a target IOP, incorporating patient factors such as age, race, corneal thickness, refractive error, amount of visual field loss and nerve damage. However, none of these has been shown to be practically applicable or demonstrated any accuracy or effectiveness in clinical studies.

On the surface, target IOP seems like a good idea. We all know that glaucoma is a challenging disease; the condition is incurable and associated with progressive and irreversible damage. Additionally, glaucoma is notorious for 'breeding complacency'.

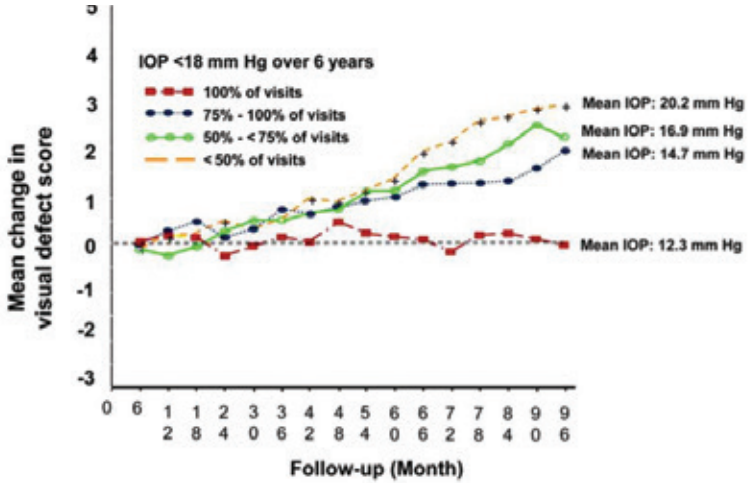
In the busy, relentless practice of the modern-day ophthalmic practitioner, not only do we need to check the IOP, examine for optic disc changes and assess visual fields for deterioration, there is also an increasing number of devices emerging to assist us in monitoring for glaucoma progression. Optical coherence tomography (OCT) of the retinal nerve fibre layer (RNFL), Heidelberg Retina Tomography (HRT) of the optic disc, and analysis of the ganglion cell complex are some of the technologies in the armamentarium of the glaucoma clinician.

Invariably, at least one piece of information among the above will contradict the rest, and it is easy to deem the tests 'unreliable' or 'inconclusive' and continue the patient on the same regimen, with a plan to repeat the tests again in six months. The same scenario is just as likely to recur six months later.

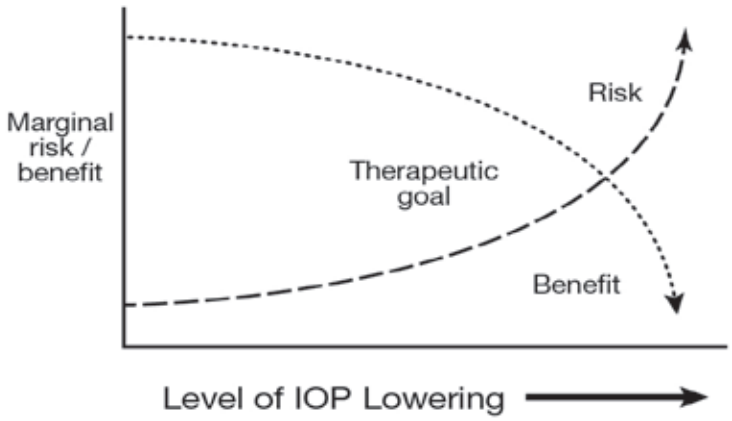
Because lowering IOP is the only proven treatment for reducing glaucoma progression, it makes sense to set a target IOP early in the patient's disease and alter the treatment when the measurement deviates from the target. Similarly, if the other parameters progress despite the fact that target IOP is met, then a lower target should be set and treatment adjusted accordingly.

There are IOP thresholds above which all clinicians would recommend treatment, even without current evidence of disc cupping, visual field loss or nerve fibre layer thinning. For example, when a patient presents with acute angle closure and an IOP of > 50 mmHg, responsible clinicians would recommend treatment because it is recognised that an IOP of 50 mmHg is incompatible with long-term retinal ganglion cell survival.

There are also patients who go blind from glaucomatous optic disc damage without ever having elevated IOP. It is easy to overlook the fact that blindness results from damage to the optic disc and its axons, not from elevated IOP. IOP is, at most, a risk factor and at other times simply a surrogate measure of the disease.



▲ Figure 1. Associative analysis from the Advanced Glaucoma Intervention Study[1]



▲ Figure 2. The therapeutic goal of glaucoma management: balancing risks and benefits[7]

The limitation of monitoring a patient by a surrogate measure such as IOP is that it may or may not be consistent with the actual parameters of interest, such as the RNFL, optic nerve head or visual function. If the RNFL, optic nerve head and visual function worsen despite an IOP within target, it may be that the target IOP was not set at an appropriate level, or it may be that there are other factors causing optic disc damage.

The patient's blood pressure can influence glaucoma progression, both in the form of uncontrolled systemic hypertension and nocturnal hypotension due to over-treated hypertension. Lack of compliance is also well-recognised among glaucoma patients and can account for disease progression despite seemingly adequate in-office IOPs. Additional, less well-understood factors also exist, such as blood flow, genetic factors and neuronal susceptibility, and these may not correlate with IOP but can account for worsening of disease.

There are inherent flaws in IOP itself. We rely on one diurnal IOP measurement every six months to reflect the true IOP across the entire period when we know in reality that IOPs fluctuate significantly throughout 24 hours and this fluctuation is further influenced by factors such as body position.[5,6] IOP can increase by more than 3-4 mmHg when lying down compared to sitting. We still do not have an adequate means of measuring 24-hour IOP. Additionally, we do not understand which element of IOP (the peak IOP, mean IOP, fluctuation in IOP) has the biggest influence on glaucoma progression.

Benefit versus risk

Glaucoma care, as with all areas of medicine, involves the careful balance of the benefit versus the risks of treatment and unfortunately, the definition of target IOP does not take into account risks or side-effects of treatment.[7]

While seasoned clinicians may adjust the target IOP based on the potential risks associated with the treatment required to reach the target, this flexibility is not understood within the definition itself.

There is also some evidence that there may be overall diminishing returns in progressive IOP lowering, such that the benefit derived from lowering the IOP from 20 mmHg to 18 mmHg may be higher than reducing the IOP from 12 mmHg to 10 mmHg.[8,9] Therefore with decreasing potential benefits, the balance tips towards potential risks when attempting to achieve lower IOPs (Figure 2).

As an extreme example, an elderly, low-risk patient with mild glaucoma, who is systemically unwell and unable to reach target IOP, generally should not undergo glaucoma filtration surgery as it is recognised that the side-effects and potential risks of the procedure outweigh the benefits in this situation. Strictly following target IOPs can lead to the trap of treating a number and not a patient, and inadvertently placing patients at risk by setting inappropriate IOP targets.

The subtleties of glaucoma management cannot be overemphasised. It is a challenging disease that is still one of the leading causes of blindness in the world. While the practice of setting target IOPs may simplify a clinician's life, it does not necessarily improve patient care.

A target IOP may be a useful surrogate marker of treatment, but rather than adhering strictly to a single number, setting a target IOP range may be more practically useful. The clinician should also be mindful that IOP lowering is not an end in itself but a strategy to prevent the patient from glaucoma-induced disability, that all treatment should be a careful balance of benefit versus risks, and they need to look beyond the slitlamp and consider the whole patient. ▲

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Subtle glaucomatous damage detectable using 10-2 visual fields

Dr Jack Phu

BOptom(Hons) BSc

School of Optometry and Vision Science, Centre for Eye Health, NSW

THE GOLD STANDARD of functional assessment in glaucoma is standard automated perimetry (SAP), using instruments such as the Humphrey Visual Field Analyzer (HVFA).[1]

The test pattern that is most commonly used in glaucoma assessment is the 24-2 grid, due to its ability to detect the most common glaucomatous visual field defects within a reasonable time and with less variability than a 30-2 grid.[2] The Swedish Interactive Thresholding Algorithm (SITA) of the HVFA offers benefits when using the 24-2: it is quick, has less test-retest variability, has excellent sensitivity and specificity for glaucoma, and is reasonably well-tolerated by patients.[3-5]

However, while the 24-2 has been widely accepted as the standard for visual fields testing in the majority of glaucoma cases, the 10-2 pattern has also been proposed to be used in some exceptional cases, aside from other retinal diseases such as bullseye maculopathy and age-related macular degeneration. The 10-2 pattern tests the central 10 degrees with two-degree spacing of the points, resulting in 68 points tested within the central visual field. This compares to the 24-2 or 30-2, which test only 12 points within that central area (Figure 1).

Most notably, the 10-2 is useful in cases of advanced glaucoma, where only the central-most visual field remains,[6] where there is no point in testing more peripheral locations. When using the 10-2 pattern, it can also be seen that visual field loss is not necessarily concentric and symmetrical, but biased towards the superonasal region, with the inferotemporal region most commonly intact within the central 10 degrees, a finding that can be masked by the wider (six degrees) spacing of the 24-2. Therefore, a 10-2 visual field could be more useful in monitoring such patients.[7]

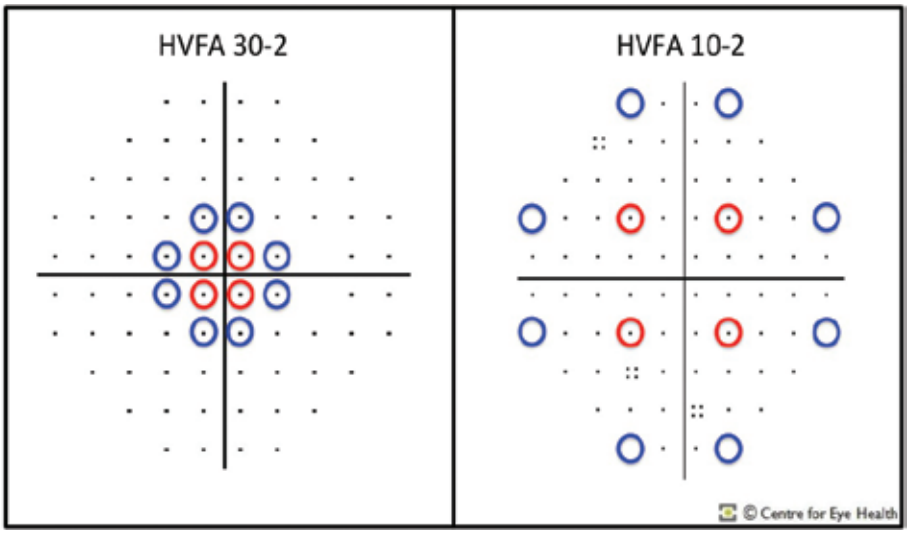
More recently, the 10-2 has been suggested as an alternative or adjunct to the conventional 24-2 pattern even for earlier stages of glaucoma. One reason for this is that increased test point density has been shown to have superior detection ability for early visual field defects.[8]

The papillomacular bundle was previously thought to be relatively spared in early glaucoma due to its higher density of retinal ganglion cells;[9] however, recent studies have shown that some defects in early glaucoma may be detected using the 10-2, in the context of a normal 24-2 result,[10] due to early macular changes in glaucoma.[11]

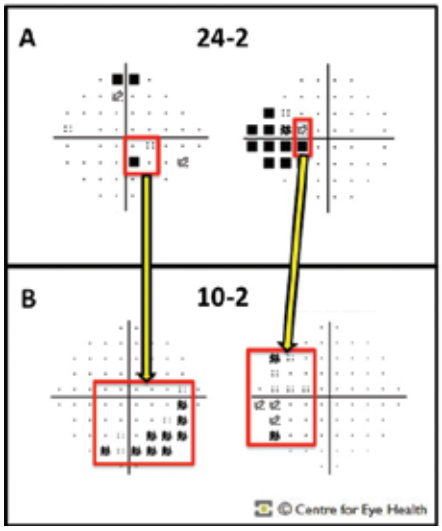
The ability of the 10-2 to detect defects has been shown not only in event analysis, but also trend analysis over time in cases of parafoveal scotomas.[12] A representative patient is shown in Figure 2, where a 30-2 visual field reveals classical a nasal step defect (A) but misses central depressions as close as three degrees away (B), and points flagged as abnormal centrally (C) are more precisely described with the 10-2 (D).

It is not always practical to perform both 24-2 or 30-2, and 10-2 on the same patient on the same day for reasons including patient fatigue, length of the consultation and work flow. Studies have suggested a high index of suspicion in cases where there are defects within the central 10 degrees found on the 24-2 pattern, that is, the central 12 points, even at relatively low levels of significance of $p < 5\%$, alongside an abnormal macular ganglion cell-inner plexiform layer (GCIPL) thickness.[13]

Another subgroup of patients that may benefit from 10-2 testing is those with normal- or low-tension glaucoma (NTG). Patients with NTG have been shown to have visual field loss that is closer to fixation in comparison to



▲ Figure 1. Schematic for HVFA 30-2 and 10-2 test patterns. Red circles denote points that are tested with both points. Blue circles show the boundary of the 10-degree test region of the 30-2 and 24-2, which miss the rest of the central points of the 10-2.



▲ Figure 2. Right and left eye 24-2 and 10-2 visual field results for a patient with NTG (truncated for clarity). The 10-2 visual field is able to more accurately map out the losses in central vision that appear suspicious in the 24-2 result.

high-tension glaucoma or exfoliative glaucoma.[14-16] While NTG may progress slower over time,[17] its propensity to affect the central visual field may make it more impactful on day-to-day life.[18,19] In these patients, a 10-2 visual field could be considered to monitor for such defects.

One limitation in 10-2 visual fields is that it cannot detect peripheral field defects that are common in glaucoma.[20] A 10-2 result cannot be directly compared to a 24-2 or 30-2 result, and therefore, performing one type of test at one visit essentially means a lack of a comparable result over time for the other.

There is also a lack of in-built statistical packages that facilitate objective measures of trend analysis over time with the 10-2. The structure-function relationship between the 10-2 and objective measures of retinal structure is also not well-established. More studies are required to overcome these limitations, but the future of visual field testing for glaucoma may be test patterns with differing densities across the visual field,[21] which respect the differences in spatiotemporal characteristics that facilitate increased sensitivity for disease detection, particularly in early stages.[22-25] Future testing patterns could incorporate points from both 30-2 and 10-2 test patterns into one.

Conclusion

The 10-2 pattern plays an important role in functional testing for glaucoma, not only in end-stage disease but also in its early stages and in cases where perimetric defects may affect the central points first, such as in NTG. Threats to central vision can severely affect quality of life in glaucoma patients, and these are best detected with 10-2 rather than the conventional 24-2 or 30-2. Due to its inability to detect peripheral defects, the 10-2 should be considered in conjunction with conventional 24-2 or 30-2 patterns for patients with glaucoma. ▲

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Pseudoexfoliation glaucoma

Hayley J McDonald

BMedSc(VisSc) MOpt

Graeme Jenkins Optometrists
Aldinga, SA

PSEUDOEXFOLIATION glaucoma (PXG) is an aggressive and sight-threatening condition that may be more difficult to manage than primary open angle glaucoma.

Clinical signs of pseudoexfoliation (PXF) that aid diagnosis include pseudoexfoliative deposits on the lens and iris, transillumination defects and iris pigment granule dispersion. These changes lead to accumulation of material in the trabecular meshwork, inhibiting aqueous outflow and causing the IOP to rise.[1]

CASE REPORT

The ocular health of a now 77-year-old Caucasian man (SG) had been examined over a 15-year period. No family history of glaucoma was present and there were no other systemic risk factors present with the exception of systemic steroid treatment.

The fluctuation in IOP control can be seen in Figure 1, noting that only the left eye has PXG with no pathology or clinical signs present in the right eye.

PXF material was first noted in the left eye in 2003, with IOP of OD 17 and OS 21 mmHg and cup/disc ratios 0.7 OU at the time. Perimetry testing showed no abnormalities.

The patient's IOP continued to rise steadily until 2007 when IOP reached OD 15 and OS 25 mmHg. The visual field remained unaffected but PXG was diagnosed at this time and OS latanoprost 0.005% nocte was initiated.

In 2009 he was diagnosed with polymyalgia rheumatica, a chronic inflammatory disorder that causes pain and stiffness in the hip, shoulder and other large joints.[2] Systemic steroids are the mainstay of treatment and are used to manage the symptoms of the disease, with a slowly tapering dose.

The steroid treatment in this case caused a profound rise in IOP (peak of 30 mmHg). To maintain control, brinzolamide 1% bid was prescribed in addition to the current prostaglandin analogue. The patient remains on low dose oral steroids to manage the symptoms of this systemic condition.

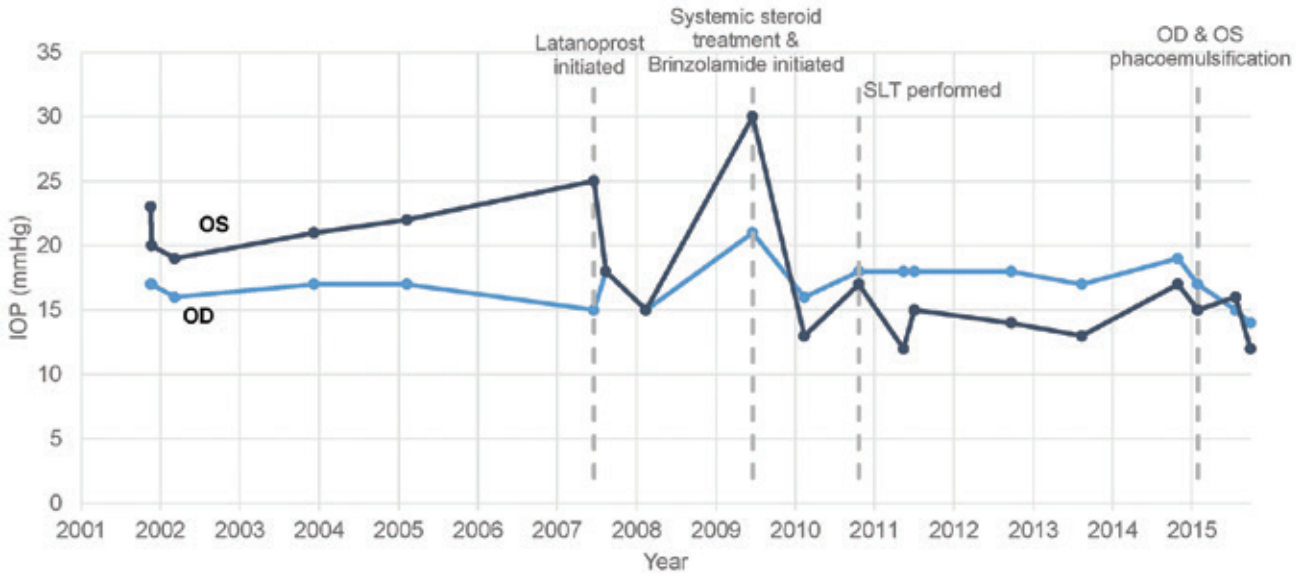
Further fluctuations in IOP can be observed in 2010 and 2015, when 180-degree SLT, and bilateral phacoemulsification and IOL insertion were performed respectively.

Discussion

Pseudoexfoliation

PXF is a systemic disorder, with deposits found around the blood vessels of connective tissue. Organs affected include the lung, liver, kidney and meninges; however, no causation of cerebrovascular and cardiovascular diseases or increase in mortality has been shown.[3]

The diagnosis of PXF is based on its characteristic clinical appearance: two annular zones of white deposits on the anterior lens capsule, separated by a clear zone where the iris contacts and rubs against the capsule.[4] Flaky white material and loose pigment cells can also be deposited throughout



▲ Figure 1. IOP response over time

- Primary open angle glaucoma (POAG): some Scandinavian regions consider PXG to be a form of POAG
- Pigment dispersion syndrome
- True lens exfoliation is a rare condition caused by a splitting in the lens capsule, due to exposure to high temperatures but not to increased IOP
- Chronic angle closure glaucoma
- Amyloidosis: a systemic condition caused by the accumulation of insoluble proteins; deposits may form on the lens, iris or trabecular meshwork, resembling pseudoexfoliation material

▲ Table 1. Differential diagnosis of pseudoexfoliation glaucoma[3-5]

- Dilation and thorough assessment of the anterior chamber are critical to diagnosing PXF
- Management of PXG is broadly similar to that of POAG; however, there may be a lesser therapeutic hypotensive response and the practitioner must retain a low threshold for altering treatment
- Latanoprost and travoprost monotherapy, and dorzolamide/timolol combination therapy have all been shown to achieve a 30 per cent IOP reduction in PXG
- SLT and trabeculectomy are excellent treatment options if medical therapy alone is not successful
- The presence of PXF increases the risk of cataract formation and also the risk of surgical complications; however, phacoemulsification can reduce IOP by 20 per cent

▲ Table 2. Pseudoexfoliation glaucoma key points

the anterior segment. Dilation is critical to diagnosis, with up to 79 per cent of PXF missed when examining undilated patients.[5] These characteristic signs of PXF are linked with reduced aqueous outflow via the trabecular meshwork.[1]

Other less visible changes to ocular structures are frequently linked with damage caused by matrix metalloproteinases mediated clearance of PXF material. These include poor response to mydriatic or miotics due to fibrotic and disorganised iris muscles, low endothelial cell density, and weakened zonules prone to subluxation or dislocation.[6]

In eyes with PXF, the risk of developing glaucomatous damage is 5.3 per cent and 15.4 per cent in five and 10 years, respectively.[6-8] In addition to a higher risk of developing glaucoma, eyes with PXF tend to have worse visual fields at the time of glaucoma diagnosis, require a greater number of treatment steps, have a more severe clinical course, and are more likely to require laser or surgical interventions.[9]

The prevalence of PXF within populations varies greatly, with the highest rates reported in Scandinavian countries.[10] PXF is present in 5.9 per cent of Indigenous Australians but there is a very low association with glaucoma.[11] The Blue Mountains Eye Study found a rate of 2.3 per cent among Caucasian Australians.[12]

Several genetic variants have been found that predispose a person to developing PXF. Most notable is the LOXL1 gene, involved in the crosslinking of collagen and elastin fibres in the extra-cellular matrix.[13] Carriers of the gene are 100 times more like to develop PXG.[14]

Medical therapy

As with other glaucoma conditions, the primary method of treatment is the reduction of IOP. The treatment approach for PXG is largely the same as that for POAG. A target pressure of 30 per cent reduction is generally considered appropriate, although somewhat harder to reach with a lower hypotensive response to topical medications.[4,15] The efficacy of a treatment regime over time and the target pressure must be constantly reevaluated due to the resistant and aggressive nature of PXG disease.

Topical hypotensive medication is the first line of therapy for PXG, just as it is for POAG. Monotherapy is recommended initially but a low threshold for changing or combining drops is required to ensure that the pressure is adequately controlled.

Statistically significant results, with a clinically significant 30 per cent IOP reduction, have been shown for latanoprost 0.005% and travoprost 0.004% monotherapy in addition to dorzolamide 2% + timolol 0.05% combination therapy.[16,17]

Dorzolamide 2% and timolol 0.5% monotherapies have been shown to be slightly less efficacious but still achieve a 20 per cent IOP reduction in PXG patients.[17]

Laser trabeculoplasty and glaucoma surgeries

Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) increase aqueous outflow through the trabecular meshwork. Both demonstrate a 20 to 30 per cent reduction in IOP, with no statistically significant difference between the two treatments in PXG.[18,19]

SLT has been shown to have equivalent IOP-lowering results in both PXG and POAG when used as either a first-line or secondary therapy.[18,20] Additionally, PXF does not appear to increase the risk of complications.[18-20]

The majority of literature on surgical interventions for PXG investigate trabeculectomy. When compared to POAG, PXG patients undergoing trabeculectomy had statistically lower IOP levels initially but were more likely to require additional medication, have treatment failure overall and progress to blindness.[9,21] Despite this, there is no apparent difference in complication rates following surgery.[9]

The indications for laser and surgical procedures are similar in PXG to those of POAG with broadly equivalent results.[15,21]

Cataract surgery

The presence of PXF greatly increases both the risk of cataract formation and the risk of surgical complications. However, phacoemulsification procedures have been shown to reduce IOP in eyes with PXF by 20 per cent (compared to a 3.6 per cent change in control eyes) in the year following, and maintain a lowered IOP for up to seven years.[8,22]

Continued page 32

Pseudoexfoliation glaucoma

From page 31

The mechanism that causes the reduction in IOP is unknown but has been hypothesised to be linked with aspiration of pseudoexfoliative material or wash-out effect on the trabecular meshwork.

Conclusion

Despite the more severe prognosis for PXG compared to POAG, it is a condition that is readily able to be managed by optometric clinicians. Thorough screening, timely diagnosis and continued monitoring are critical to ongoing patient care. ▲

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*Please note changes in Product Information.

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