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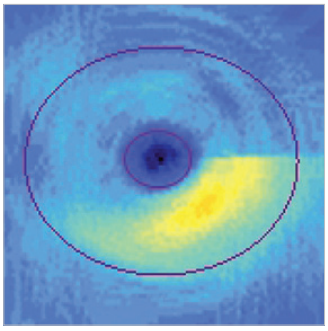

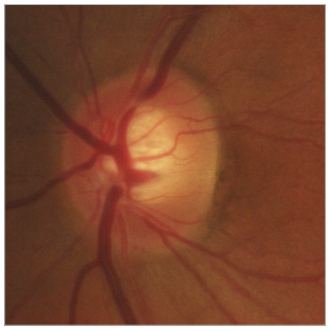

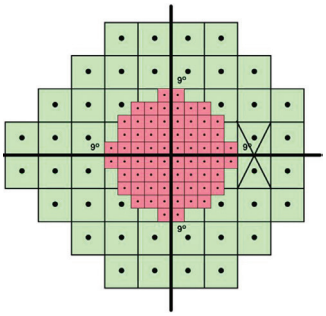

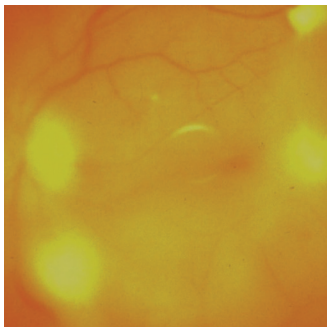

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Optometry AUSTRALIA

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Novartis draws on a long history of advancing science in the interest of better health. Today, we continue to build on this heritage, focusing on the unmet needs of patients worldwide. As most healthcare providers already know, many of these needs are the result of a growing, ageing population—a significant proportion of which will develop glaucoma.

Healthcare professionals will need to develop new strategies to meet the ever-increasing challenge of confronting glaucoma world-wide. The impact on the lives of those with glaucoma is hard to overstate. Effective diagnosis and treatment for at-risk patients is the key to preventing blindness from glaucoma.

Because it is often asymptomatic and undetected, optometrists play a crucial role in the identification, treatment and support of those with glaucoma. Early detection remains the vital first step in a sequence of measures that prevents the progression of nerve damage.

Novartis is proud to support *Pharma* in its ongoing efforts to inform the practicing optometrists of Australia and New Zealand of innovations in the growing areas of healthcare. Through our shared commitment, we hope to increase early detection and suitable treatment options that will ultimately yield the best patient outcomes.

Sleep apnoea and POAG

Continuous positive airways pressure treatment and elevated IOP

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Primary open angle glaucoma (POAG) is the most common form of glaucoma, accounting for more than 90 per cent of the cases.[1] An individual's chance of developing POAG increases based on several risk factors including: elevated intraocular pressures (IOP), central corneal thickness (CCT), age, family ocular history, gender, myopia, certain systemic diseases and ethnicity.[2-5]

Studies have confirmed a higher prevalence of POAG in people of African descent between the ages of 40–80 years old compared to any other ethnicity.[4,6-8] The Baltimore Eye Survey Report found African-Americans to be at a four times higher risk of developing POAG compared to Caucasians.[4]

IOP remains the only modifiable risk factor in preventing or delaying glaucoma progression.[9] As primary eye care providers, it is important to maintain a consistent management plan appropriate in achieving target IOP levels. With advances in technology, research, surgery and pharmacological agents, we are developing better means of providing care for our patients.

CASE REPORT

TM, a 48-year-old African-American male, was first referred in 2012 for a glaucoma diagnosis. He had a complex medical history of significant hearing loss and sleep dysfunction. He was currently taking Motrin and Flexeril for previous medical injuries. TM also has a family history of glaucoma.

On examination, unaided visual acuity was 6/6 in each eye. The patient had significant bilateral floppy eyelids, and pupils revealed a Marcus Gunn afferent defect in the left eye (LE). Anterior chamber angles were open (ciliary body 360 degree in each eye using gonioscopy). CCT measurements were within normal limits (RE 560µm, LE 552µm). IOP measurements at 5:00pm by Goldmann applanation tonometry were 20 mmHg in the RE and 23 mmHg in the LE. No pseudoexfoliation or cataract was observed in either eye. Dilated fundus examination (DFE) showed a healthy right optic nerve (C/D ratio 0.4) and abnormal left optic nerve with superior erosion, laminar pores and superior optic pit.

DFE findings were confirmed with optical coherence tomography (OCT) and automated perimetry using a Humphrey Field Analyzer (HFA). The right eye was normal in both tests. The left eye OCT confirmed a superior RNFL loss at the disc in the left eye and HFA found a significant inferior macular bundle defect (Figures 1 and 2).

Continued page 4

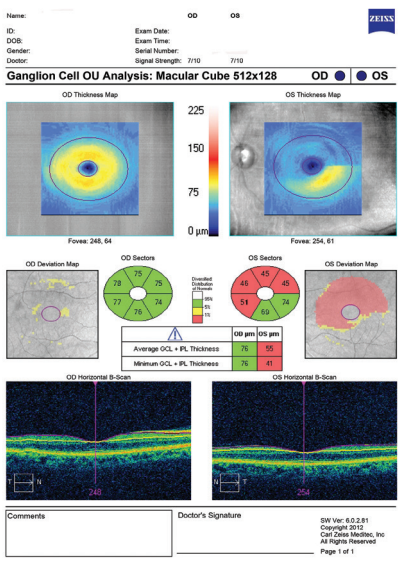

Figure 1. OCT confirms superior RNFL loss at the disc in the left eye. (Image: Dr J. James Thimons, OD, FAAO)

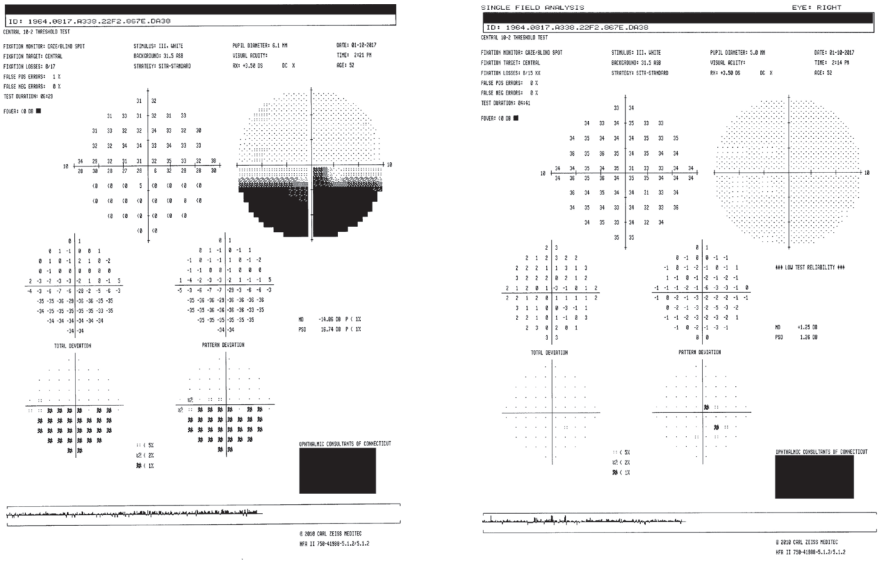

Figure 2. Humphrey Field Analyzer shows significant inferior macular bundle defect in left eye (Image: Dr J. James Thimons, OD, FAAO)

CPAP

From page 3

TM was placed on Alphagan P 1 drops twice a day and referred for a full blood workup to rule out the possibility of vascular insult. He was also referred to a sleep study for further investigation of suspected undiagnosed sleep apnoea.

FOLLOW-UP

TM was diagnosed in late 2012 with severe sleep apnoea during REM sleep with oxygen desaturation. He was recommended to commence Continuous Positive Airways Pressure (CPAP) treatment and pursue weight loss to achieve an ideal body weight. TM was on a three-month review schedule for one year at our clinic to closely monitor his IOP fluctuations and evaluate the efficacy of monotherapy drops via fundus, IOP, OCT and VF tests.

In 2013 TM's IOP was unstable and fluctuated at each of his six-month reviews. In an effort to lower his IOP, the therapeutic drops were changed three times trialling Travatan, Asopt and Combigan, respectively. All of which proved to be insufficient in maintaining a low target IOP.

It wasn't until 2014 that TM was prescribed Simbrinza suspension (three a day) that his IOP dropped within target range and maintained stable pressures. To this day, he maintains a healthy target IOP and is still undergoing treatment for his severe sleep apnoea.

DISCUSSION

Sleep apnoea is a common chronic disorder and requires life-long care. It has been found to be more prevalent in males than females.[10] It has also been documented previously to be associated with ocular diseases such as glaucoma, non-arteritic anterior ischaemic optic neuropathy (NAAION), bilateral disc oedema, floppy eyelid syndrome, blepharitis, ptosis, papillary conjunctivitis, filamentary keratitis, retinal vascular tortuosity and central serous chorioretinopathy.[11] Previous studies have shown a strong implication of sleep apnoea with NAAION, thus it is important to consider and rule out suspicions of NAAION as a differential diagnosis to glaucoma.[12,13]

In a report, patients with sleep apnoea and currently undergoing CPAP have demonstrated an associated increase in IOP, especially at night.[14] The mechanism of CPAP on raised IOP is not well understood, but theories hypothesise an elevated CPAP intrathoracic pressure may cause a rise in venous circulation pressure, thus reducing the outflow of aqueous through the episcleral veins.[14] Normally, aqueous humour production at night decreases, but there is an increase in episcleral venous pressure due to lying in the supine position.[15] They found a significant drop in IOP was observed when CPAP was ceased for 30 minutes. This is important as it was found that diurnal IOP variation is linked to significant visual field loss. It has been reported that there is a 30 per cent chance of visual field loss with every 1 mmHg increase over a five-year increment.[16]

Monotherapy is not always sufficient in managing and maintaining a target IOP and/or preventing glaucoma progression. According to the Ocular Hypertensive Treatment Study (OHTS), 40 per cent of patients require a second ocular hypotensive eye drop in order to achieve a targeted reduction of 20 per cent.[17] Benefits of fixed-drop combination therapies include increased likelihood of patient compliance, reduced exposure to preservatives and less chances of sequential medication washout.[11] However, until recently, beta-blockers (particularly timolol 0.5%) were the most commonly-used agent in fixed-combination eye drops. Due to local allergy or systemic side effects associated with use of beta-blockers, these drugs have been contraindicated in many patients with cardiac issues. Not recommended for first line treatment, fixed-combination eye drops are mainly used if a prostaglandin analogue (PGA) or other agent is unsuccessful in lowering IOP, and can be useful additives in achieving target IOP.

Simbrinza suspension is an effective fixed-combination eye drop that is also the only fixed-combination agent that does not contain timolol 0.5%. It comprises of brinzolamide 1% and brimonidine tartrate 0.2%. Brimonidine is a selective alpha-2-adrenergic agonist that acutely reduces aqueous production and increases uveoscleral outflow during the day. On the other hand, its nocturnal profile was not sufficient in maintaining low IOP, thus a carbonic anhydrase inhibitor (CAI) such as Brinzolamide is a great additive in controlling nocturnal IOP fluctuations.[18]

Studies were conducted in order to evaluate the efficacy of lowering IOP using brinzolamide/brimonidine fixed-combination (BBFC) therapy. The results found that this combination was significantly superior in its IOP-lowering activity 20–35 per cent from baseline and had a consistent safety profile compared to its individual components.[19-22]

In 2016, a six-week, randomised, double-masked, study investigated the additive effect of Simbrinza as an adjunct to PGA. They found at two hours post-instillation, BBFC reduced a mean IOP of 7.1 mmHg (31 per cent) from PGA baseline.[23] A potential limitation to this study was that the degree of reduced IOP was evaluated based upon the eye with the highest baseline IOP. Future studies with longer duration may provide supplementary information regarding the efficacy of adjunct therapy of BBFC+PGA.

As with all therapeutic management, proper precautions and contraindications should be exercised before prescribing Simbrinza to your patient.

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Monitoring glaucoma patients

Did a patient's past drug use lead to current troubles?

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CASE REPORT

A 58-year-old Caucasian male presented complaining of progressively decreased, dim, tunnel-like vision and colour abnormalities in the right eye. He had noticed the symptoms worsening over the previous six months. Past ocular history revealed that a year prior to the visit, he had had his first eye examination and was diagnosed with glaucoma in both eyes. He reported the intraocular pressure (IOP) at the time of diagnosis was 25 mmHg in the right eye. He had been using Travatan Z every bedtime in both eyes since the diagnosis and was started on Combigan twice a day in the right eye about a month prior to his current visit.

The patient admitted to poor compliance with topical medications. He denied any history of trauma or ophthalmic surgery. The patient's medical history revealed a Mallory-Weiss tear that had been surgically repaired in 1985. He also reported taking steroids for bodybuilding for about a year more than 20 years ago. The patient was taking 20 mg of the oral medication Omeprazole every day for high cholesterol. Family history was positive for glaucoma of unknown type in the patient's grandmother. It was not known whether she had gone blind.

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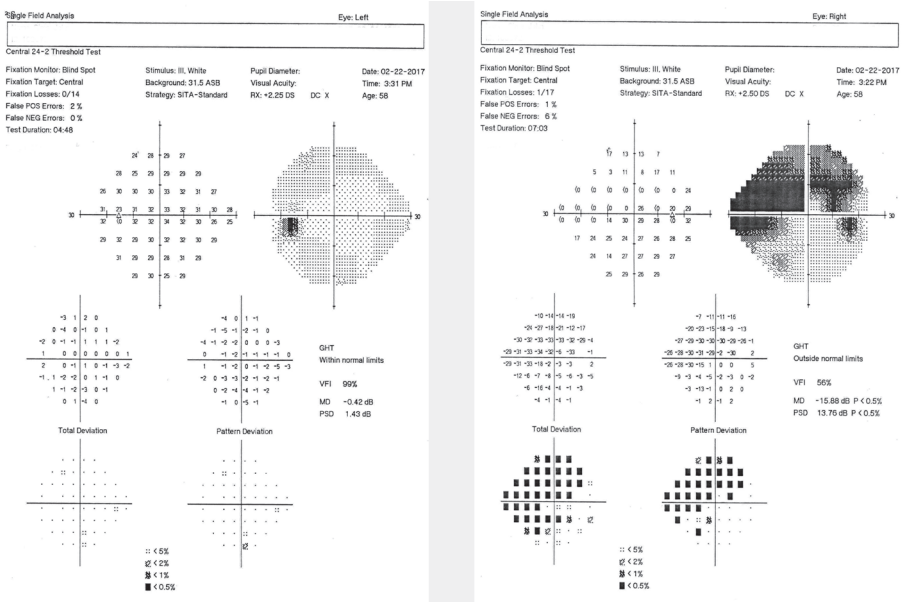


Figure 1. Visual field test revealing superior and inferior visual field defects in the right eye.

Glaucoma patients

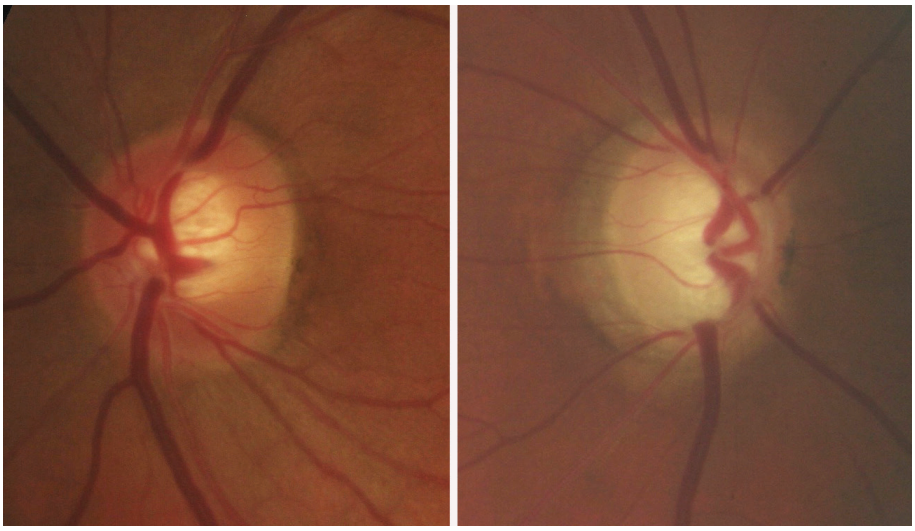
From page 5

The patient denied suffering from allergies to any medications. He denied smoking, stated he occasionally drank beer, and reported consuming two cups of coffee per day. The patient's mood and affect were normal and he was oriented to person, place and time. The patient's blood pressure was measured at 153/90 at 2:13 pm.

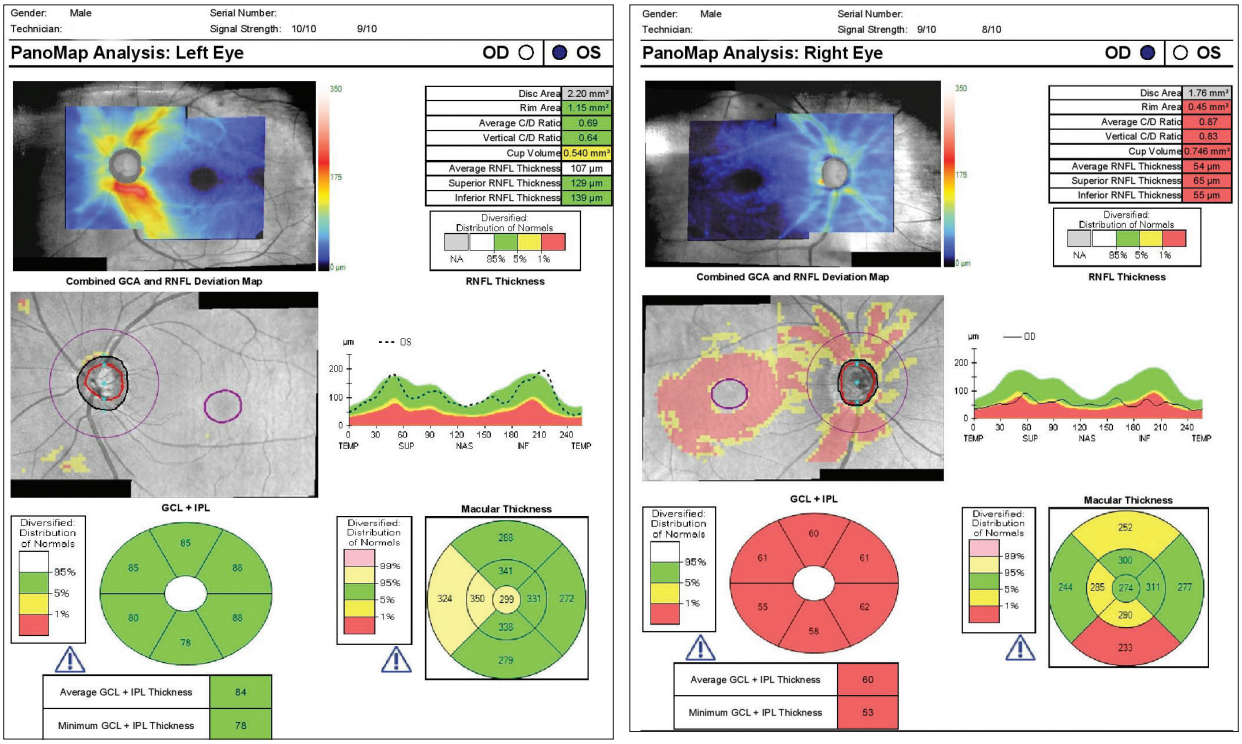
Uncorrected distance visual acuities were 6/6^{-2} in the right eye and 6/6 in the left eye. Pupils were equal, round and reactive to light without an afferent pupillary defect in either eye. Ocular motility was normal in both eyes. Colour vision testing revealed a blue-yellow defect in the right eye, but was normal in the left eye. Humphrey Field Analyzer was reliable in both eyes and revealed a dense superior arcuate scotoma and inferior nasal field defect in the right eye (Figure 1).

Slitlamp examination of the anterior segment revealed mild dermatochalasis of both upper eyelids. There was no proptosis observed in either eye. Meibomian gland capping was observed in both eyes with quiet lid margins. Conjunctiva exhibited mild hyperaemia in both eyes and there was an early pinguecula present temporally in the right eye. Cornea was clear in both eyes; neither keratic precipitates nor Krukenberg's spindles were observed in either eye. Anterior chamber was deep and quiet in both eyes. Iris was flat and intact, brown and without any transillumination defects in either eye. Lenses were clear in both eyes and there was no pseudoexfoliation of the lens capsule in either eye. IOP was 19 mmHg in both eyes measured by applanation tonometry at 2:50 pm.

Gonioscopy revealed ciliary body band



Figures 2A and 2B. Colour optic nerve photos demonstrating cupping in the right eye (2B). Note the advanced neuroretinal rim tissue thinning in the inferior, infero-temporal and temporal regions as part of temporal unfolding in the right eye. Note the temporal loss of RPE in the beta zone and mild hypo- and hyper-pigmentation changes in alpha zone of the right eye. Bayoneting of the vein can be observed at the inferior disc edge of the right eye.



Figures 3A and 3B. OCT demonstrating RNFL and GCL loss in the right eye

360 degrees in both eyes with regular approach and 1+ trabecular meshwork pigmentation in both eyes. There was no peripheral anterior synechiae, no recession, no neovascularisation and no blood present in Schlemm's canal in either eye. Dilated retinal fundus examination revealed a clear vitreous in both eyes. The optic nerve was pink and distinct in both eyes with advanced cupping and extensive peripapillary atrophy observed in the right eye (Figures 2A and 2B).

The cup-to-disc ratio was estimated to be 0.90/0.95 in the right eye and 0.50/0.55 in the left eye. Disc haemorrhages were not observed in either eye. Maculae were flat and dry with few small drusen in the foveal region of both eyes. Vessels were normal in both eyes. Retinal periphery was flat and intact 360 degrees in both eyes.

Central corneal thickness was measured at 601 µm in the right eye and 605 µm in the left. Optical coherence tomography (OCT) was reliable and revealed retinal nerve fibre layer (RNFL) thinning and retinal ganglion cell (RGC) loss in the right eye (Figures 3A and 3B).

We concurred with the patient's previous diagnosis of primary open angle glaucoma in the right eye. Given the patient's age, good systemic health and advanced field loss in the right eye, we set the target IOP in the right eye in the low teens. We advised the patient to continue instilling Combigan twice a day in the right eye and Travatan Z in both eyes at bedtime and to start Dorzolamide twice a day in the right eye. We discussed our findings with the patient, stressing the progressive nature of glaucoma and the importance of his compliance with the prescribed treatment and regular follow-up examinations. In light of the patient's previous struggles with compliance, we referred him to a glaucoma specialist for continuation of care.

DISCUSSION

Glaucoma is a heterogeneous group of diseases with multiple primary and secondary factors that lead to irreversible vision loss from the dysfunction and death of retinal ganglion cells (RGC).[1] Elevated IOP is considered to be one of the initial causes of insult in glaucomatous atrophy.[1] Prolonged treatment with corticosteroids is known to cause significant increase in IOP, which may lead to open angle glaucoma.[2] It is believed that corticosteroid use increases outflow resistance of the aqueous by inhibiting the degradation of extracellular matrix material in the trabecular meshwork.[3]

Early detection and treatment of glaucoma leads to slower progression;[4] however, our patient's history revealed he used steroids for bodybuilding. These substances belong to the androgenic-anabolic (AAS) derivatives group.[5] It is unlikely they contributed to the development of glaucoma in the right eye. While AAS misuse has been associated with disturbance of endocrine, immune, cardiovascular, urogenital and psychiatric function,[6] the literature does not reveal any reports of adverse ophthalmic side-effects. On the contrary, studies have shown that women suffering from primary and secondary Sjögren's syndrome are androgen-deficient.[7] There is evidence that the androgen deficiency may lead to meibomian gland dysfunction, altered lipid profiles in meibomian gland secretions, tear film instability, and evaporative dry eye.[7,8] Androgen receptor modulators are being studied for treatment of dry eye disease.[9]

	Corticosteroids	Androgenic-anabolic steroids
What are they?	Closely related to cortisol, a hormone which is naturally produced in the outer layer of the adrenal glands	Synthetic derivatives of the male hormone testosterone
How do they function?	Act on the immune system producing anti-inflammatory, immunosuppressive and anti-mitogenic effects by stimulating production of lipocortin which inhibits the activity of phospholipase A2	Promote the growth of skeletal muscle (anabolic effect) Promote the development of male sexual characteristics (androgenic effects)
When are they prescribed?	Treatment of autoimmune and inflammatory conditions (vasculitis, rheumatoid arthritis, lupus, gout, myositis, Sjögren's syndrome)	Treatment of conditions that occur due to testosterone deficiency (delayed puberty, certain types of impotence)
Systemic side-effects[5,6]	• reduction in bone formation and increase bone resorption • reduction in serum sex hormone levels • hypercalciuria • myopathy • increased serum lipids • hyperglycaemia • hypertension • gastritis • peptic ulceration • psychiatric disorders	• increase in sexual drive • acne vulgaris • increase in body hair • aggressive behavior • mood disturbances • hypertension • lower serum HDL, HDL2 and HDL3 cholesterol levels
Ocular side-effects[2,7]	• cataracts • increased IOP • central serous chorioretinopathy • papilloedema	Improvement in lipid production by the meibomian glands

Table 1. Comparison of corticosteroids and androgenic-anabolic and their common side-effects

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Selective laser trabeculoplasty for

SLT has emerged as a viable first-line treatment option

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Treatment of open angle glaucoma (OAG) typically follows the standard procedure of initial therapy with topical intraocular pressure (IOP) lowering medications, followed by laser surgery including selective laser trabeculoplasty (SLT) and finally, incisional surgery if other measures fail.[1-3]

Surgical procedures are classically reserved for patients who have had disease progression with maximally tolerated medication use.[2,3] With widespread use of ancillary diagnostic technology, earlier diagnosis of open angle glaucoma often involves initiation of medical treatment at a younger age.[4] As patients require lifelong therapy, earlier treatment with topical therapy increases the potential for medication failure and intolerable side-effects during a lifetime.[2]

With known patient challenges with adherence to topical ocular medications, alternative options for first-line therapy including SLT, which does not rely on patient adherence, have been evaluated.[1,2,5-7] SLT has gained notoriety as a viable first-line therapy in patients with OAG.

Challenges with topical medications

Although generally safe and effective, medical treatment of elevated intraocular pressure has significant patient barriers to success, such as patient adherence with prescribed treatment.[5,8] As a chronic asymptomatic disease, especially in early and moderate cases, the goal of treatment of open angle glaucoma is not to improve vision, but rather to slow or prevent vision loss.[2] With up to half of patients not adherent with glaucoma medications 75 per cent of the time, adherence is a major barrier to treatment success.[8]

Cost of medication, forgetfulness, hand tremor, limited understanding of the permanently blinding nature of the disease and the side-effect profile of topical medications are also barriers to adherence with topical medication use.[5,8] Ocular side-effects of medical treatment range from mild to intolerable and include redness, ocular surface disease and cosmetic changes including pseudo-enophthalmos and periorbital darkening.[5,8] Systemic side-effects range from mild to life threatening and may significantly detract from the patient's quality of life.[5,8]

SLT indications

SLT is used to lower IOP in the treatment of OAG and ocular hypertension including primary open angle glaucoma (POAG), pigmentary glaucoma, pseudo-exfoliative glaucoma, steroid-induced glaucoma, and retinal detachment repair requiring silicone oil.[2,3]

Treatment of OAG with SLT decreases necessity of adherence with medications and may prolong the need of further intervention including additional medications or incisional surgery.[1-3] SLT may have a positive impact on quality of life in patients with glaucoma.[9] It is an alternative treatment to be considered for pregnant patients, which can be performed in all three trimesters, and may be used as first-line therapy or to reduce the number of medications during pregnancy.[2,4]

How SLT works

SLT utilises a Q-switched, frequency-doubled, 532 nm Nd:YAG laser directed towards the trabecular meshwork.[2,10] Although smaller areas, (180 degrees) of trabecular meshwork may be treated, the current trend is to treat 360 degrees of trabecular meshwork unless significant risk factors for complications such as a heavily pigmented trabecular meshwork exist.[2,6,7]

The mechanism of action by which SLT lowers IOP is not completely understood. It is generally accepted that laser energy selectively targets and stimulates melanocytes in the trabecular meshwork, which results in recruitment of macrophages and monocytes from the spleen to the trabecular meshwork.

These monocytes and macrophages phagocytose trabecular meshwork debris, ultimately lead to reduced resistance to aqueous outflow.[2,3,6,11] The expression of inflammatory cytokines may lead to remodeling of the juxtacanalicular extracellular matrix, reducing aqueous outflow resistance through a cellular mechanism.[12]

A precursor to SLT, argon laser trabeculoplasty (ALT) was the first laser procedure evaluated as a first-line treatment in OAG.[13] ALT lowers IOP through thermal stimulation and scarring of the trabecular meshwork, which results in mechanical opening and increased outflow of areas adjacent to treated trabecular meshwork.[14]

The Glaucoma Laser Trial (GLT) evaluated the efficacy of ALT compared to topical medications and determined that ALT was at least as effective as topical medications in lowering IOP; however, this study was performed prior to the availability of prostaglandins.[13] As a result of the permanent scarring of the trabecular meshwork, repeat treatment is not considered to be effective.[3,6]

In contrast to ALT, SLT uses a very short pulse duration, which does not cause permanent destruction or scarring of surrounding tissues.[2,3] SLT uses lower energy levels in

open angle glaucoma

shorter pulses over a larger area and is comparable to ALT in terms of efficacy and safety.[14,15] Less pain and inflammation are often described following SLT compared to ALT, which is likely to be due to the less than one per cent total energy applied with SLT.[16]

Success of SLT

SLT is effective in lowering IOP but not all patients will respond to treatment.[1-3,10] Response rate ranges from 40 per cent to 82 per cent, depending on the definition of success.[2,3,10,17] The IOP-lowering response of one eye can be used to predict whether the fellow eye will have a positive response to treatment.[18] SLT has also been shown to be effective in dampening IOP fluctuations and achieving IOP stability during a 24-hour period when the trabecular meshwork is treated 360 degrees.[17,19] However, travoprost is more effective in IOP dampening during daytime hours than SLT.[19]

SLT efficacy decreases with time.[2,3] Treatment typically lasts between one and five years with an average of approximately two years.[1,2,6,7,15] Due to the lack of permanent trabecular meshwork damage following primary SLT, the procedure may be repeated.[6,20] Repeat SLT results in comparable levels of IOP-lowering following initial treatment. (That is: repeat SLT can re-establish the IOP achieved after primary treatment).[6,15,20]

There has been no correlation of IOP-lowering success with SLT with age or sex.[21] Concurrent treatment with IOP lowering medications does not impact the efficacy of SLT.[22] The most widely-accepted factor influencing a greater IOP-lowering effect is a higher pre-treatment IOP.[21] However, SLT may be used successfully in patients with open angle glaucoma with statistically normal pressures, often termed normal tension glaucoma (NTG).[21] Although SLT targets melanocytes, the amount of trabecular meshwork pigmentation and type of OAG have not been shown to predict IOP-lowering response.[21]

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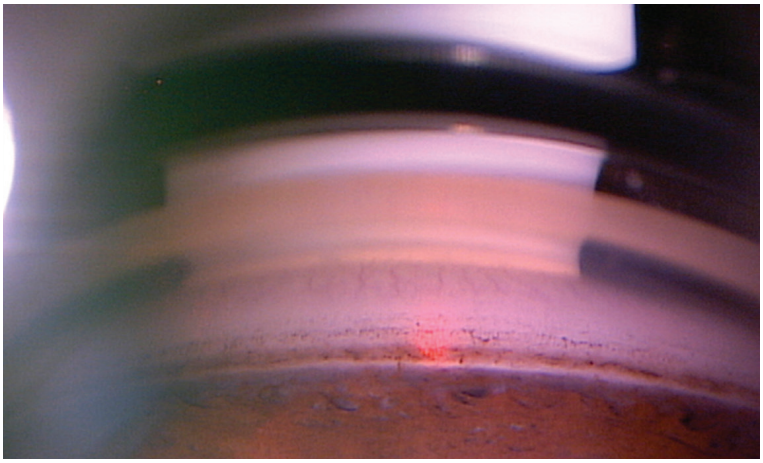

Figure 1. Aiming helium-neon (HeNe) laser beam of the SLT device focused on the trabecular meshwork Image: Dr Neal Whittle

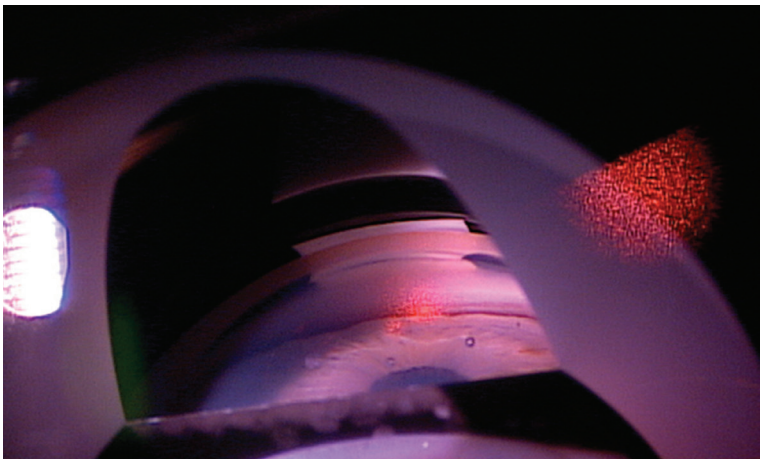

Figure 2. HeNe laser beam focused on lightly pigmented trabecular meshwork Image: Dr Neal Whittle

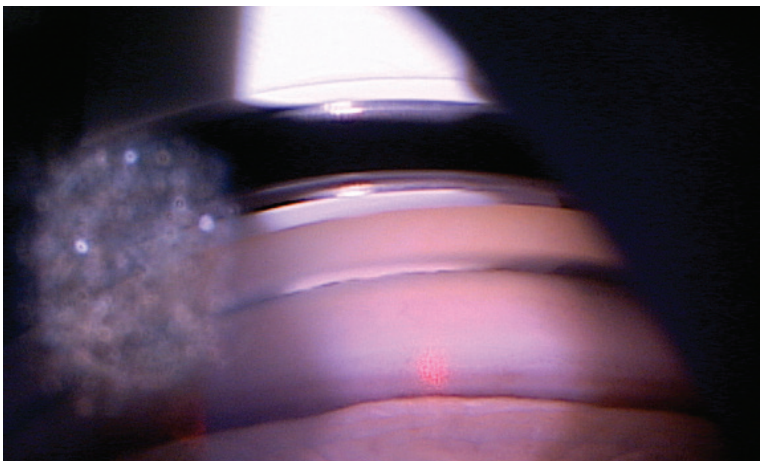

Figure 3. HeNe laser beam focused on the trabecular meshwork in a patient with minimal pigmentation Image: Dr Neal Whittle

SLT

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SLT as a first line treatment

Classically, laser and incisional surgery are reserved for cases of inadequate IOP with maximally-tolerated topical therapy. SLT with treatment 360 degrees has been shown to be as effective as a topical prostaglandin analogue in lowering IOP in patients with OAG as a first line treatment.[1,7,15]

Complications of SLT

Side-effects experienced after SLT are generally mild and temporary, and can be managed with topical medical measures.[10,15] The most common side-effects after SLT are transient IOP elevation, anterior chamber reaction, redness and discomfort.[10,15,23,24]

Post-operative inflammation typically occurs two-to-three days following SLT and resolves in about five days without treatment.[23] The use of post-operative steroid or nonsteroidal anti-inflammatory drugs (NSAIDs) is generally not recommended in patients who have undergone SLT, due to its presumed mechanism of action, which relies on recruitment of inflammatory cells.[23] However, the use of post-operative NSAIDs or steroid topical medication has not been shown to reduce the efficacy of treatment following SLT.[23]

Patients with heavily-pigmented angles, like those with pigmentary glaucoma, as well as patients with previous compromise to the trabecular meshwork, like those who have undergone previous ALT, or patients with traumatic trabecular meshwork damage are at a greater risk of IOP elevation following the procedure.[24] In these patients, prophylactic IOP-lowering medication, such as apraclonidine or brimonidine, are typically instilled to dampen the IOP rise after treatment.[24]

Less common side-effects after SLT include cystoid macular oedema and corneal haze.15 Those who may be at increased risk of cystoid macular oedema are those patients with pre-existing pseudophakic macular oedema, diabetic retinopathy or history of retinal vein occlusion.15 Transient corneal haze and temporary decreased endothelial cell count may occur hours after the procedure with full resolution within one month without treatment.[2]

Bottom line

SLT is safe and effective, with generally transient mild side-effects. Its efficacy is comparable to a prostaglandin analogue for about a two-year period as a first-line therapy and once treatment wears off, SLT may be repeated. Many glaucoma patients require more than one medication to control IOP during their lifetime.

Although SLT is not a permanent cure for the disease, it may allow for the reduction in the number of topical medications or delay the addition of IOP-lowering medication. Using SLT as a first-line therapy in the treatment of OAG eliminates patient medication side-effects and drug costs while averting the dilemma of patient adherence required for treatment success. Despite a growing body of supportive evidence that establishes the efficacy and safety of SLT as a first-line treatment in open angle glaucoma, its use in clinical practice remains limited.

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An overview of optical coherence tomography angiography (OCT-A)

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Optical coherence tomography angiography (OCT-A) is an emerging technology that provides a detailed vascular map of the posterior pole through decorrelation techniques which detect changes between consecutive b-scans taken at the same cross-section due to moving erythrocytes (motion contrast).[1]

OCT-A is a non-invasive imaging tool that has many potential applications in posterior segment disease as it provides structural vascular information as well as functional blood flow information for both the retinal and choroidal vasculatures without the use of dye. Different segmentations can be used to isolate different layers, some of which include the vitreo-retinal interface, the superficial retinal layers, the deep retinal layers, the choriocapillaris and the choroid. Over the past few years, numerous applications have emerged using OCT-A, some of which are discussed in this article.

Diabetic retinopathy

Diabetic retinopathy is a retinal microangiopathy characterised by microaneurysms (the leakage of which leads to diabetic macular oedema), as well as capillary non-perfusion and ischaemia within the retina (which leads to retinal neovascularisation). Using OCT-A, microaneurysms can be visualised as demarcated saccular or fusiform shapes of focally dilated capillary vessels in the inner retina.[2,3]

Even though the sensitivity of OCT-A in detecting microaneurysms may be lower than that of fluorescein angiography, OCT-A has the advantage of allowing their three-dimensional localisation within the inner retinal layers.[4,5] Retinal neovascularisation on the other hand, appears as a hyper-flow signal above the internal limiting membrane and can be visualised using segmentation of the vitreo-retinal interface (VRI).

As microaneurysms and retinal neovascularisation can sometimes be indistinguishable on fluorescein angiography, OCT-A is an invaluable method for differential diagnosis and respective management.[6] Capillary non-perfusion can be seen as areas of lack of flow signal, commonly referred to as capillary drop-out. When it affects the foveal area, it leads to an enlarged and remodelled foveal avascular zone (FAZ), a characteristic of foveal ischaemia that leads to decreased vision in its moderate-to-advanced stages. The presence of capillary drop-out and enlarged FAZ are predictors of diabetic retinopathy progression.[7]

Choroidal neovascular membranes (CNVMs) are characterised by the presence of abnormal blood vessels that originate from the choroid and may be seen in various conditions such as wet age-related macular degeneration (AMD), high myopia and central serous chorioretinopathy (CSCR). OCT-A features associated with CNVMs may include patterns described as small filamentous vessels forming anastomoses (lacy wheel or sea fan), as well as vessels associated with a central trunk (Medusa).[8,9]

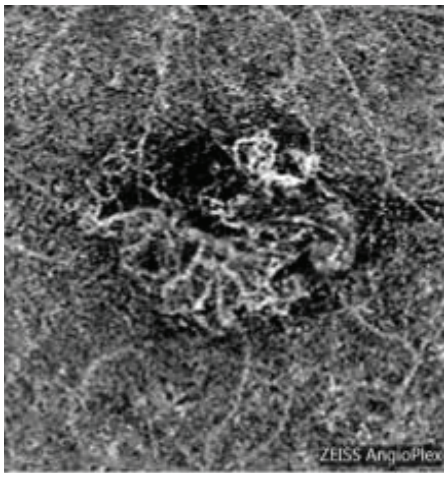

Figure 1. Visualisation of a CNVM demonstrating hyper-flow in a 'sea fan' pattern using a segmentation of the choroid

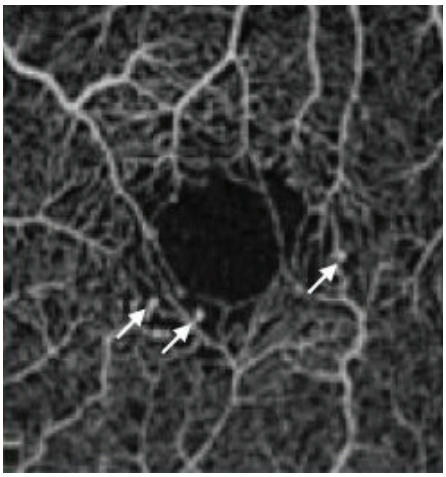

Figure 2. Visualisation of microaneurysms (arrows) as well as a remodelled and enlarged FAZ in a patient with diabetic retinopathy

OCT-A vs FA

In contrast to fluorescein angiography which remains the gold standard in detecting and classifying CNVMs, OCT-A allows a three-dimensional visualisation of the fibrovascular network, including their multi-planar location and morphology, which can be monitored to assess more accurate responsiveness to treatment. Its sensitivity may range between 50 per cent and 100 per cent depending on the underlying aetiology of the CNVM.[8,10-13] For example, the presence of an overlying massive haemorrhage, which is more likely to occur in wet AMD, limits the visualisation of a

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OCT-A

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CNVM by blocking the signal.[9,12] In addition, OCT-A will detect a blood vessel only if its blood flow speed is higher than a minimum threshold, or slowest detectable flow, which is determined by the time between two sequential OCT b-scans.[14] CNVMs may show areas of reduced blood flow, potentially making them completely or partially undetectable on OCT-A.

Polypoidal choroidal vasculopathy, an essential differential diagnosis of AMD, is characterised by the presence of polypoidal lesions with or without branching network on indocyanine green angiography, which remains the gold standard in its diagnosis. However, OCT-A may be useful in identifying these structures without the need of a dye. Using segmentation of the choriocapillaris, the branching vascular network will appear as a hyper-flow lesion whereas the polypoidal lesion, which, in comparison, is likely to have unusual blood flow, will demonstrate lower flow, and will frequently appear as a hypo-flow round structure.[15]

Glaucoma

Numerous studies have used OCT-A to determine characteristics of optic neuropathies including glaucoma. It has been shown that there is decreased peripapillary capillary density in glaucomatous eyes and that this decrease correlates well with the severity of glaucoma, as well as with ganglion cell complex thickness, retinal nerve fibre layer thickness and visual fields, in terms of both location and extent.[16-18]

OCT-A is therefore a promising tool in detecting and monitoring progression in glaucoma. In eyes with optic atrophy due to chronic optic neuropathies, decreased peripapillary capillary density is seen corresponding to the region with retinal nerve fibre layer thinning.[19,20] The characterisation of various optic neuropathies using OCT-A could provide a tool that would facilitate their differential diagnosis, allowing for their prompt and accurate management.

Limitations

Even though OCT-A is a powerful tool, it is not without limitations. The main limitation of OCT-A is the potential presence of artifacts. Motion artifacts occur due to the principle that the detection of movement in the back of the eye is translated as blood flow. Therefore, patient movements or fixation losses result in the false appearance of areas of flow signal. Conversely, blinking blocks light from reaching the back of the eye, which translates into no movement and therefore into areas of absence of flow signal on the OCT angiogram, leading to the false appearance of capillary drop-out.

Shadow artifacts, or 'ghost images' occur due to moving shadows created by moving erythrocytes in more superficial vessels, giving the false appearance of blood flow in deeper layers. In addition, although erythrocytes are hypothetically the only moving structures in the back of the eye, white noise artifacts from moving non-vascular structures can occur, especially if the patient is moving.[14] Finally, obscuration from structures present in more superficial layers such as haemorrhages blocks light from getting to deeper layers, which results in areas of absence of flow signal on the OCT angiogram.

OCT-A is a non-invasive tool that allows for the visualisation of retinal and choroidal vasculature, and is invaluable in the diagnosis and management of various chorioretinal diseases. It has also enhanced our understanding of the pathophysiology of many posterior segment diseases including optic neuropathies, which opens doors to more indispensable clinical applications in the future.

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GUIDE

VISUAL FIELD CHAIR-SIDE REFERENCE GUIDE PAGES 14-15

Visual Fields: past present and future

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Performing visual fields (VFs) is no easy task, not just for the patient, but also for clinicians and technicians. Although it is an essential component of the ophthalmic examination, there has been a recent paradigm shift towards increased reliance upon automated technologies such as optical coherence tomography (OCT).[1] In contrast to the quick, painless, repeatable and objective measurements obtained using the OCT,[2] VF testing is a long, tiring and variable process that relies on the subjective responses of an inexperienced observer.[2] Learning effects are known to be present with VF testing, and defects need to be repeatable for a conclusive diagnosis.[3,4]

The question then is: why do we continue to assess VFs in clinical practice, given its numerous disadvantages?

Past – Standard automated perimetry (SAP) as the clinical standard of VF assessment

Previous papers have presented an overview of the development of perimetry.[5] Methods for measuring the VF have evolved from qualitative techniques such as the tangent screen,[6] to instruments that could quantify VF sensitivity.[7,8] The age of supercomputers boosted the potential for quicker quantitative measurements, and many fast adaptive algorithms have since usurped the traditional staircase method for determining sensitivity across the VF.[9] SAP has subsequently become the clinical standard for quantitative VF assessment since its introduction in the 1970s.[7,8,10]

SAP uses an achromatic stimulus of fixed size (Goldmann size III) briefly presented for a constant duration (200 ms) upon an achromatically lit background (10 cd.m^{-2}). These parameters have become the clinical standard in both practice and large-scale clinical trials.[11-14] Common instruments that have been developed for SAP testing include the Humphrey Field Analyzer (HFA), the Octopus perimeter and the Medmont Automated Perimeter.

Present – Using SAP in current clinical practice

Visual field results analysis

SAP printouts differ between instruments, however, several features are consistent to all, and careful examination of these features is important for accurate interpretation (Figure 1). Reporting of

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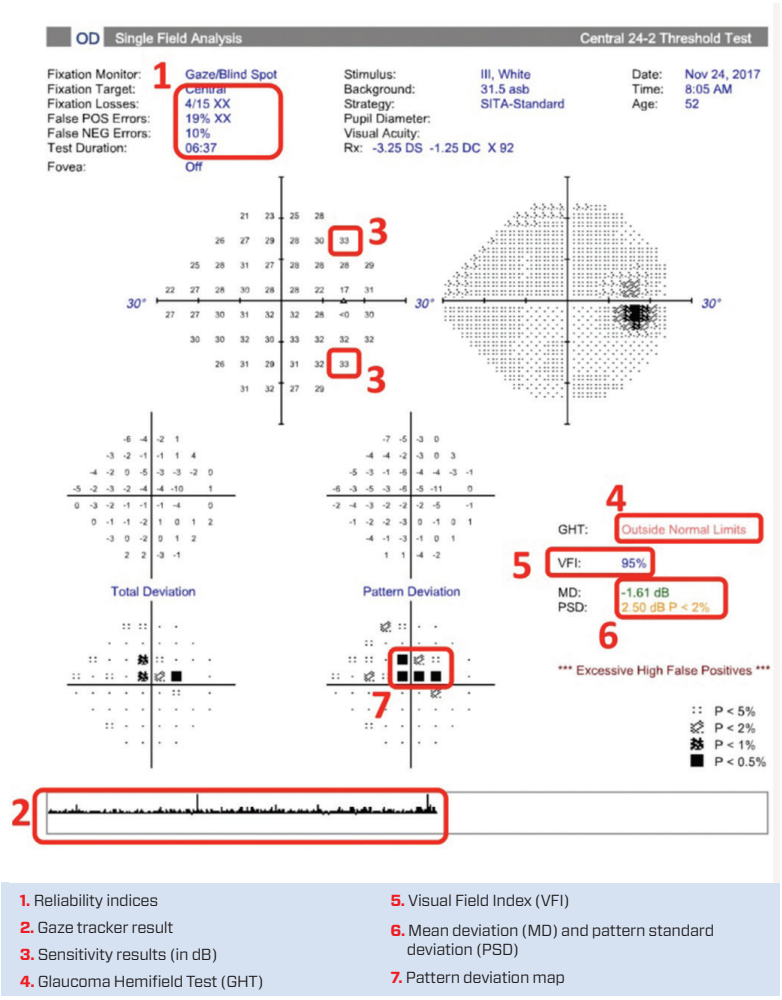


1. Reliability indices
2. Gaze tracker result
3. Sensitivity results (in dB)
4. Glaucoma Hemifield Test (GHT)
5. Visual Field Index (VFI)
6. Mean deviation (MD) and pattern standard deviation (PSD)
7. Pattern deviation map

Figure 1. Analysis of a typical Humphrey Field Analyzer printout. These or similar indices may also be available on different instruments. To understand the different maps and indices reported by the instrument, a careful reading of the manufacturer's manual is strongly recommended. There may be variability in the meaning of the automated analyses.

Chair-side Reference: Visual Field

Visual field examination, in particular, standard automated perimetry, remains the most commonly-utilised functional assessment. Many ocular and neurological diseases and conditions are known to exhibit distinct visual field loss patterns, and thus, visual field testing may therefore assist with a differential diagnosis.

The ability to map the depth, extent and change of visual field defects should be considered in clinical management decisions.

The more common types of visual field defects and their differentials are outlined below. Results must be interpreted critically (reliability and repeatability) and in conjunction with other clinical signs, symptoms and examination findings.

Vertical Field Loss Pattern

Vertically-oriented field defects should always raise the suspicion of pathologies on the visual pathway beyond the retina, particularly if it respects the vertical midline.

Differentials

Unilateral:

- Retinal disease
- Pre-chiasmal or anterior chiasmal lesion (compressive lesions)

Bilateral (homonymous):

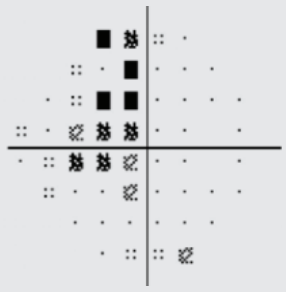
- Post-chiasmal lesion (compressive lesions, stroke, injuries)

Bilateral (bitemporal/binasal):

- Chiasmal lesions (pituitary adenoma, meningioma, parasellar carotid artery aneurysm, meningioma, craniopharyngioma, glioma)
- Tilted disc

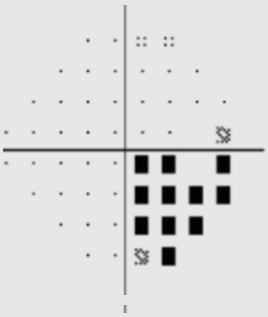
Vertical field loss can be classified into the four following patterns:

1. Vertical Step



Generally respects the vertical midline with at least 2 points outside 15° of fixation.

2. Quadrant



Visual field loss that respects both the vertical and horizontal midline. Suggestive of neurological involvement if bilateral. All points within the quadrant must be $p < 5\%$.

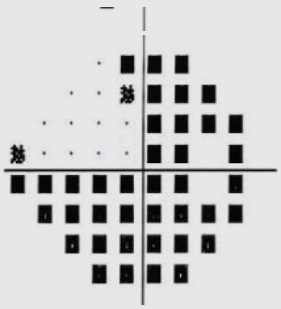
Note: Pituitary gland adenoma gives more superior defects ('pie-in-the-sky') while parasellar lesions give more inferior losses ('pie-on-the-ground').

3. Hemianopia

Loss of the vertical hemifield respecting the vertical midline either partially or completely.

Note: Monocular temporal hemianopia may occur if the lesion is more anterior and only affecting the nasal crossing fibres from the ipsilateral eye.

4. Three Quadrants



Three quadrants with all points at least $p < 5\%$.

Partial three quadrant losses does not have all points $p < 5\%$ but is greater than a complete hemianopia.

Note: Multiple lesions or pathologies may need to be considered.

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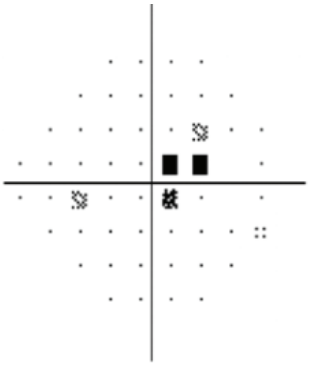
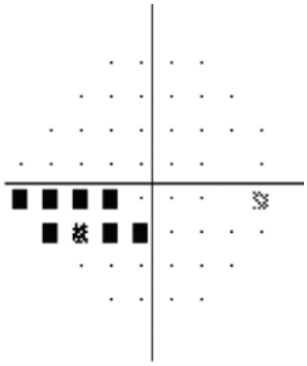


Description: Field loss extending from blindspot to fixation. Must include fixation and does not obey horizontal midline. Usually due to damage of the papillomacular bundle.

Differentials:
- Optic neuritis
- Cilioretinal artery occlusion
- NAION/AION
- Macular disease
- Retinal disease

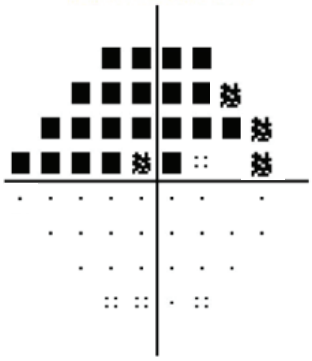
Nasal Step



Description: Field loss respecting the nasal horizontal midline with at least 1 abnormal point outside 15°. No more than 1 point may be on the temporal side.

Differentials:
- Glaucoma
- Papilloedema
- Optic nerve drusen
- Optic neuritis
- High myopia
- Retinal disease

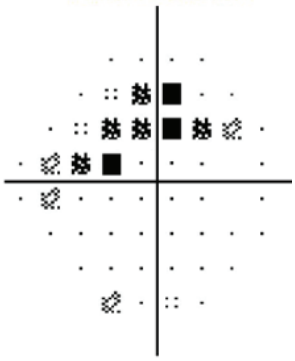
Altitudinal



Description: Field loss that respects the horizontal midline.

Differentials:
- Branch retinal artery/ vein occlusion
- NAION/AION
- Retinal disease
- Advanced glaucoma
- Cortical disease (if bilateral, rare)

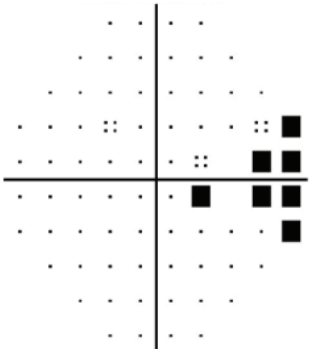
Arcuate



Description: Field loss extending from the blind spot to the nasal field with at least one point outside 15° nasally and at least one abnormal point temporally.

Differentials:
- Glaucoma
- Papilloedema
- Optic nerve drusen
- Optic neuritis
- High myopia
- Branch retinal artery/vein occlusion
- Retinal disease

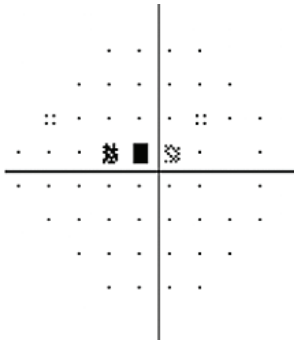
Temporal Wedge



Description: Small visual field defect temporal to blind spot.

Differentials:
- Optic neuritis
- Glaucoma (rare)
- Retinal disease

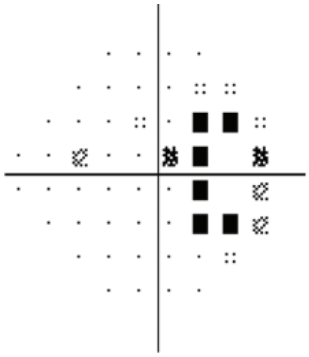
Paracentral



Description: A small visual field abnormality not contiguous to the blind spot and within 15° of fixation.

Differentials:
- Glaucoma
- Papilloedema
- Optic nerve drusen
- Optic neuritis
- High myopia

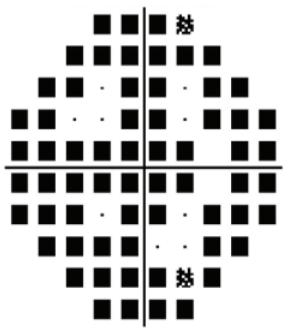
Enlarged Blind Spot



Description: Visual field loss involving at least two points contiguous to the blind spot.

Differentials:
- Papillioedema
- Glaucoma (rare)
- Large peripapillary atrophy
- Optic disc drusen
- Optic nerve coloboma
- Staphyloma
- Megalopapillae
- Titled disc syndrome

Clover Leaf



Description: Diagonal paracentral points show normal or near-normal sensitivity but all other points reduced. This is often due to patient responding normally at the start of the test only as the visual field instrument generally test these points first. Often accompanied by high fixation loss and false negative.

Differentials:
- Inattentive patient
- Poor supervision
- Malingerer
- Retinal disease

Chair-side Reference: Visual Field

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Structure/Function

The relationship between the retinal nerve fibre layer location and corresponding visual field is complex due to significant individual variations (Lamparter et al. 2013). The following shows a 'typical' structure/function relationship for the right eye, adapted from Ferreras et al. 2008

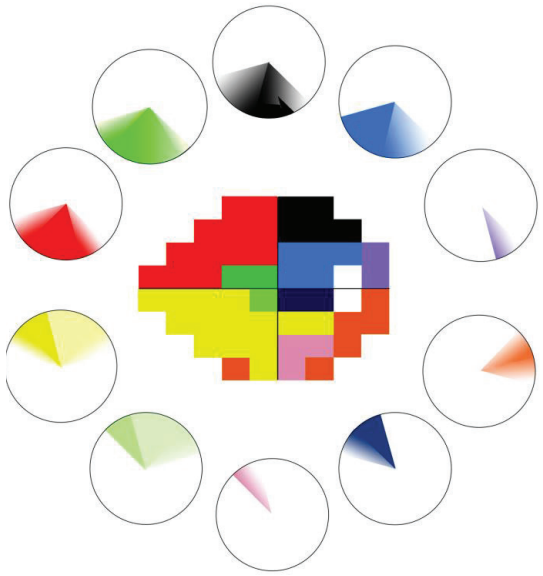


Figure 1. A map showing the relationship between RNFL sectors and test points on a 24-2 field test adapted from Ferreras et al. *IOVS* 2008.

Visual Pathway

There are many ocular and neurological conditions that can lead to field defects with the following diagram showing the possible location of a visual pathway defect based on the pattern of field loss. Note, however, that:

- field loss often does not precisely follow the pattern as outlined below
- partial losses or losses that are not entirely symmetrical are common

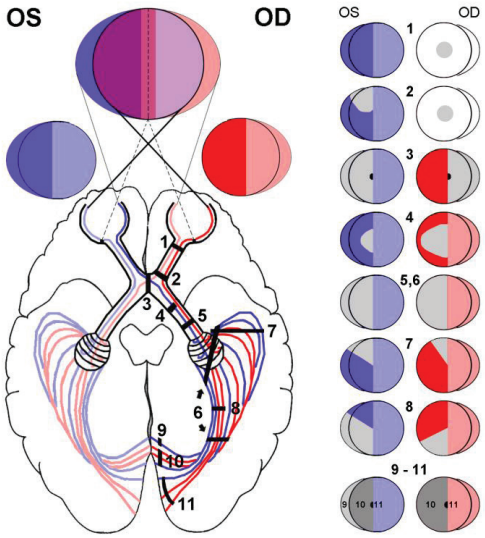


Figure 2. A diagram showing the visual pathway and field loss that may result from different injuries. Grey denotes scotoma on the right hand diagrams. (Zangerl et al *Clin Exp Optom* 2017)

Clinical Pearls

Reliability

- Unless there is a correlating structural finding, field defects need to be repeatable before they can be considered to be clinically significant due to large variability, especially in the periphery.
- Visual field measurement errors generally result in falsely low sensitivity rather than falsely high (Heijl et al. 1987).
- False positive errors have a greater effect on visual field reliability than the fixation loss or false negative errors.
- Increased false negative errors are correlated with the severity of visual field loss, even with reliable visual field takers (Bengtsson and Heijl 2000).
- In the presence of severe temporal field defects or micropapillae, blindspot based fixation monitoring is generally ineffective, and other forms of fixation monitoring such as gaze-monitoring and practitioner observation needs to be used instead.

Interpretation

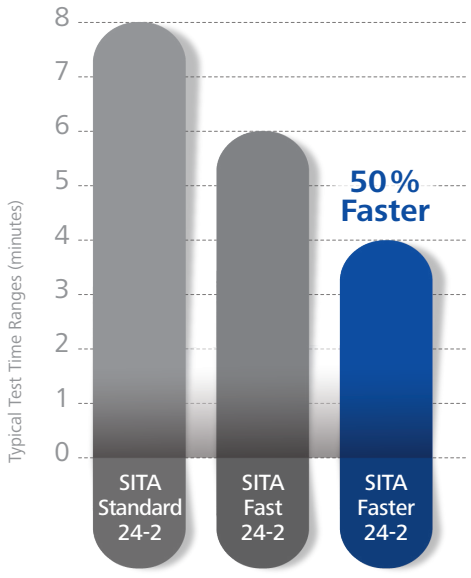
- A visual field area with 'complete loss' (< 0dB for Humphrey's field) is not necessarily completely blind. A target with a greater luminance or size may still be visible.
- As blindspots are generally 6 degrees in size, blindspot based fixation monitoring cannot detect fixation loss less than 3 degrees (which equates to half the distance between test locations for 24/30-2). On the contrary, eye movement monitoring technique can record fixation loss as small as 1 degree. Thus, this should be considered in conjunction with the traditional reliability method when interpreting visual field. (Ishiyama et al. 2015)

Glaucoma

- In glaucoma, either structural loss or functional loss can occur first depending on the sensitivity of the devices used to detect the loss (Keltner et al. 2006).
- Central field loss may be seen in as many as 50 per cent of glaucoma cases (Schiefer et al. 2010) and thus, a 10-2 field or equivalent may be useful.
- 24-2 is designed for glaucoma assessment; if a non-glaucomatous defect is suspected, utilise a 30-2 instead.

Reduce visual field testing time.

ZEISS HFA3 with SITA Faster



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1. Based on data from internal validation trials

Visual Fields

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the significance of these features and associated pass-fail criteria however differ between instruments as well as between associated studies and grading systems.[15] Some automated indices, such as mean deviation (MD), pattern standard deviation (PSD) and the Glaucoma Hemifield Test (GHT) may be more conducive to a quick overview of the SAP result, but they are also confounded by subtle sensitivity variations. Therefore, careful examination of each map in the printout is critical (Figure 1; also see Phu et al. 2017 *CXO* for examples of artefacts seen in VF testing).[16]

1. Reliability indices

The instrument flags results that are outside of the manufacturer's limits.

2. Gaze tracker result

Blips above the midline indicate eye movements. Larger blips indicate bigger movements. Blips below represent either blinks or tracking errors.

3. Sensitivity results (in dB)

Careful examination of sensitivity results may reveal subtle changes in the Hill of Vision. The sensitivities flagged in the red boxes (33 dB) are higher than expected, and thus have raised the patient's Hill of Vision, affecting statistical analyses on the deviation maps.

4. Glaucoma Hemifield Test (GHT)

The GHT states the results of asymmetry analyses across mirrored zones about the horizontal midline. It is used by many clinical studies as an index of abnormality. Note that this index uses probability scores, not sensitivity results.

5. Visual Field Index (VFI)

This is the percentage of VF loss following age correction, calculated based on the amount of reduction of all locations with a significant depression. Note that this index is not typically used in clinical trials as a diagnostic tool.

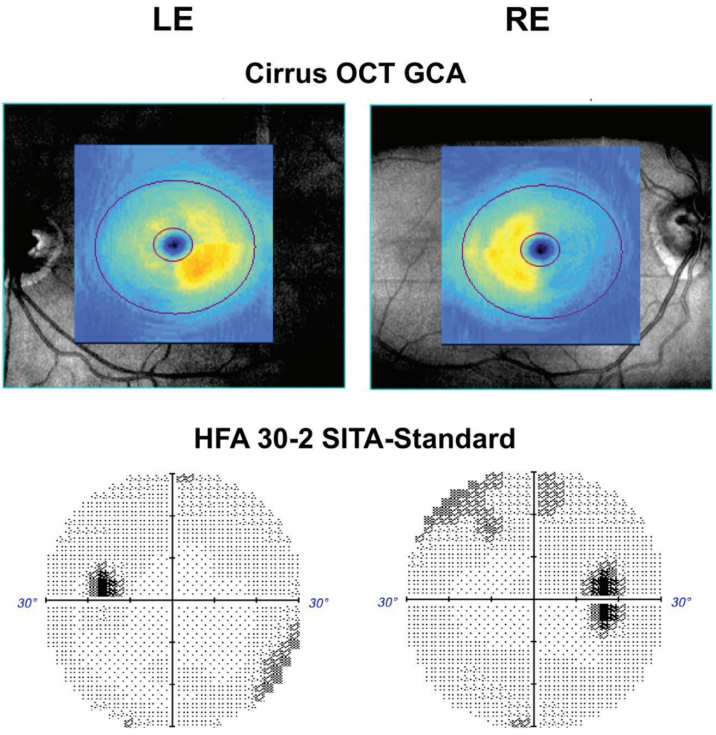

Figure 2. A 70-year-old Caucasian male with a previous pituitary tumour treated with surgical excision. Cirrus OCT results are shown on top (Ganglion Cell Analysis thickness map). The OCT results display binasal structural loss, which are typical of chiasmal lesions. The HFA 30-2 SITA-Standard results shown at the bottom do not show a typical bitemporal defect expected in a patient with a chiasmal lesion. This is because of the visual recovery following surgical treatment performed in 1995. Note that results have been shown as per typical visual field analysis (right eye [RE] results on the right and left eye [LE] results on the left).

6. Mean deviation (MD) and pattern standard deviation (PSD)

MD is the 'average' amount of depression (with location-specific weighting). It is typically used for staging and monitoring glaucoma. PSD is the standard deviation of these depressions and highlights focal defects.

7. Pattern deviation map

This helps highlight patterns of focal loss. It is typically used for diagnosis ($p < 5$ per cent) and does not highlight the exact depth of defect, as these are probability values (see the squares flagged in this example).

Tip 1: Automated indices that are used in grading scales and progression studies may differ, depending on the instrument.

VF printouts typically provide a map that reports the statistical likelihood of abnormality (that is: a 'deviation' map). Examining patterns of statistically-significant VF loss may be useful in identifying the locus of structural loss (that is: retinal, optic nerve, chiasm or higher cortical areas). We have recently reviewed the applications of SAP to different ocular and neurological diseases,[16] and the **VF Chair-side Reference** printed in this issue highlights types of VF defects associated with different diseases. Below, we highlight the continued role of SAP in current practice, and offer some debates regarding its clinical efficacy.

SAP vs selective perimetry

Although it is the current clinical standard for functional assessment in glaucoma, SAP is thought to be relatively insensitive to loss of early visual function in glaucoma, with a poor structure-function relationship in early stages of the disease.[17,18] Recent studies have suggested that structural loss in glaucoma may be detectable prior to the onset of functional defects on SAP. This is known as 'pre-perimetric glaucoma'.[19-22]

	Reported category	Structural	Functional	Both
OHTS (Kass et al 2002)	Medication	50.0%	41.7%	8.3%
	Observation	57.3%	32.6%	10.1%
EMGT (Ohnell et al., 2017)	MD ≥ -6 dB	20.0%	80.0%	0.0%
	-12 dB ≤ MD < -6 dB	20.3%	79.7%	0.0%
	-16 dB ≤ MD < -12 dB	0.0%	100.0%	0.0%
CNTGS (1998)	Treated	11.5%	88.5%	0.0%
	Untreated	10.7%	89.3%	0.0%
EGPS (Miglior et al 2005)	All progressors	40.0%	60.0%	0.0%
Recent studies on pre-perimetric glaucoma	Kim et al (2015)	59.7%	16.7%	23.6%
	Jeong et al (2014)	53.7%	26.8%	19.5%

Table 1. Proportion of patients reaching structural or functional endpoints for glaucoma in various major clinical trials. Where possible, different reported categories of patients within the trials are also distinguished.

Alternative methods of assessing the VF have been suggested. Some of these have come to be known as 'selective perimetry' as they purportedly test specific visual functions.[23] Such techniques include flicker perimetry (available on the Medmont automated perimeter), frequency-doubling technology (using the Matrix perimeter) and flicker-defined form perimetry (Heidelberg Edge Perimeter). There is debate regarding their efficacy; initial studies showed promise in greater detection rates using these instruments compared to SAP, but later studies have shown equivocality. Thus, current recommendations are that SAP remains the clinical standard.[24]

Tip 2: SAP remains the clinical standard for assessment of the visual field. Alternative perimeters may be considered adjunctive to the clinical examination.

SAP and OCT: which is more useful?

Pre-perimetric glaucoma

There is a common misconception that 25–33 per cent of retinal ganglion cell loss occurs prior to the manifestation of VF defects,[18,25] such as in pre-perimetric glaucoma. Actually, the majority of landmark clinical trials more commonly showed detection of progression using SAP (functional) testing (see Table 1). However, these studies were performed prior to spectral domain OCT. More recent studies on pre-perimetric glaucoma detected progression in up to four times more glaucoma patients with structural findings compared to functional (Table 1).[19,20] As a result, it is suggested that SAP and OCT may be more clinically useful at different stages of glaucoma.[26] Early in the disease process, OCT may detect subtle changes missed by SAP. When the measurement floor is reached by the OCT, SAP may be able to better track disease progression.

Why then do we continue to use SAP in glaucoma assessments? Recent studies comparing OCT and SAP for assessment of glaucomatous progression have shown that each technique may actually identify cases missed by the other. In other words: no one technique identifies all cases perfectly.[27] Some patients may have atypical optic nerve head configurations that are more suited to SAP, rather than OCT testing.

Tip 3: Many studies use different criteria for VF or structural endpoints, and thus need careful consideration when comparing across studies.

Retrograde degeneration

As mentioned, studies have suggested that OCT may be able to detect more abnormalities in early disease when compared to SAP. However, in retrograde degeneration, the converse may occur; patients may show significant functional loss prior to detectable structural loss using OCT.[28] Studies have also shown that treatment of lesions in the higher visual pathway such as tumours at the chiasm may have no or slow ganglion cell recovery on OCT imaging, but SAP may show recovery more quickly (Figure 2).[29]

Tip 4: Though structural loss may precede functional loss in many cases of disease, there are instances where VF examination may detect conversion to disease, progression of disease or recovery from disease, prior to appreciable structural changes.

Future – will we be using SAP?

Currently, there is a slew of research being undertaken in structure-function relationships in normal and diseased

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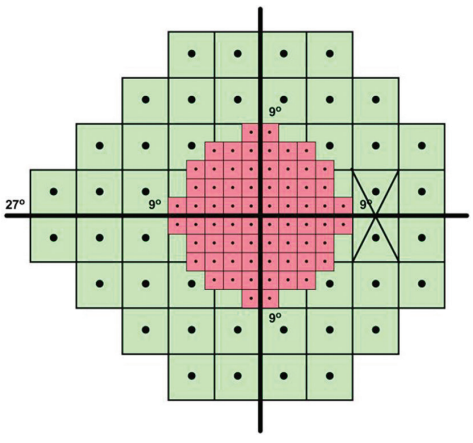

Figure 3. The 24-2 test grid (green) with 54 test locations spaced six degrees apart. Because of the sparse testing density, subtle loss within 10 degrees of fixation may be missed. The 10-2 test grid (red) offers a higher test density (two degrees spacing) within the central 20 degrees, and may help to detect early defects in the macula. In the future, superimposition or modification of test grids may become the norm.

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eyes. Recent advances in the area include customising functional testing based on the structure of the eye, such as using the fovea-to-disc angle and the temporal raphe to adjust the orientation of the VF to match the retinal nerve fibre layer projections.[30]

There have been recent innovations in the area of adaptive algorithms for increasing the efficiency of SAP testing. A new iteration of the Swedish Interactive Thresholding Algorithm (SITA) available on the Humphrey Field Analyzer (HFA) is SITA Faster, which is available on current or new HFA3 models. Similar advances are anticipated to be available in other perimetric instruments in the future. Some algorithms have also been developed to target specific areas of interest to improve the reliability of measurements at scotomata.[31]

Other areas of interest in VF are also being studied. Specifically for glaucoma, the central 10 degrees of the VF has been highlighted as an area of interest, as it has a denser testing grid (Figure 3).[32,33] The far peripheral field however is more important for navigation, and so it is likely that a combination of peripheral and central VF assessment will become the norm in the future.[34-36]

Recent commentary has also reminded us of the precedent nature of current stimulus parameters used in SAP.[37–40] Work from our laboratory conducted in modifying parameters of the test has shown promise in earlier detection of VF defects in glaucoma.[37,39] In the future, it may be possible to individually tailor stimulus parameters to test different stages of glaucoma from diagnosis to end-stage monitoring.[37,39]

Conclusion

VF testing is certainly not the most exciting part of the ophthalmic examination. Although the printout, procedure and instrument may appear to be simple, clinicians should be vigilant and judicious in its use in practice. Nevertheless, VF testing is still central to patient diagnosis and management in clinical practice, and so it is not yet time to replace our perimeters solely with advanced imaging devices like OCTs.

Key clinical pearls:

* Carefully examine all aspects of the VF printout: individual sensitivity values provide important information that can then be correlated with automated indices (see Phu et al., 2017 *CxO* for more information).

* Describing the VF defect is important to localise the likely site of anatomical anomaly, in other words: structure-function analysis (see the CFEH Chair-side Reference on Visual Field Interpretation in this issue of *Pharma* and Zangerl et al., 2017 *CxO* for more information).

* SAP is the current clinical standard; other perimetric techniques are recommended as adjunctive methods.

* Combining structural and functional measurements is essential for effective patient care.

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Therapeutic NEWS of note

Associate Professor Mark Roth

BSc(Pharm) BAppSc(Optom) PGCertOcTher NEWENCO FAAO OAM

The growing burden of AMD in Australia

Australia will need to increase the number of low vision rehabilitation services to cope with the projected increase in AMD, say the authors of The Australian National Eye Health Survey.

In a study published in *JAMA Ophthalmology*, age-related macular degeneration was attributed as the main cause of vision loss in 11.1 per cent of non-Indigenous Australians and 1.1 per cent of Indigenous Australians.

The study authors say that it is not clear why the AMD rate for Indigenous people is so low, but suggest that people with higher levels of retinal pigmentation may be protected from oxidative damage. Lower life expectancy in Indigenous populations may also play a role, given that increasing age is a key risk factor for AMD.

In line with data from other Caucasian populations, AMD remains a leading cause of vision loss in Australia, and with increasing life expectancies, the prominence of AMD is projected to grow.

Overall, the study reinforced the importance of regular eye checks for those in the at-risk population (anyone over 60 years old, particularly with a family history of AMD) as well as the need to increase the number of low-vision rehabilitation services for those whose vision will be affected by AMD in the future.

JAMA Ophthalmol. Oct 2017. doi:10.1001/jamaophthalmol.2017.4182

Lucentis and Eylea in the top ten in cost to Australian government

Eylea (aflibercept) and Lucentis (ranibizumab) were listed fifth and sixth, respectively, in the top 10 subsidised drugs for the year July 2016 to June 2017. The list appeared in the December issue of *Australian Prescriber.*

The cost to the Australian government for aflibercept (Eylea) was $261 million, with more than 203,000 prescriptions, and $213 million for ranibizumab (Lucentis) with more than 169,000 prescriptions, placing the anti-VEGF treatments solidly among the most expensive drugs of the year.

www.nps.org.au/australianprescriber

IVMED-80, an eye drop used for keratoconus

The US Food and Drug Administration (FDA) has granted 'orphan drug designation' to IVMED-80, an eye drop used for cross-linking the cornea to treat keratoconus.

IVMED-80 is the first eye-drop, non-surgical, non-laser treatment for medical crosslinking of the cornea. It biomechanically strengthens the cornea through the daily application of a non-invasive, proprietary eye-drop. IVeena Delivery Systems, the US-based

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Visual Fields

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News

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biopharmaceutical company behind the drug, said it will begin clinical development of IVMED-80 in 2018.

The Orphan Drug Act provides incentives for companies to develop products for rare diseases affecting fewer than 200,000 people. Incentives may include tax credits related to clinical trial expenses, FDA assistance in clinical trial design and potential market exclusivity for seven years following approval.

www.iveenamed.com

Adjustable post-operative IOL to improve vision approved by FDA

The US Food and Drug Administration (FDA) has approved the RxSight Light Adjustable Lens (RxLAL) and the Light Delivery Device (LDD) for patients with pre-existing astigmatism of ≥ 0.75 D undergoing cataract surgery.

According to a press release by the FDA, RxLAL is the first medical device system that can make small adjustments to the artificial lens' power after cataract surgery so that the patient will have better vision when not using glasses.

RxLAL is made of a unique material that reacts to UV light, which is delivered by the LDD, two-to-three weeks after surgery. Patients receive three or four light treatments over a period of one-to-two weeks, each lasting about 40–150 seconds, depending upon the amount of adjustment needed. The patient must wear special eyeglasses for UV protection from the time of the cataract surgery to the end of the light treatments to protect the new lens from UV light in the environment.

The device is intended for patients who have astigmatism (in the cornea) before surgery and who do not have macular diseases.

www.rxsight.com

Non-antibiotic drugs for antibiotic resistance?

A team of biomedical engineers from Duke University in the US say they may have found a way to disrupt or even reverse the growing prevalence of antibiotic resistance, without antibiotics.

Writing in the journal *Nature Communications*, the scientists say there are drugs that can both stop the sharing of genes and decrease the rate at which they are passed on through reproduction.

The scientists maintain that reducing the use of antibiotics will not be enough because of conjugation, a process by which bacteria quickly share the ability to fight antibiotics by swapping genes between species and then maintain their resistance even in the absence of antibiotics.

One drug, 'a benign natural product', is known to inhibit conjugation, while the other, an FDA-approved antipsychotic, encourages resistance genes to be lost.

'We found that without the presence of antibiotics, we could reverse the bacteria's resistance in four of the pathogens we tested and could stop it from spreading in the rest', the researchers wrote.

The next step for the team is to identify additional chemicals that can fill these roles more effectively.

Nature Communications. Nov 2017. doi: 10.1038/s41467-017-01532-1

Measuring IOP in patients with obstructive sleep apnoea

Another link between obstructive sleep apnoea syndrome (OSAS) and glaucoma may have been discovered in a recent study on corneal hysteresis (CH).

Researchers at the University Malaya Medical Centre, Kuala Lumpur conducted a cross-sectional, observational study to look at the association between CH and severity of OSAS, and whether CH could be another link between OSAS and the development of glaucoma.

Measuring central corneal thickness using biometry, corneal hysteresis using ocular response analysis, IOP and Humphrey visual field, a total of 56 patients were classified as normal and mild categories and placed into group 1, and 61 patients were moderate and severe and made up group 2.

Corneal hysteresis was lower in group 2, according to researchers. They found a significant difference in corneal hysteresis between the OSAS groups. 'This may be another link between OSAS and the development of glaucoma' they wrote. 'Further studies are indicated to determine the significance of this connection.'

The results of this study suggest that although obstructive sleep apnoea can't be considered a predictor of glaucoma, patients with the condition should be monitored for the earliest signs of the disease.

Optometry and Vision Science. Oct 2017. doi: 10.1097/OPX.0000000000001117

Fewer signs of inflammation with daily disposable contact lenses

Higher ocular inflammatory responses were found in reusable contact lens wearers than in daily disposable (DD) contact lens (CL) wearers.

Researchers compared the concentrations and ratios of tear cytokines and changes to conjunctival cell morphology in healthy habitual daily disposable (DD) and reusable soft contact lens wearers.

Thirty-six established daily CL wearers, including 14 DD and 24 reusable wearers, were enrolled. Symptoms and ocular surface integrity were evaluated.

The study found that reusable soft contact lens wear was associated with higher concentrations of tear cytokines, more conjunctival staining and greater conjunctival epithelial metaplasia compared with daily disposable contact lens wear.

Although the results suggest that reduction in pre-inflammatory changes might contribute to the improvement in comfort after switching to daily disposable lenses, the study authors emphasised the need for further studies to evaluate factors affecting eye discomfort and inflammation—not just contact lens replacement schedule, but also lens material and design.

Optometry and Vision Science. Nov 2017. doi: 10.1097/OPX.0000000000001129

Infantile nystagmus syndrome

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Infantile nystagmus syndrome (INS) is a rare condition which presents as involuntary, oscillatory, conjugate eye movements along the horizontal plane with an age of onset of two to four months.[1] Patients usually have reduced visual acuity with no other contributing eye health issues, and while it is a genetic condition, there is not always a family history.

INS patients may have a detectable 'null point,' a direction of gaze where nystagmus has lowest intensity, and when this is not in primary gaze the patient may adopt an anomalous head turn to access this position of gaze most of the time. Some patients exhibit less nystagmus on convergence, a phenomenon called 'convergence damping'.

The null point is important as it is used during management, which is aimed at damping the nystagmus movement and improving vision and cosmetic appearance. It is also crucial to exclude abnormalities of the visual pathway, systemic conditions or brain lesions as they can be life-threatening. Surgical intervention for INS can also be beneficial under certain conditions.

CASE REPORT

A seven-year-old Caucasian male presented with a history of reduced vision and nystagmus from the age of two months. His parents were not aware of any changes since its onset. The patient had seen an optometrist two years previously, wore glasses of bilateral -0.75 obtained from that visit, and no other management options had been discussed.

No other ocular conditions were noted and the patient reported no oscillopsia. Clinical observation showed horizontal nystagmus in a jerk pattern which was present in all directions of gaze. Nystagmus was at lowest intensity on right gaze and he had a constant left head turn of approximately 20 degrees.

He also exhibited convergence damping, full eye movements and normal pupil reactions. Best corrected distance visual acuity was 6/18 in each eye with no head turn and a spectacle prescription of R -0.75/-0.25 x 170 L -1.00. Interestingly, with the left head turn the visual acuity improved to 6/12. In this position he achieved N5 reading vision and reduced nystagmus. He showed binocularity with no strabismus and normal stereopsis. Colour vision with Ishihara and confrontation visual fields were normal.

Ocular health was unremarkable. To rule out structural brain disorders, the patient was referred to a paediatric ophthalmologist for MRI and CT scan of the optic nerve, chiasm and brain with normal contrast, which came back normal. During the consultation at the paediatric ophthalmologist, they measured his IOP under sedation, which gave a reading of 13 mmHg each eye. The patient also had a full systemic check by his family GP.

We referred the patient for ocular movement recordings and the results confirmed a jerk nystagmus with a null zone at 10–20 degrees right gaze. Given these findings and an exclusion of all differentials, the patient was diagnosed with INS.

Management consisted of the spectacle correction R -1.75/-0.25 x 170 L -2.00 (an over-correction of -1.00) with yoked prisms incorporating 4 Base Left and 4 Base Out prism in each lens. The final distance visual acuity was 6/9, N5 reading vision and the angle of left head turn was approximately halved, which was considered a good improvement. While surgical intervention to correct the remaining head turn was considered, given his full binocular status the possible benefit of this was outweighed.

Because contact lenses improve subjective visual quality in patients with INS,[2] this was offered as a treatment option. The parents decided to delay this option until he was more mature. Overall, the patient achieved an improvement of two-to-three lines of visual acuity and a reduction of both the nystagmus and the head turn. A three-month review was arranged.

Differentials

• Sensory deprivation: including cataracts, media opacities, optic nerve and retinal disease, Leber's congenital amaurosis, achromatopsia, and any abnormality of the afferent visual pathway. However, ocular health was normal. VEP and ERG should be performed to confirm retinal dystrophy or Leber's if suspected.

• Structural brain disease, including lesions of the brainstem or cerebellum: this was ruled out by MRI and CT scan.

• Toxic-induced nystagmus: history-taking should reveal drug use or illness.

• Opsoclonus: important to diagnose due to the association with paraneoplastic syndrome and encephalitis. Tested by MRI and toxicology screen, blood testing for metabolic and serum electrolytes and paraneoplastic antibodies. However, it would feature multidirectional nystagmus [3] and neurological symptoms.

• Spasmus nutans: associated with gliomas of the anterior visual pathway and ruled out by MRI. It presents with nystagmus that can be constant, intermittent or 'shimmering,' typically with head nodding.

• CNS disorders: for example: multiple sclerosis, adrenoleukodystrophy. Suspected with relative afferent pupillary defect, optic atrophy or abnormal MRI testing.

• Latent nystagmus: can co-exist with infantile nystagmus, detected by nystagmus increasing with monocular cover and often occurs with a strabismus.

MANAGEMENT APPROACHES

Ocular movement recordings

The only laboratory currently offering ocular movement recordings is located

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in Melbourne. It is a valuable test to quantitatively evaluate the pattern of eye movement and to classify the nystagmus. A jerk movement of the eye in nystagmus consists of a slow and a fast phase. Assessment of the slow phase can actually help locate causative lesions of the ocular motor subsystem as well as objectively locating any null points.[4]

Spectacles and prisms

Considering that the refractive error for patients with INS ranges from -7.88 to +4.00 with a mean of -1.37,[5] the basic correction of refractive error shouldn't be overlooked. Strabismus, if present, should be corrected to improve binocularity.[6] Patients with INS may indicate that their vision worsens under visual stress, and indeed it has been shown that when faced with tasks containing a higher mental load, visual recognition times increase for people with INS compared to a control group.[7] This further supports the emphasis on correcting refractive errors and reducing visual stress.

If the patient shows convergence, damping the use of base-out prism and -1.00 overcorrection creates a convergence demand and in this way reduces nystagmus.[6,8] In addition, if the patient exhibits a lateral null point, which can be tested by observing eye movement intensity in different directions of gaze, yoked prisms can shift the visual image from lateral to primary gaze and correct abnormal head postures. This can be done effectively without degrading image quality only when the angle of null is minor. The amount of prism can be determined by trialling lenses while observing the nystagmus intensity and repeating visual acuity, with patient feedback when possible.

Contact lenses

A study by Pavitra et al[3] compares the visual results with spectacles, soft contact lenses (SCL) and rigid gas-permeable contact lenses (RGP) in INS. While there was no statistically-significant difference, the numbers of patients who reported visual improvement with SCL and RGP compared to spectacles were 30 per cent and 40 per cent, respectively. It is thought that contact lenses dampen nystagmus via trigeminal afferent feedback mechanisms. Weighing up the risk factors for contact lens wear, which include microbial infections and physical ocular damage, versus the subjective visual improvement, contact lenses constitute a considered management option.

Surgery

Surgery aims to shift and widen the null zone and reduce overall eye movement intensity, thereby eliminating abnormal head posture and improving vision. The Kestenbaum-Anderson technique involves a paired recession and resection of the antagonistic rectus muscles in each eye to move the null zone to primary position. If convergence damping is present, a combination of the Kestenbaum-Anderson with a paired surgical divergence of the horizontal rectus muscles gives the best results.[9] The presence of a lateral null zone is required to obtain best results from these techniques.

Four-muscle recession is a surgical intervention aimed to weaken the muscular force of all four rectus muscles. A study demonstrated improved vision with this technique, more so for participants under the age of 10 years who improved an average 1.9 lines of distance visual acuity compared to participants over the age of 10 who improved 1.4 lines.[10] However, visual acuity improvements must be larger than the test-retest variable (two lines on the Snellen chart)[9] to be considered clinically effective. Large limitations of ocular motility post-surgery were demonstrated, as well as cases of post-operative nerve palsy and exotropia.[11]

Lastly, extraocular muscle tenotomy involves cutting and reattaching the extraocular muscles at the same site of attachment. The exact mechanisms of action aren't known but could involve disruption of motor neuron proprioceptive signals. For this technique, published reports have demonstrated improved nystagmus and visual function with no significant adverse effects.[12] However, these studies have a low number of participants and further studies are required.

For our young patient, the risks of post-surgical ocular motility limitations and exotropia outweighed the benefits because he was achieving satisfactory vision and we did not want to interrupt his full binocularity.

Prognosis

Nystagmus waveforms and frequencies typically decrease until the age of six-to-eight years and remain stable afterwards.[13] If changes do occur, they need to be investigated because a diagnosis of INS does not preclude the possibility of developing other neurological or ocular issues.

Aetiology

INS is understood to be genetic, and studies have demonstrated a mutant gene FRMD7 for X-linked idiopathic INS.[14] However, it can appear without a known family history. The aetiology is not currently well understood. One theory by Brodsky[15] suggests that INS occurs when foveal motion sensitivity is slow to mature in infancy. This causes a secondary delay in development of the high-frequency cortical pursuit pathways which are usually responsible for suppressing the optokinetic motion perceived during eye movements and nystagmus subsequently develops.

A contrasting theory by Harris and Berry[16] proposes that nystagmus develops in the retina lacking maturation as a compromise to enhance contrast sensitivity on a retina by use of motion while maintaining some foveal fixation. Work by Dell'Osso et al[17] created a computer model simulation which proposes that pendular nystagmus in INS is due to a loss of damping of the normal pursuit-system velocity oscillation. Furthermore, electron microscopy studies of extraocular muscle tissue in INS subjects found anomalous nerve endings and vascular endothelial cells.[18] Whether this could contribute to INS is still being researched.

Conclusion

If a patient presents with nystagmus, it is important to perform a thorough history and clinical examination. INS is based on characteristics including age of onset and typical features; however, it is also a diagnosis of exclusion because the differentials can be life-threatening. There is a number of management approaches and this case study demonstrates the opportunity optometrists have to improve the quality of vision for these patients.

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Floaters

A clinical and surgical update

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Recent studies have confirmed anecdotal findings that floaters are very common with between 76 per cent and 84 per cent of study participants reporting floaters on questioning.[1,2] Although most patients with floaters are not very troubled by them, the same studies confirm that a minority of patients complain of significant visual symptoms.

In symptomatic patients, the impact on quality of life can be significant, even in the absence of marked clinical findings. Historically, the management of floaters has involved a 'wait and see' approach with a recommended period of adjustment and resolution with time despite clinical findings to suggest otherwise.[3] More recently, vitrectomy and YAG vitreolysis have presented options for the motivated, symptomatic patient.

Here we present a short review on the clinical assessment and surgical management of floaters, highlighting recent advances in the care of this condition.

What are floaters?

Floaters originate from molecular changes occurring within the vitreous body or at the vitreoretinal interface. Although most cases are related to the ageing process, a variety of endogenous and exogenous factors may contribute to the development of floaters (Figure 1). The severity of symptoms and signs are often related to the type and location of the floaters, so an understanding of these may assist in the diagnosis and management of the patient's condition.

Primary vitreous floaters arise from structures within the vitreous body itself.[4] Collagen fibres within the vitreous continue to increase in number, thickness and irregularity throughout life. As these fibres move across the patient's visual axis, the light is scattered, or, if significant, they cast a shadow onto the retina, leading to the presence of dark lines across the visual field. Progressive liquefaction

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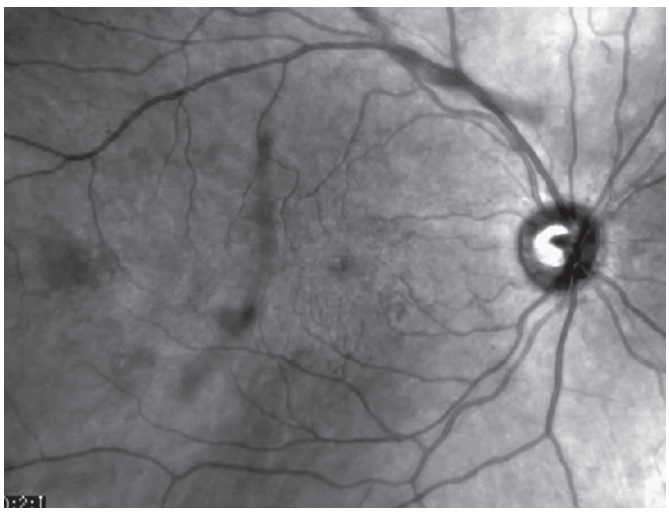

Figure 1. Age-related degenerative floaters on fundus examination

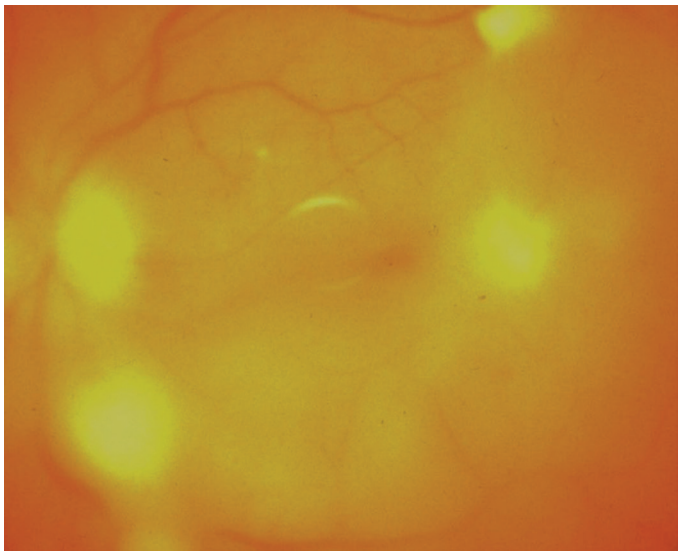

Figure 2. Floaters as a result of fungal infection

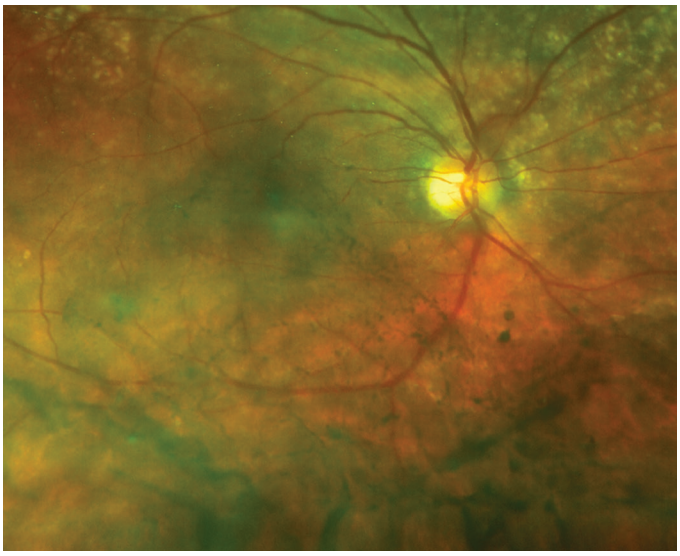

Figure 3. Inflammation leading to vitreous floaters

Floaters

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and mobility of the vitreous with age increases light scatter by the collagen fibrils, and increases the potential clinical impact for the patient.

Posterior vitreous detachment: the end result of this process, in approximately 60 per cent of patients, often leads to a sudden increase in primary floaters.[5] Clear noodle- or worm-shaped floaters are separately described and reflect the presence of the existing hyaloid structure. Rarely do these floaters lead to patient discomfort.

Secondary floaters originate from changes exogenous to the vitreous body and may occur as a result of inflammation, infection or haemorrhage, or following intraocular surgery. The presence of secondary floaters is often accompanied by visual disturbances (Figure 2).

Assessment

A detailed patient history remains the foundation for clinical assessment. Acute onset and increasing numbers of floaters are indications for urgent assessment. Associated ocular symptoms such as flashing lights, visual field defects or blurred vision may indicate the presence of a retinal tear or retinal detachment. Patients with uveitis may present with floaters caused by inflammatory cells which have gained access to the vitreous cavity via a compromised blood-retina barrier. Patients should be asked about possible features of uveitis such as photophobia, redness or discomfort, as well as features associated with systemic causes of uveitis such as fever, cough, joint pain or rashes. Systemic conditions associated with uveitis include a wide variety of autoimmune, infectious and idiopathic conditions (Figure 3).

Of importance generally, floaters may represent the early clinical signs of a broader infectious process. A recent review from the Royal Victorian Eye and Ear Hospital identified floaters and blurred vision as the presenting sign in a series of patients who were later diagnosed with ocular syphilis despite an absence of redness and ocular discomfort.[6] A history of intraocular surgery may be relevant. Intravitreal injections of triamcinolone can result in residual white particles within the vitreous, which tend to gravitate inferiorly. Tiny lens particles in the anterior vitreous are commonly

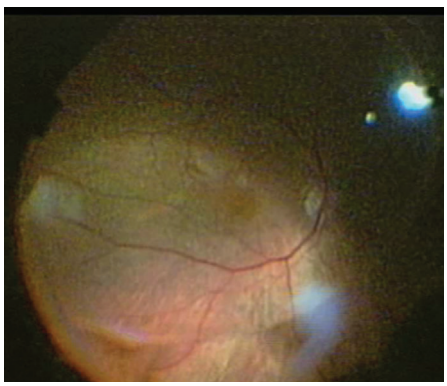

Figure 4. Lens fragments within the posterior chamber following cataract surgery

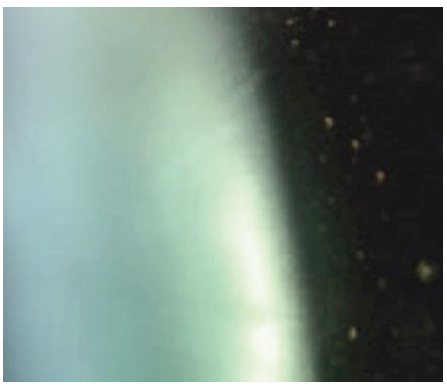

Figure 5. Slitlamp assessment of vitreous

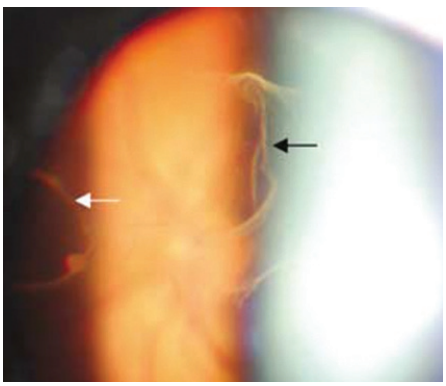

Figure 6. Weiss Ring as seen on vitreous examination

seen following phacoemulsification surgery in the early post-operative period (Figure 4).

Patients may also become more aware of pre-existing floaters and become symptomatic after cataract surgery when their vision has improved. Multifocal intraocular lenses are increasingly utilised for patients seeking optical independence following surgery. The multiple focal points inherent to these lens designs can make these patients particularly prone to symptoms from floaters as they may more easily see floaters at multiple planes within the vitreous cavity.

Slitlamp biomicroscopy allows for a thorough examination of the vitreous. Using a bright thin slit beam offset by 10 degrees from the visual axis enables the examiner to visualise the posterior hyaloid membrane behind the lens in patients with an advanced posterior vitreous detachment (Figures 5 and 6). A search for the presence or absence of floaters, pigment ('tobacco dust'), red blood cells or white cells behind the lens should be done. Asking the patient to look down and then straight ahead mobilises the vitreous and may bring cells within the inferior vitreous into view.

All patients presenting with floaters should be assumed to have a retinal tear present until proven otherwise by careful assessment of the peripheral retina. Approximately 10 per cent of retinal tears cannot be seen with commonly-used 90 D lenses as they are located anteriorly near the ora serrata, mandating the need for scleral indentation (Figure 7).

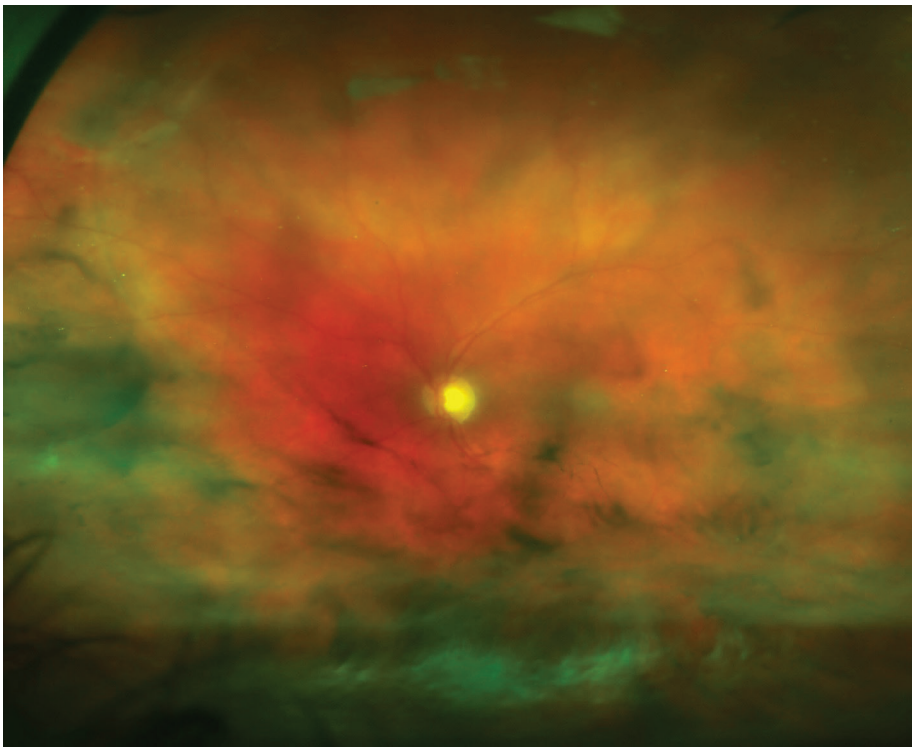

Figure 7. Peripheral retinal tear with vitreous haemorrhage

When examining floaters, consider their location (anterior/posterior or diffuse/inferior), colour (white/brown, red), shape (ring/strands, snowball or clumps), size and mobility as these features provide information regarding the possible aetiology of the floaters, their visual impact and the potential treatment options. Imaging of the floaters, using a retinal camera or a scanning laser ophthalmoscope (often incorporated in many OCTs) may be useful for patient education and documentation.

When no floaters are visible to the examiner in a patient complaining of floaters, OCT may be helpful to visualise floaters located within the pre-macular bursa area. The pre-macular bursa is an optically empty vitreous cistern located immediately anterior to the macular. Floaters in young patients are often located within the pre-macular bursa and can be extremely difficult to see on slitlamp examination. Due to their proximity to the retina, floaters in the pre-macular bursa are typically well defined and can cause a high level of symptoms. It is not uncommon for patients with floaters in the pre-macular bursa to have visited

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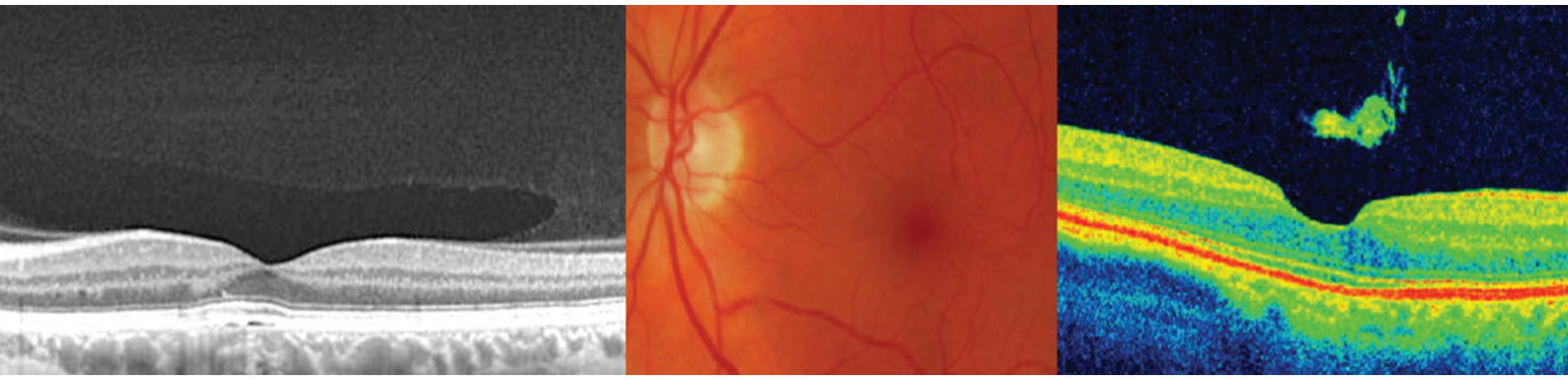

Figure 8. Ocular coherence tomography of pre-macular bursa (left), fundus imaging of pre-macular bursa floater (middle), OCT of same eye indicating pre-macular bursa (right)

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numerous eye-care practitioners who have been unable to identify the troublesome floaters.[7] OCT may show the floaters located anterior to the macular (Figure 8).

Treatment

If significant, floaters may warrant surgical intervention. The decision to proceed with treatment is determined by numerous factors including the impact of the floaters on the patient's quality of life, patient expectations, age, location and contributing cause of the floaters.

YAG laser vitreolysis is a relatively recent innovation in which a YAG laser is used to vaporise floaters and prevent them from obstructing the visual axis. The procedure is performed in the clinic using slitlamp visualisation, averting the need to visit an operating theatre. Multiple treatment sessions may be needed and complete symptom resolution is often not possible. YAG laser vitreolysis works best for patients with a small number of large, easily-visible floaters located in the mid-vitreous cavity not too close to the lens or the retina. The ideal patient is middle-aged with a large symptomatic Weiss ring.

YAG laser vitreolysis is not suitable for patients with floaters that cannot be easily visualised on slitlamp examination, those with large numbers of floaters or those with floaters located close to the lens or retina, due to the potential for the laser to inadvertently hit these structures. A large proportion of patients aged younger than 35 years are unsuitable because they frequently have floaters located in the pre-macular bursa which are too close to the macula for safe application of laser.

Published case series describing the efficacy of YAG laser vitreolysis have reported generally positive results. A recent randomised control trial comparing laser vitreolysis against sham treatment demonstrated both subjective and objective improvements for patients treated with laser.[8] There have been case reports of secondary cataract caused by the laser inadvertently hitting the crystalline lens, highlighting a potential risk of the procedure.[9–10]

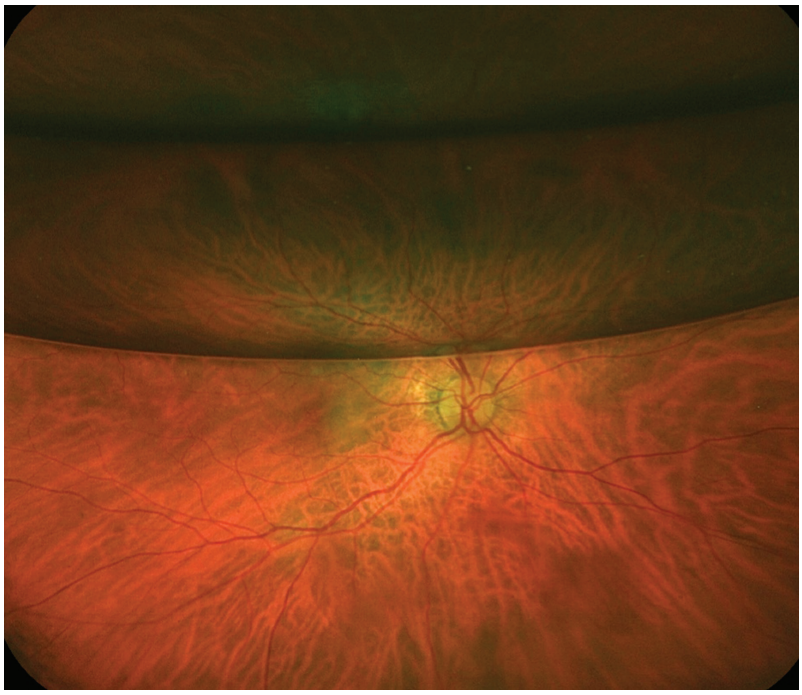

Figure 9. Bubble post vitrectomy

Vitrectomy surgery to remove floaters is an option if symptoms significantly affect the patient's quality of life and the patient has been unresponsive to or unsuitable for YAG laser vitreolysis. Vitrectomy surgery typically allows removal of all symptomatic floaters and results in high levels of patient satisfaction. The main disadvantage of vitrectomy surgery is the premature development of cataract. In patients aged older than 50 years at the time of surgery, cataract formation typically develops within one year and requires cataract surgery. The most serious risks of vitrectomy surgery include endophthalmitis (approximately one in 1,000) and retinal detachment (up to one per cent)[11] (Figure 9).

Summary

Floaters are very common and their impact on quality of vision is highly variable. Accurate diagnosis and careful clinical assessment are essential to exclude sight-threatening conditions such as retinal detachment or uveitis. Motivated patients may benefit from surgical intervention which has largely been shown to be safe and effective. Consideration of age, the causative factor of the floaters and patient expectations are essential prior to considering surgical options.

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