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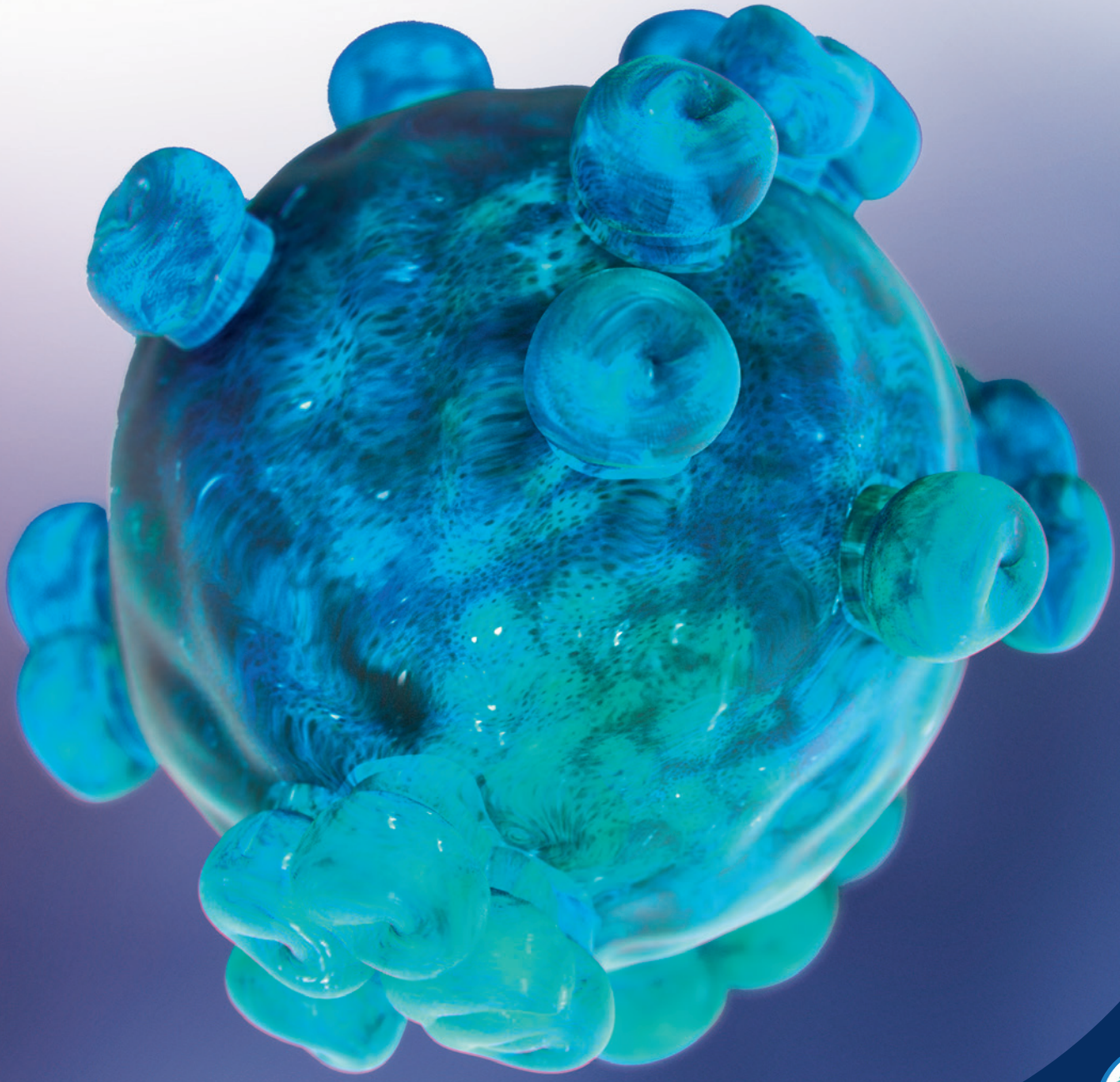

ZIKA VIRUS

Ophthalmic manifestations

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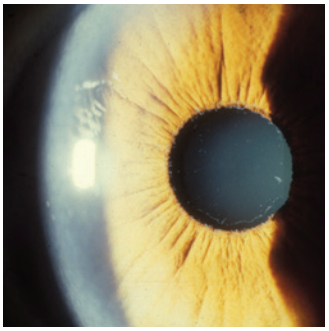

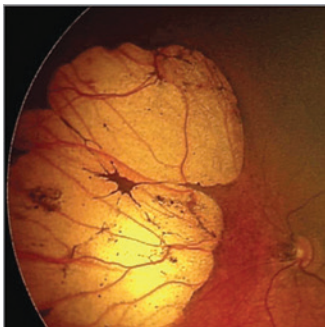

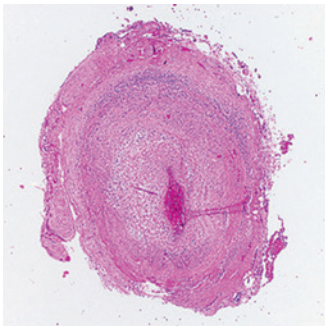

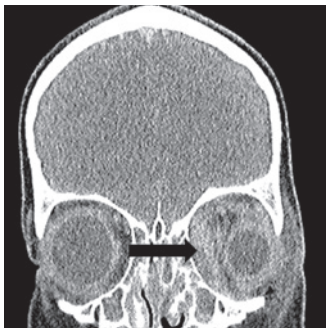

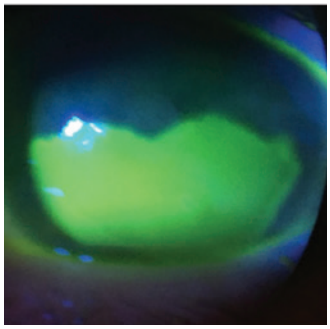

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Pseudoexfoliation of the lens capsule

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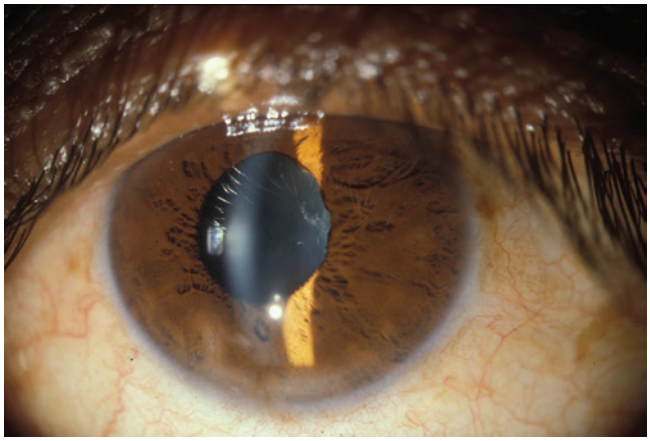
PHOTO CLINIC



▲ Figure 1. Pseudoexfoliation in a 44-year-old Sri Lankan male

A 44-YEAR-OLD Sri Lankan male presented to the Optometry Clinic at QUT. He was an accountant and was struggling to see at near. It was his first eye examination.

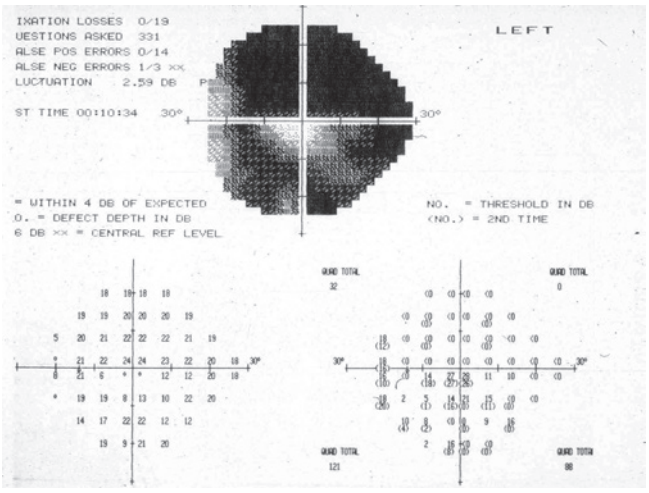
Visual acuity was R 6/6 L 6/6 with a small hyperopic refraction and R N5 L N5 with an appropriate reading addition. There were no relative afferent pupil defects and intraocular pressures (IOP) were R 15 L 25 mmHg at 10 am. Slitlamp examination revealed a normal right anterior segment; the left showed a slightly distorted left pupil together with white pseudoexfoliation material on the left anterior lens capsule (Figure 1).

The right fundus was normal and the left optic disc was markedly cupped. Visual fields, examined with the Humphrey Field Analyzer, revealed a normal right field and advanced glaucomatous field loss in the left eye (Figure 2).

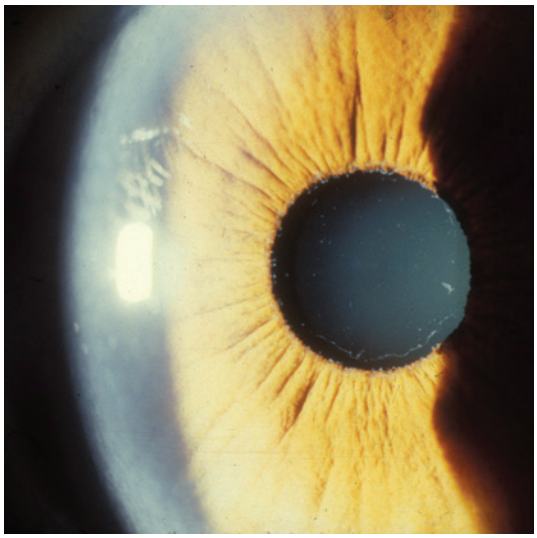
The patient was lost to follow-up before a management plan could be initiated.

This patient's case was interesting because of his age at diagnosis. Pseudoexfoliation material, which appears to be systemically synthesised and is similar to amyloid, is usually seen deposited on structures in the anterior segment and in many organs of the body. It is typically diagnosed in older patients, predominantly women, and rarely under the age of 50 years.

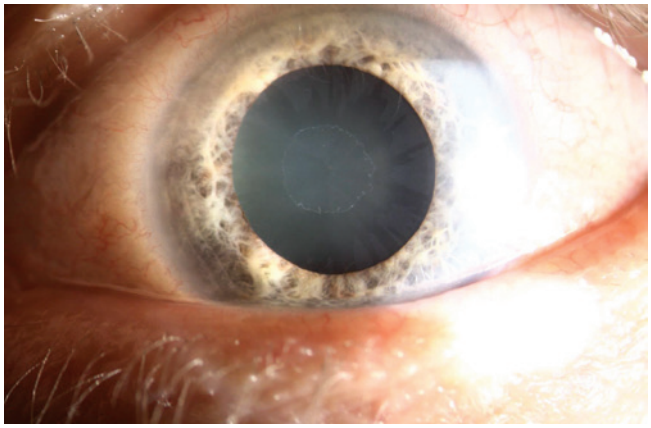
Most races of the world can be affected but the condition is more common in Scandinavia for reasons that are not well understood. Pseudoexfoliation is a term originally coined to distinguish it from true exfoliation of the lens capsule, a rare condition seen in



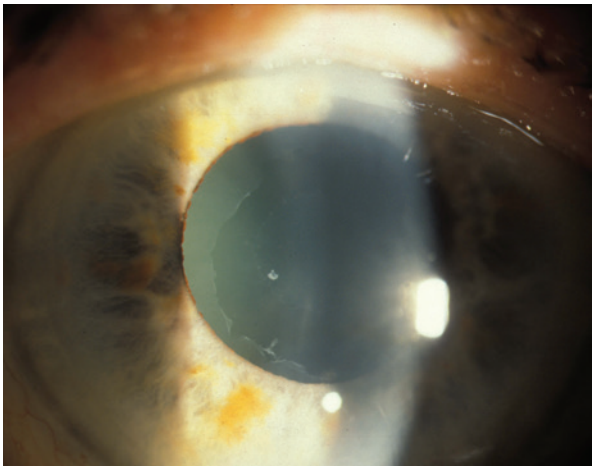
▲ Figure 2. The left visual field showing advanced glaucomatous field loss



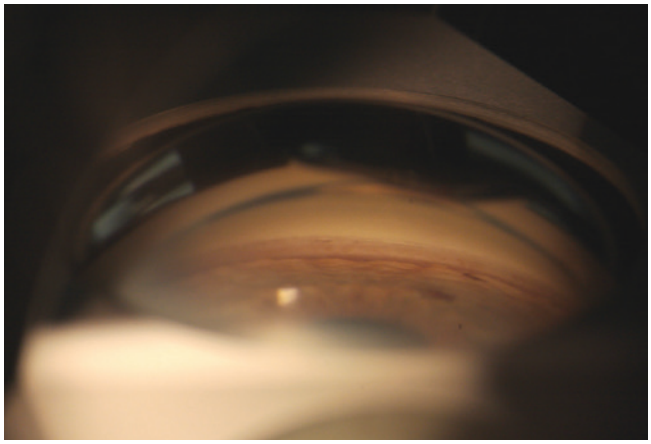
▲ Figure 3. Pseudoexfoliation material on the anterior capsule and the pupil border



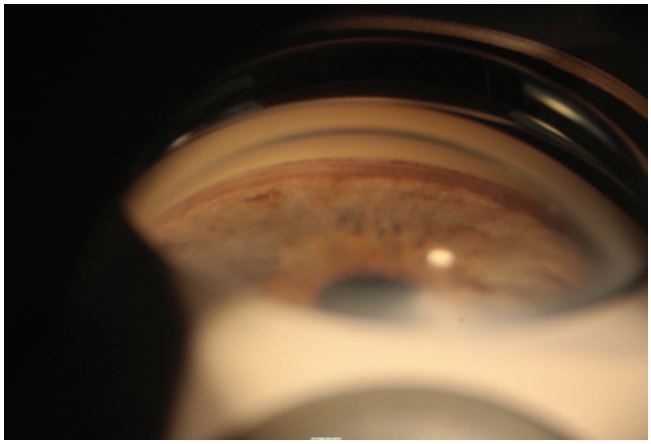
▲ Figure 4. Central disc of deposits on the anterior capsule



▲ Figure 5. Peripheral band of material



▲ Figure 6. Gonioscopic view of the left inferior angle of an 80-year-old white male with pseudoexfoliation in the other eye



▲ Figure 7. A gonioscopic view of the patient's right inferior angle; pigment dispersion was also present and the angle was more pigmented

people exposed to infrared radiation and intense heat sources such as glassblowers.

White flaky deposits are seen on the anterior lens capsule and frequently the pupil border (Figure 3). There is usually a central disc of material (Figure 4); a clear zone where deposits have been removed by rubbing from iris movement; and a peripheral band, the anterior edge of which frequently appears serrated (Figure 5).

Pigment dispersion is often a feature in these patients. Gonioscopy may reveal trabecular hyperpigmentation (Figures 6 and 7). Pigment and pseudoexfoliation material can impede aqueous outflow and lead to secondary open angle glaucoma. A weakening of the lenticular zonules and capsule is a potential issue when cataract surgery is contemplated. The condition is best observed through a dilated pupil although these patients tend to dilate poorly.

It is important to examine the anterior segment again when the pupil is dilated as pseudoexfoliation can be subtle and effectively hidden by the iris. Repeated IOP measurements after dilatation are also important as pressure spikes can occur.

If glaucoma develops in these patients, medical therapy is the same as for primary open-angle glaucoma; however, this alone may not be enough to control IOP. Argon laser trabeculoplasty may be required and is usually initially successful although its effects can wane with time. Selective laser trabeculoplasty may be preferred as it is repeatable. Surgical intervention in the form of a trabeculectomy may be considered if IOP is still not at a desired level.

These patients must be most carefully followed. If they do not have glaucoma, a thorough review should be undertaken at least every 12 months.

Acknowledgement

The author thanks optometrist Wesley Robertson for his permission to use Figure 4. ▲

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Giant cell arteritis

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GIANT CELL arteritis (GCA) is a granulomatous vasculitis that affects medium-sized muscular arteries, particularly the cranial arterial branches of the aortic arch. Risk factors include age (≥ 50 years), gender (female predominance) and being of Northern European/Caucasian descent. It remains unclear whether previous infections have a role in the pathogenesis of GCA; in particular, *Chlamydia pneumoniae*, parvovirus B19, herpes virus type 1 and type 2, and varicella zoster virus have been investigated.[1]

Patients with GCA often present to their optometrist or ophthalmologist with anterior ischaemic optic neuropathy (AION) causing acute severe monocular vision loss, which can rapidly progress to become bilateral. Inflammation of the posterior ciliary arteries can cause a posterior ischaemic optic neuropathy (PION).

In either case, vision loss is often preceded by ischaemic symptoms of ocular pain, diplopia, ptosis, amaurosis fugax or coloured positive transient visual obscurations (TVOs). TVOs suggest transient choroidal ischaemia and hypoperfusion of the optic nerve head. In GCA, the duration varies from minutes to hours, unlike the briefer episodes experienced in papilloedema.

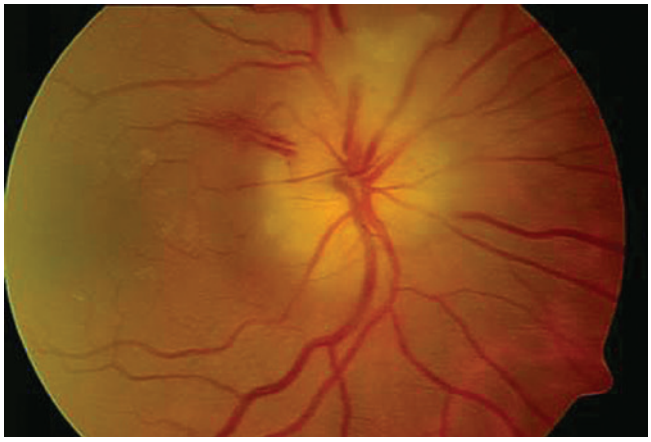
Systemic symptoms including jaw claudication, headache and scalp tenderness are important features to characterise in the clinical history.

Jaw claudication refers to masseter muscle pain after a brief period of chewing. Headache is typically new or different, severe and throbbing in quality, and diffuse or localised to the temporal or occipital regions. Patients with scalp tenderness often complain of pain when combing their hair or an aversion to wearing hats.

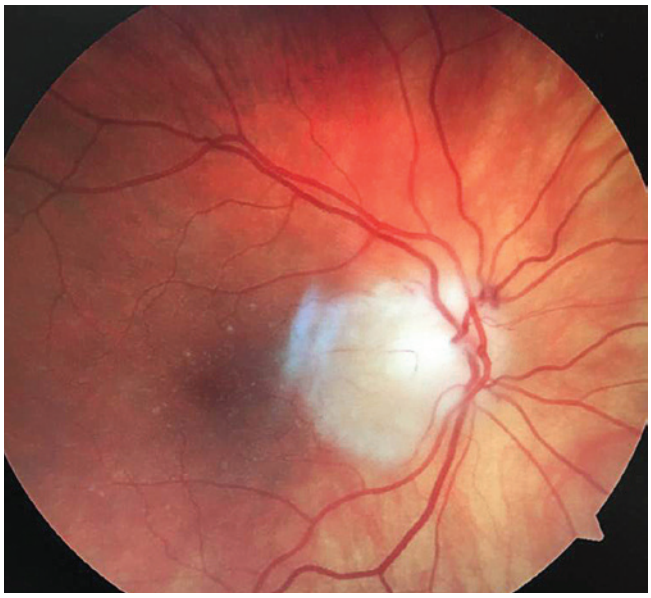
Concurrent polymyalgia rheumatica in GCA is common, which manifests as morning stiffness and pain of the axial and large joints (neck, shoulders and hips). Prominent constitutional symptoms include malaise, weight loss and fever. Occult GCA occurs in 20 per cent of patients, where associated symptoms are absent.[2]

Examination

Vision loss is often severe, to the magnitude of 6/60 or worse, particularly for GCA associated with arteritic AION (AAION). If vision loss is unilateral, there will be a relative afferent pupillary defect. Eye movements and cranial nerve examination are important. Diplopia can be caused by single or multiple cranial neuropathies, or localised



▲ Figure 1. AAION of the right eye. Diffuse 'chalk-white' or pallid optic disc oedema is characteristic of giant cell arteritis.



▲ Figure 2. AAION with cilioretinal artery occlusion of the right eye. Cilioretinal artery ischaemia is highly suggestive of giant cell arteritis.

ischaemia of ophthalmic artery branches supplying the extraocular muscles. Diplopia correlates with a positive temporal artery biopsy (TAB) and is associated with incident and subsequent vision loss.[3,4]

Ocular ischaemic syndrome is a rare complication of GCA that often precedes the development of AION. Relevant signs include hypotony (subclinical ciliary body ischaemia), corneal oedema, uveitis and cotton wool spots. Fundus examination typically demonstrates diffusely 'chalk-white' optic disc oedema (Figure 1). Simultaneous occlusion of the central retinal artery and cilioretinal artery is a pathognomonic sign (Figure 2).

External signs of GCA are a thick, tender, non-compressible and non-pulsatile temporal artery, and in advanced cases, scalp necrosis. Scalp tenderness can be elicited by light palpation in the region of the temporal arteries.

Diagnosis

There remain no validated diagnostic criteria for GCA. The American College of Rheumatology states that three out of five criteria are required to diagnose GCA: age ≥ 50 years, new-onset localised headache, tender or reduced pulsatility of superficial temporal artery, ESR ≥ 50 and abnormal biopsy specimen. However, its clinical utility has been refuted in favour of a TAB in all patients to guide management.[5] Jaw claudication, neck pain and raised CRP have the highest association with TAB-positive specimens.[2] Currently, a new chewing gum test is being developed and validated as a standardised clinical assessment of jaw claudication.[6]

As soon as the diagnosis is considered, the patient needs to be urgently referred to an ophthalmologist for a same-day consultation. If not available, patients must be directed to an emergency department for admission under neurology or rheumatology, with input from ophthalmology. High-dose steroid therapy should not be deferred for the TAB and should be commenced immediately, as it improves visual outcomes and prevents vision loss.[7]

Differential diagnosis

GCA should not be a diagnostic consideration in anyone younger than 50 years of age. Rheumatological conditions associated with non-GCA arteritic AION that can mimic GCA include:

- polyarteritis nodosa
- ANCA-associated vasculitides (granulomatosis with polyangiitis, Churg-Strauss syndrome)
- systemic lupus erythematosus
- rheumatoid arthritis.

Investigations

- **Systemic**

On blood tests, inflammatory markers CRP and ESR are often elevated, with a combined sensitivity of 97 per cent. However, there can be non-concordance, which is typically a high CRP and normal ESR.[8] Patients on systemic immunosuppressants can have normal inflammatory markers, so negative blood tests do not exclude GCA.

TAB is the gold-standard diagnostic test for GCA. It can be performed up to 10 days from starting steroid treatment. A specimen of at least 2 cm in length should be taken, with fine serial sections of 0.5 mm examined. Histopathology of an abnormal biopsy will demonstrate intimal thickening containing regions of granulomatous inflammation and endovascular occlusion (Figure 3). A contralateral biopsy can be performed if the ipsilateral side is negative, but only up to five per cent of such specimens are positive.[9]

- **Ophthalmic**

Standard automated perimetry is useful in documenting visual field defects in GCA, particularly in the contralateral eye. AION scotomas tend to occur in an altitudinal or arcuate pattern respecting the horizontal meridian, while central scotomas predominate in arteritic PION.[10]

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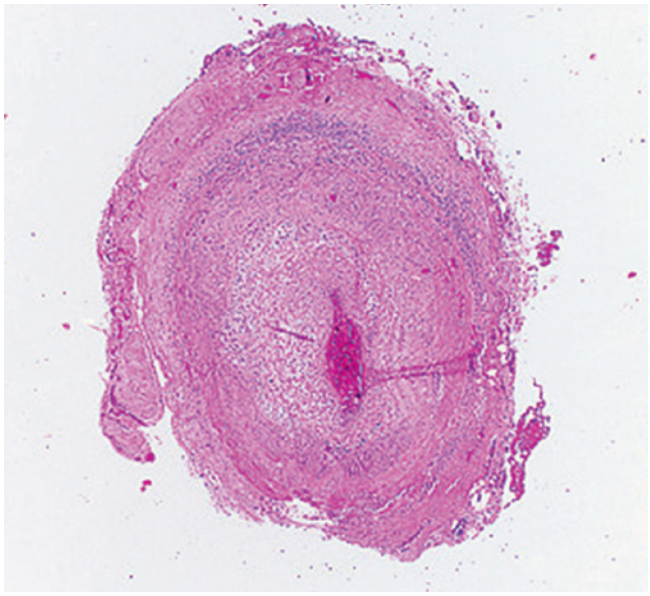
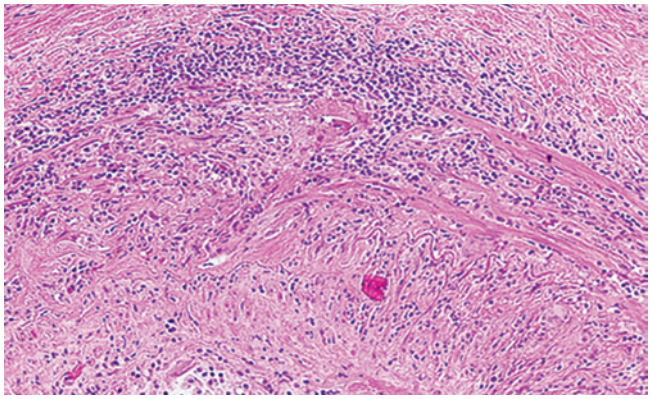


▲ Figure 3A. Haematoxylin and eosin-stained slide of a TAB specimen demonstrating intimal thickening and narrowed arterial lumen. Reproduced with permission (Kuo et al[6])



▲ Figure 3B. Higher magnification demonstrates an inflammatory infiltrate of lymphocytes and macrophages. Reproduced with permission (Kuo et al[6])

Giant cell arteritis

From page 5

Optical coherence tomography can be used to provide a baseline for the affected eye or show early oedema in the contralateral optic disc. Fluorescein angiography is a useful adjunct for demonstrating delayed or patchy choroidal filling, and delayed central retinal arterial filling.

Management

GCA is a sight- and life-threatening ophthalmic emergency and must be treated promptly. Delaying treatment can lead to disease progression to the fellow eye and irreversible vision loss in one-third of patients within one day, one-third in one week and one-third in one month.[11] Involvement of the carotid circulation can cause transient ischaemic attacks or strokes.

High-dose steroid therapy is often required for 18-24 months. There is no accepted weaning regimen, though most clinicians will reduce the dose based on symptoms and inflammatory markers (ESR and CRP).

Prognosis

The aim of promptly treating GCA is to protect the fellow eye and prevent visual deterioration. In untreated GCA, the risk of AAION in the fellow eye is 25-50 per cent. With appropriate treatment, the risk of recurrent AAION in the fellow eye drops to < 10 per cent.[12]

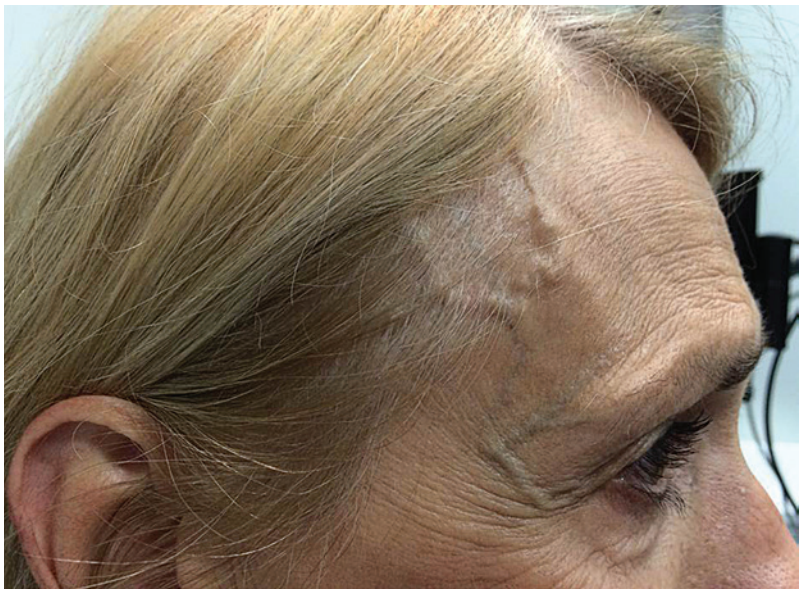
The same eye often has a very poor prognosis for recovery and up to 30 per cent may even deteriorate after steroids have been initiated. Only four to five per cent of patients demonstrate mild improvement in visual acuity and visual fields.[12] Earlier commencement of steroid therapy may improve prognosis. Ongoing review and collaboration with ophthalmologists and physicians is necessary throughout the treatment period and thereafter.

CASE REPORT

A 65-year-old woman presented with horizontal double vision, which was worse at distance. She complained of scalp pain while combing her hair and had stopped wearing her golf cap. Her diet had consisted exclusively of soups for the previous week. She reported occasionally waking with generalised stiffness and ache causing difficulty getting dressed but attributed this to ageing. Her medical history included varicella during infancy, hypertension and type 2 diabetes mellitus. Her ocular history was significant only for bilateral cataract surgery.

Best corrected visual acuity was 6/60 OD and 6/9 OS. Pupil examination revealed a subtle right RAPD. On cover test, the right eye had a subtle esotropia in primary gaze. On ocular motility testing, there was limited abduction of the right eye, suggesting a right abducens nerve palsy. IOP was 14 mmHg OD and 16 mmHg OS. Dilated fundus examination revealed diffusely pallid right optic disc oedema. Her right superficial temporal artery was tender, thickened and non-pulsatile on palpation (Figure 4).

She was admitted to hospital for intravenous steroids, and a temporal artery biopsy confirmed giant cell arteritis ▲



▲ Figure 4. In giant cell arteritis, the superficial temporal artery is prominent due to being thickened and dilated. On palpation, it is often tender, non-compressible and non-pulsatile.

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Beware of unilateral lid swelling and erythema

The importance of early diagnosis of orbital cellulitis

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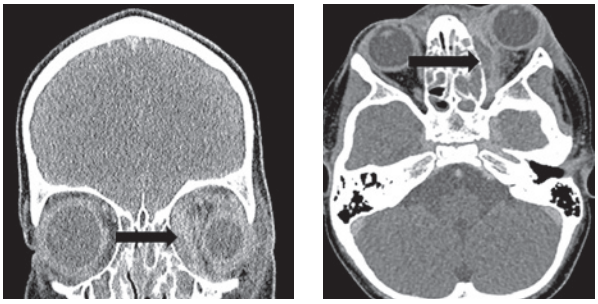

▲ Figures 1A and 1B. CT scan of the orbits reveals a multiloculated subperiosteal abscess

CASE REPORT

AK PRESENTED to the emergency department with a 24-hour history of unilateral left eyelid swelling. Initially he was diagnosed with preseptal orbital cellulitis and discharged with chloramphenicol 0.5% one drop qid to the left eye and fluorometholone 0.1%, one drop qid to left eye.

One day later, he re-presented with increased left eyelid oedema, and a fever of > 38 degrees Celsius. Laboratory results showed an increased white cell count of 14.9 x 10^9/L (neutrophils 11.7 x 10^9/L) and an increased C-reactive protein level of 42 mg/L. The working diagnosis was changed to orbital cellulitis. Systemically, he seemed well and an examination revealed no other abnormalities.

He was admitted to hospital and treated with intravenous antibiotics. After discussion with the infective diseases team, he was given intravenous ceftriaxone and flucloxacillin (each 50 mg/kg).

A CT scan of his orbits (Figures 1A and 1B) revealed a multiloculated subperiosteal abscess (30 x 8 x 12 mm AP x transverse x cranio-caudal) along the medial wall of the left orbit and extending from the medial canthus posteriorly to the orbital apex. This exerted a mass effect on the intraorbital structures, causing crowding at the orbital apex and proptosis.

The abscess was considered to be a probable complication of asymptomatic extensive sinonasal inflammatory disease.

Within 24 hours, AK was taken to theatre and under general anaesthetic, the abscess was drained by the ear, nose and throat team via a nasal approach. Intraoperative eye examination did not reveal any optic nerve swelling. Postoperatively he recovered well.

An intraoperative pus swab grew Haemophilus influenza (not type B), which was sensitive to ampicillin and cefotaxime. Blood cultures did not yield any bacterial growth. At day two postoperatively, the infectious diseases team rationalised his antibiotic therapy to single therapy ceftriaxone,[1] which continued for five days in total. On day three postoperatively, he was discharged under the care of the 'Hospital in the Home' service.

After two days at home, the left eyelid became swollen again. A second CT scan (Figure 2) revealed a left medial orbital wall subperiosteal collection, which could either represent a residual abscess or a recurrence of the original abscess. Despite its smaller size (23 x 5 x 23 mm), this collection caused a marked mass effect on the intraorbital structures. There was a new soft tissue abscess in the left lower eyelid measuring 7 x 14 x 7 mm.

Intravenous cefotaxime was commenced. The ear, nose and throat

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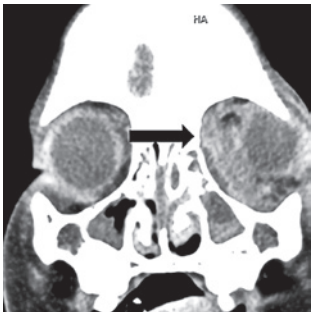

▲ Figure 2. A second CT scan, performed after the initial drainage, revealed a left medial orbital wall subperiosteal collection. This could represent either a residual abscess or a recurrence of the original abscess

Unilateral lid swelling and erythema

From page 7

team again drained the collection under general anaesthetic, via the same nasal approach. In addition to the antibiotic treatment, AK received 48 hours of intravenous dexamethasone treatment (0.15 mg/kg) to reduce the eyelid swelling.

Five days after the second abscess drainage, AK was discharged home on oral Augmentin. He had some residual diplopia that was improving and was thought to be due to residual orbital swelling. The ophthalmic examination was otherwise unremarkable.

Discussion

This case highlights the importance of early and accurate diagnosis of orbital cellulitis, which can be sight- and even life-threatening.[2] This is in contrast to the more common preseptal cellulitis, which affects subcutaneous tissue anterior to the orbital septum. Preseptal cellulitis is often caused by minor skin trauma, such as lacerations, insect bites or acute hordeolae.

Orbital cellulitis, affecting tissues deep to the orbital septum, commonly originates in the paranasal sinuses. It can also progress from preseptal cellulitis, dacryocystitis or dental infections.

Key clinical signs that may suggest orbital cellulitis include proptosis, chemosis, conjunctival injection and painful ophthalmoplegia; and optic nerve dysfunction such as reduced visual acuity, reduced colour vision or a relative afferent pupillary defect. ▲

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The Zika virus:

Ocular abnormalities associated with ZIKV exposure

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THE RIO OLYMPICS are now over and the attention of the world has moved on but the threat of the Zika virus (ZIKV) remains. In this article, we present a very brief update on the Zika virus and its presumptive ocular associations, and provide some primary management guidelines.

The Zika virus is a single-stranded RNA Flavivirus. Other viruses in this family include the dengue fever virus and the yellow fever virus. ZIKV is transmitted by mosquitoes, especially the species named *Aedes aegypti*, but rare cases of sexual and vertical transmission have also been reported.[1]

Not a new virus

The Zika virus was first identified in Uganda in 1947 in macaque monkeys and then in humans in 1952.[2] There have been subsequent outbreaks in tropical Africa, Southeast Asia and the Pacific Islands. More recently, the Zika virus has infected millions of Brazilians and is spreading rapidly throughout the Americas and into other parts of the world.

The Zika viral infection itself is rarely life-threatening, manifesting as a self-limiting non-specific viral illness with fever, non-specific rash, arthralgia and conjunctivitis, or it may be completely asymptomatic. However, a link has also been reported[3] between Zika virus and a more severe illness, Guillain-Barre syndrome, a disease of the nervous system causing muscle weakness or paralysis.

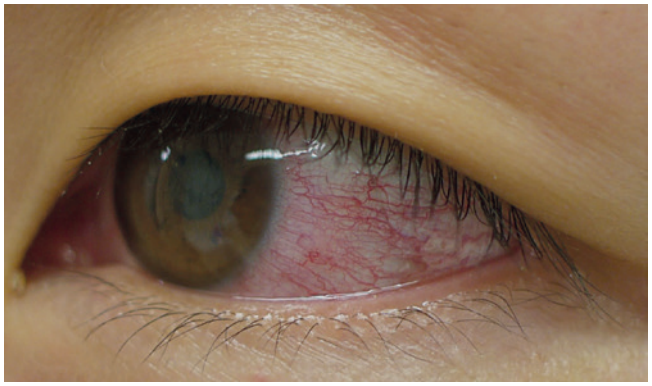
Recently, scientists from the American Center for Disease Control and Prevention (CDC) reported there is now enough evidence to conclude that Zika virus infection during pregnancy is a cause of microcephaly and other severe foetal brain defects and has been linked to problems in infants, including eye defects, hearing loss and impaired growth.

Scientists are studying the full range of other potential health problems that the Zika virus infection during pregnancy may cause. The World Health Organization has declared the Zika virus a 'Public Health Emergency of International Concern.'

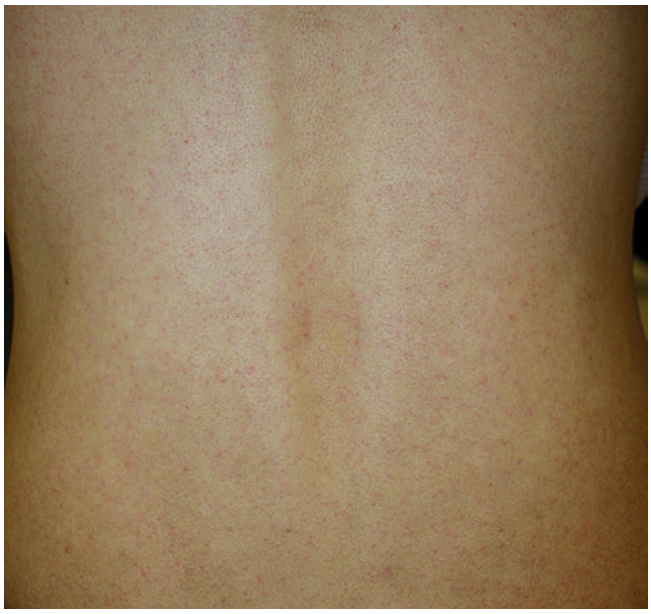
Currently, there is no commercial test available. To diagnose the Zika virus, the most important step is history-taking. Diagnostic testing includes a real-time reverse transcription-polymerase chain reaction (rRT-PCR) test which needs to be performed within the first 14 days of the infection. However, cross reaction with other Flaviviruses occurs. The more specific IgM test and neutralising antibodies test can take a few weeks.

Early this year, a Brazilian group published ocular findings in infants with microcephaly.[5] The study, conducted over three weeks, examined 31 babies with microcephaly. The usual causes of congenital infection (toxoplasmosis, rubella, CMV, HSV, syphilis and HIV) were ruled out. Most of the mothers seemed to have signs and symptoms of a non-specific viral illness in the first trimester.

a brief update



▲ Figure 1. Conjunctivitis in a case of imported Zika virus infection from French Polynesia to Japan, January 2014. Although the patient was afebrile upon examination, both bulbar conjunctivas appeared conjested.[4]



▲ Figure 2. Maculopapular rash on the back in a case of imported Zika virus infection from French Polynesia to Japan[4]

Of the babies with microcephaly, 10 (30 per cent) of the infants had ocular signs and a majority of these signs were bilateral. The examples of these were pigmentary mottling and chorioretinal atrophic lesions; some so severe they resembled coloboma. In some cases, the optic disc was involved with increased cup-to-disc ratio or optic disc hypoplasia.

Threat risk

In Australia, North Queensland harbours the vector mosquito and has had confirmed cases of Zika virus, but these appeared in people arriving from South America. No cases of local transmission have been reported in Australia.

The current recommendation is for all infants born with microcephaly in endemic areas to have an ophthalmic examination.

Pregnant women are advised not to travel to endemic areas. If women do travel to endemic areas, physical and chemical prevention of mosquito bites are recommended. If possible, pregnancy should be deferred for three months after travelling to endemic areas. Men in endemic areas should practise safe sex. Men with confirmed Zika virus infection should abstain from sex for three months.

If a pregnant woman who has recently travelled to an endemic area presents with conjunctivitis, she should be referred to her obstetrician for further management. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists has issued guidelines on the care of women with confirmed Zika virus infection during pregnancy.[6]

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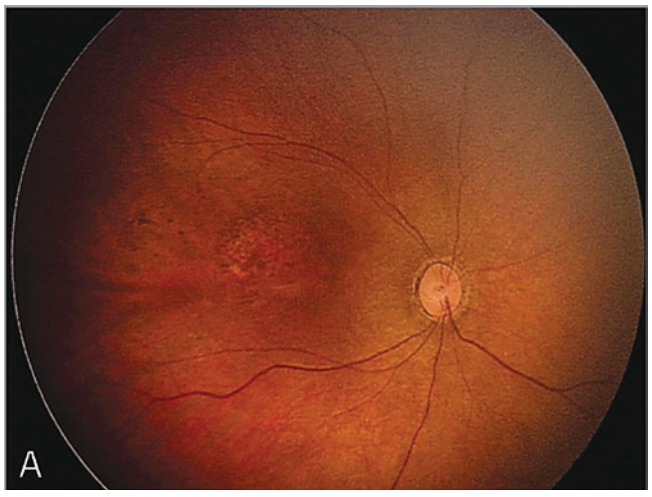
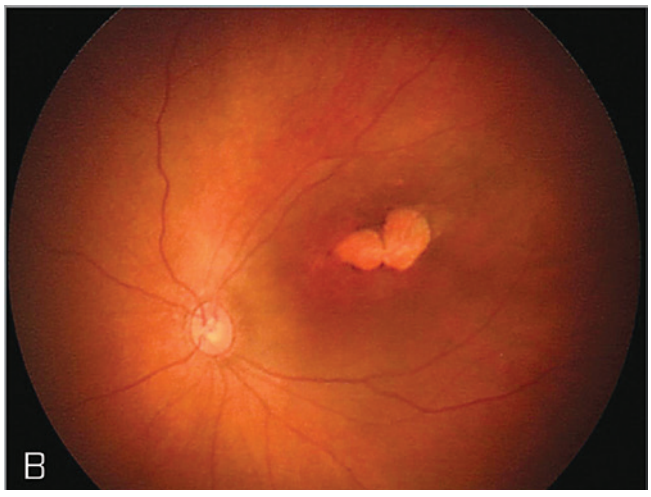
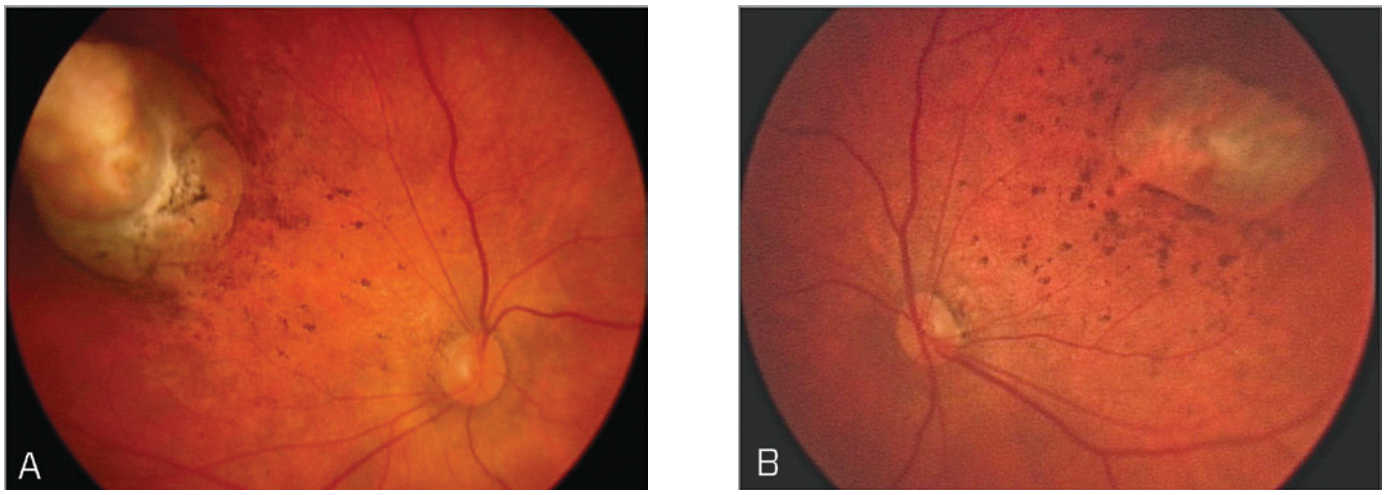
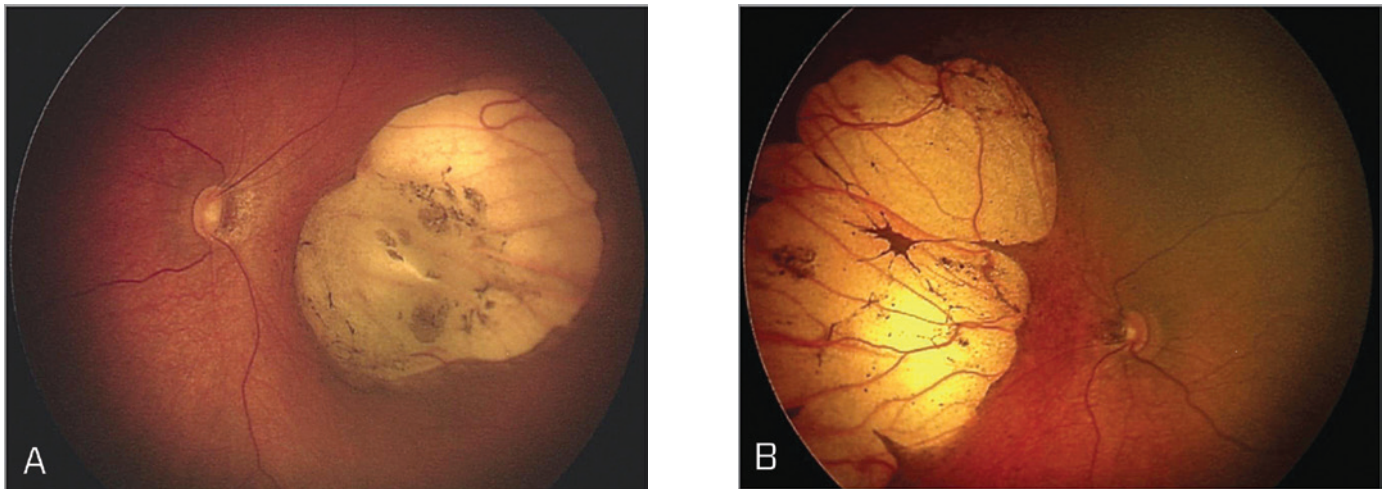




▲ Figures 3A and 3B. Fundus photographs of a two-month-old girl. A: The right eye has granular, pigmentary mottling in the macula. B: The left eye has a chorioretinal lobulated atrophic lesion and slight pigmentary mottling.[5]



▲ Figures 4A and 4B. Fundus photographs of a four-month-old. Both right (A) and left (B) eyes have paramacular superotemporal round chorioretinal atrophy surrounded by a hyperpigmented halo and hyperpigmented mottling.[5]



▲ Figures 5A and 5B. Fundus photographs of a 20-day-old infant. A: The right eye has optic disc hypoplasia, peripapillary nasal atrophy and an excavated nasal round lesion with a hyperpigmented halo, with a colobomatous-like aspect. B: The left eye has optic disc hypoplasia, peripapillary nasal atrophy and a retinal nasal lesion with a similar pattern.[5]

The Zika virus

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This article is based on information currently available. Regular updates on Zika virus are available from the Australian Department of Health website, the Australian Smart Traveller website and the American CDC website. ▲

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Amniotic membranes

A new option for the management of anterior segment disease

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AMNIOTIC membranes (AM) have been used clinically for more than 60 years; however, a non-surgical application of these membranes for the management of many ocular pathologies was not available until the mid 1990s.[1] Since that time, the popularity of AM has grown dramatically due to their ability to help speed healing and encourage regeneration of ocular tissues.

AM can be used in the form of a graft or as a patch. It can be sutured or sutureless. When using AM as a graft, it is intended to act as a scaffold for epithelial cells to grow. It is considered to be a biological bandage when used as a patch.[2]

Source

The AM is derived from the inner portion of fetal membranes. Fetal membranes consist of two layers. The outer layer of the fetal membrane is the chorion, which is vascular and in contact with the uterine wall. The inner membrane is the amnion, which is avascular and is in contact with amniotic fluids.

AM are derived from the inner layer of the fetal membranes and consist of three different layers: the epithelium, basement membrane and stroma which further consists of three contiguous but distinct layers: the inner compact layer, middle fibroblast layer and the outermost spongy layer.[3,4]

The amniotic tissue that is used in the development of AM is retrieved from donors undergoing elective cesarean section and who have been previously screened serologically for potentially communicable diseases including human immunodeficiency virus, hepatitis B and C viruses and syphilis.

The maternal donor is recommended to have repeated serological testing at six months to confirm the absence of any communicable diseases before the tissue is released for transplant.

The placenta is washed with antibiotics (covering gram +/-) and antifungal agents. A blunt dissection separates the amnion from the chorion, and the amnion is preserved via either cryopreservation or in a dry de-epithelialised form.

The cryopreserved AM has to be stored frozen and removed prior to installation to warm to room temperature. The dry de-epithelialised form can be stored at room temperature for two to five years and has to be rehydrated prior to use.[3]

Properties

Amniotic membranes promote epithelialisation, decrease inflammation and scarring, prevent new blood vessel growth, improve patient comfort by reducing pain and potentially have antimicrobial properties.[2,4]

The AM acts as a mechanical barrier similar to a therapeutic contact lens, increasing patient comfort and promoting epithelial regeneration by shielding a damaged cornea from the frictional forces of a blink.[2] The basement membrane of the AM is

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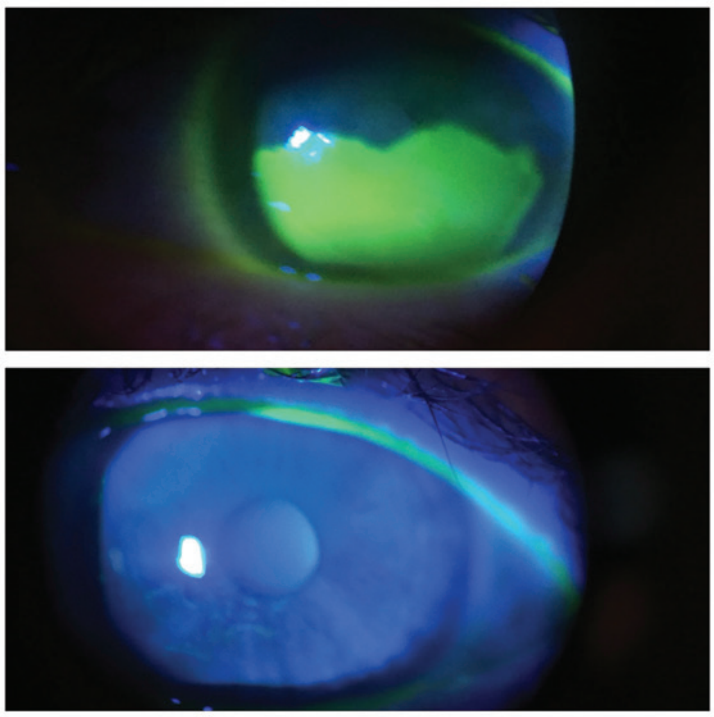

▲ Figure 1. Top: corneal staining after debridement of area affected by a recurrent corneal erosion (RCE). Bottom: cornea after treatment with a Prokera Slim AM for seven days. Image: BioTissue

Amniotic membranes

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similar to the conjunctival/cornea and provides a suitable substrate for promoting re-epithelialisation.

Regenerating corneal epithelium makes AM particularly useful for non-healing or persistent wounds, and is thought to occur from a combination of facilitating epithelial cell migration, reinforcing basal epithelial cell adhesion, promotion of epithelial cell differentiation and prevention of apoptosis.[2]

AM possess fetal hyaluronic acid, which helps to suppress the production of corneal, conjunctival and limbal fibroblasts, thus reducing scarring.[3] Pro-inflammatory mediators are suppressed/down regulated by the stromal layer of the AM helping to reduce inflammation and aiding in reducing scar formation.[2] Several anti-angiogenic factors are produced, which reduces new blood vessel growth and scarring.

Antimicrobial properties of AM are debatable. Some researchers propose antimicrobial activity from antimicrobial factors found in amniotic fluid and that the graft acts as a barrier to infection.[3]

Types

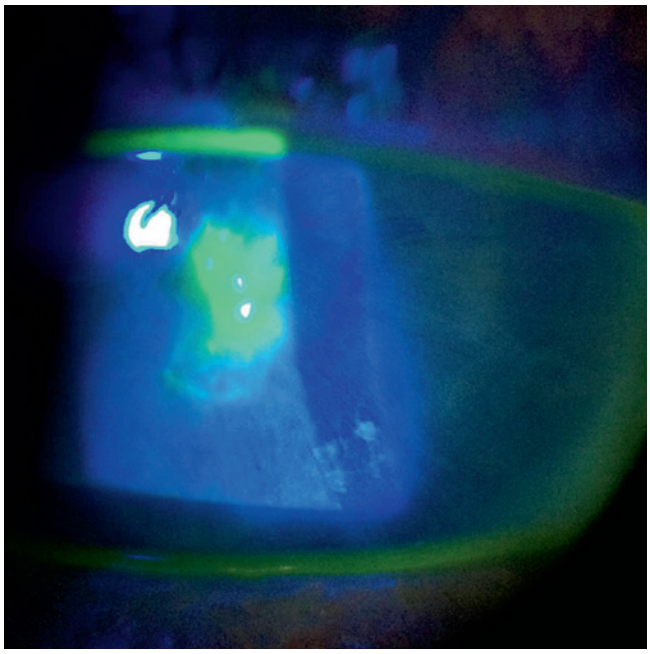
Three different types of AMs have been developed: permanent surgical grafts, dehydrated sutureless grafts and cryopreserved sutureless grafts.[3]

- **Permanent surgical grafts**

Corneal surgeons use surgical grafts when a more permanent graft needs to be sutured onto the host tissue and will later dissolve. This is commonly used during conjunctival reconstruction surgeries such as pterygium resection.

- **Dehydrated sutureless grafts**

Dehydrated sutureless grafts consist of a flat disc of tissue without a stabilising outer ring and require more finesse and dexterity during application. A lid speculum is required for applying the AM to the cornea, which is then smoothed and centred over the involved area.[5] A bandage contact lens is applied over the top of the AM. Special care must be taken when removing the lid speculum in order to not disrupt the graft by bumping it or the contact lens.[5] Two of the most common dehydrated sutureless grafts are the AmbioDisk (IOP Ophthalmics)[5] and BioDOptix (BioD).[6]



▲ Figure 2A. Patient presented with an infectious central corneal ulcer. Patient was treated and was left with a sterile ulcer. After seven days of non-healing, Prokera Slim was applied for seven days due to risk of central scarring. Image: BioTissue

- **Cryopreserved sutureless grafts**

The Prokera amniotic membrane is an example of a cryopreserved sutureless graft. These AM grafts are fastened within an ophthalmic conformer ring that is then applied over the cornea with the conformer ring resting on the sclera.[7] Prokera AMs come in three thicknesses: Prokera Slim (~100 µm thick), Prokera and Prokera Plus (~200 µm thick). The recommended thickness is based on the severity of the corneal defect being treated (the more severe the condition, the thicker the AM must be).

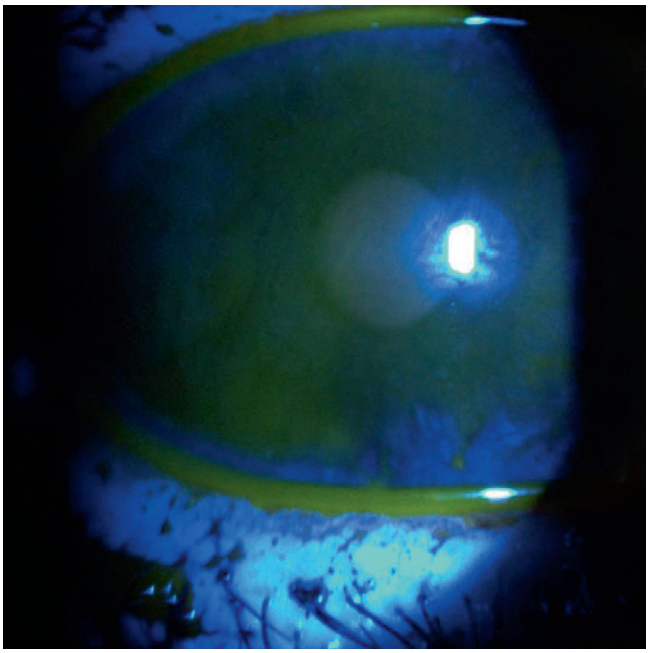
Prokera Slim is for mild-to-moderate indications such as recurrent corneal erosions,[8] Prokera is for moderate-to-severe indications such as neurotrophic epithelial defect and Prokera Plus is for very severe indications such as chemical burns. For most indications, the Prokera Slim is used as it provides more comfort to the patient.[7]

A new Prokera AM has just been released, called Prokera Clear, which has a 6-mm trephinated circle in the center of the membrane to allow some visual function and is indicated for patients who have a more peripheral inflammatory condition, for example, keratoconjunctivitis sicca.[9]

Indications

Ophthalmic indications for AM include a broad spectrum of ocular surface disorders which ultimately result in damage to the ocular surface cells, underlying stromal inflammation or any condition that leads to permanent scarring affecting the patient's vision.[4] Some of these include recurrent corneal erosion,[10] corneal sequelae of severe dry eye syndrome, neurotrophic ulcer, persistent corneal epithelial defect, chemical and thermal burn, Salzmann's nodular degeneration, acute Stevens Johnson Syndrome,[11] microbial ulcers, herpes simplex keratitis and herpes zoster keratitis.[2,3,4]

An AM may be used at any point to treat these conditions and replace the use of a therapeutic contact lens, which provides only a mechanical barrier. A therapeutic contact lens will provide patient comfort but it has no effect on scar inhibition.[12] A clinician should strongly consider an AM over a bandage contact lens in any corneal



▲ Figure 2B. Resulting cornea shows no scarring. Image: BioTissue

condition that has trouble healing on its own or may result in corneal scarring, such as in a central corneal ulcer. If a patient is currently taking adjunct pharmaceutical therapy, it is important they continue, especially when an active infection is present.

There are two groups of patients for whom the use of these membranes would be contraindicated: patients with glaucoma drainage devices or filtering blebs. Other contraindications specific to Prokera include patient allergies to ciprofloxacin or amphotericin B.[8]

Summary

AM are becoming more commonly used in the treatment and management of ocular surface disorders. As the conditions that are successfully treated with the use of AM become more understood, the role of the optometrist in the use of these treatment options will increase and be more commonplace. ▲

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New data on post-herpetic neuralgia

A STUDY REVEALS increased risks for post-herpetic neuralgia (PHN) in older zoster patients and those with severe immunosuppression, underscoring the importance of prevention.

To examine the effect of antivirals, and other potential risk factors, on PHN risk among zoster patients, researchers used prospectively collected data from the Clinical Practice Research Datalink, a UK general practice database.

Of 119,413 zoster patients, 6,956 (5.8 per cent) developed post-herpetic neuralgia. Post-herpetic neuralgia risk rose steeply with age, most sharply between 50 and 79 years. The risk was higher in women (6.3 per cent vs 5.1 per cent in men) and those with severely immunosuppressive conditions, including leukaemia (13.7 per cent) and lymphoma (12.7 per cent); autoimmune conditions, including rheumatoid arthritis (9.1 per cent); and other comorbidities, including asthma and diabetes. Current and former smokers, as well as underweight and obese individuals, were at increased risk of post-herpetic neuralgia.

The authors concluded that post-herpetic neuralgia risk was increased for a number of patient characteristics and comorbidities, notably with age and among those with severe immunosuppression.

Because zoster vaccination is contraindicated for patients with severe immunosuppression, strategies to prevent zoster in these patients, which could include the new herpes zoster subunit vaccine, are an increasing priority.

Neurology 2016; 87: 194-202.

Therapeutic NEWS of note

Associate Professor Mark Roth

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Re-esterified omega-3 for dry eyes

Oral consumption of re-esterified omega-3 fatty acids is associated with improvement in tear osmolarity, omega-3 index levels, TBUT, MMP-9 and OSDI symptom scores.

In a multicentre, prospective, interventional, placebo-controlled, double-masked study, 105 subjects were randomised to omega-3 (n = 54) and control group (n = 51).

The omaga-3 group received four softgels containing a total of 1680 mg of eicosapentaenoic acid/560 mg of docosahexaenoic acid. The control group received 3136 mg of linoleic acid, daily for 12 weeks.

Subjects from both groups were measured at baseline, week six, and week 12 for tear osmolarity, TBUT, OSDI, fluorescein corneal staining, and Schirmer test with anaesthesia. MMP-9 testing and omega-3 index were done at baseline and at 12 weeks.

The study found that a statistically significant reduction in tear osmolarity was observed in the omega-3 group versus control group at week six (-16.8 +/- 2.6 vs -9.0 +/- 2.7 mOsm/L, p = 0.042) and week 12 (-19.4 +/- 2.7 vs -8.3 +/- 2.8 mOsm/L, p = 0.004).

At 12 weeks, a statistically significant increase in omega-3 index levels (p < 0.001) and TBUT (3.5 +/- 0.5 s vs 1.2 +/- 0.5 s, p = 0.002) was also observed. The omega-3 group experienced a significant reduction in MMP-9 positivity versus control group (67.9% vs 35.0%, p = 0.024) and OSDI scores decreased significantly in omega-3 (-17.0 +/- 2.6) versus control group (-5.0 +/- 2.7, p = 0.002).

Cornea 2016; July 20 (Epub ahead of print).

The case for early intervention in pterygium

A study published in *Cornea* concludes that it is best to operate when the size of the pterygium corneal area is still small.

To establish determining factors for fast corneal sensitivity recovery after pterygium excision, study authors recruited 32 eyes of 14 males and 18 females with primary nasal pterygium.

Differences in corneal sensitivity (in the four quadrants and the centre using a Cochet-Bonnet esthesiometer), pterygium corneal area (PCA), tear osmolarity, tear break-up time, Schirmer test, and ocular symptoms were analysed before and one month after lesion excision. The relationship between corneal sensitivity recovery (difference between the two time points; CS1 - CS0) and the other features was assessed.

Corneal sensitivity recovery after pterygium excision showed important variability. The only studied factor that seems to be determinant could be pterygium corneal area.

The study authors concluded that it would be advisable to operate when the lesion is relatively small, with lower surgical injury and faster and complete recovery, thus protecting ocular surface homeostasis.

Cornea 2016 Jun 29 (Epub ahead of print).

Thumb-suckers less likely to develop allergies

Young children who suck their thumbs or bite their nails may be less likely to develop allergies later in childhood, according to a New Zealand study that spanned three decades.

Researchers analysed data from an ongoing study of more than 1,000 children born in New Zealand between the years 1972 and 1973. Parents reported the thumb-sucking and nail-biting habits of their children at ages five, seven, nine and 11 years. Researchers also tested the children for allergies using a skin-prick test when they were 13 years, and then followed up with the children again when they were 32 years.

It was found that frequent thumb-suckers or nail-biters had a lower risk of atopic sensitisation at age 13 years (odds ratio 0.67, 95 per cent confidence interval 0.48–0.92, p = 0.013) and age 32 years (odds ratio 0.61, 95 per cent confidence interval 0.46–0.81, p = 0.001). These associations persisted when adjusted for multiple confounding factors.

Children who had both habits had a lower risk of atopic sensitisation than those who had only one habit. No associations were found for nail-biting, thumb-sucking, and asthma or hay fever at either age.

The study's authors suggested that these results lend support to the 'hygiene hypothesis,' which holds that environments that have too little dirt and germs may make children more susceptible to certain conditions, including allergies.

Pediatrics Jul 2016, e20160443; DOI: 10.1542/peds.2016-0443.

Cancer, diabetes and detection bias

According to a study that appeared in the US journal *Cancer,* the association between diabetes and cancer is strongest right after a diabetes diagnosis. The finding suggests that the epidemiologic associations between diabetes and cancer can be partially explained by a detection bias around the time of a diabetes diagnosis.

Researchers conducted a retrospective, population-based cohort study of more than one million adults living in Ontario, Canada, to evaluate the

association between diabetes diagnosis and the incidence of cancer in three time periods: within the 10 years before a diabetes diagnosis, within the first three months after a diabetes diagnosis, and from three months to 10 years after a diabetes diagnosis.

During a median five years after diabetes diagnosis (or matched date), about 36,000 incident cancers were identified in those with diabetes and 33,000 in controls. Those with diabetes had a 62 per cent higher cancer risk in the first three months after diabetes diagnosis; however, they showed no elevated risk thereafter.

In addition to the findings suggesting detection bias, patients with diabetes were 23 per cent more likely to be diagnosed with cancer in the 10 years before diabetes diagnosis, relative to controls.

The results of the study show that individuals with diabetes had a significantly higher risk of most cancers, which was limited to the time periods before and immediately after a diabetes diagnosis. The highest risk period was observed within the first three months after a diabetes diagnosis, suggesting at least a partial role of detection bias.

Cancer 11 Jul 2016; DOI: 10.1002/cncr.30095.

What's a 'typical' optic nerve head?

Do atypical optic nerve head (ONH) characteristics necessarily lead to atypical biomechanical responses to elevated IOP? Do typical biomechanical responses necessarily come from ONHs with typical characteristics?

In a recent study, researchers addressed these two specific questions. They found the answer to both questions is: no.

Researchers generated 100,000 ONH numerical models with randomly-selected values for the characteristics, all falling within the ranges of normal ONHs. The models were solved to predict their biomechanical response to an increase in IOP. Researchers classified ONH characteristics and biomechanical responses into 'typical' or 'atypical' using a percentile-based threshold. They then studied the effects of varying the percentile threshold.

When researchers classified the extreme five per cent of individual ONH characteristics or responses as atypical, only 28 per cent of ONHs with an atypical characteristic had an atypical response. Almost 29 per cent of typical responses came from ONHs with at least one atypical characteristic.

Ultimately, the results challenge the assumption that ONHs with atypical sensitivity to IOP must have atypical characteristics. This finding suggests that the traditional approach of identifying risk factors by comparing characteristics between patient groups (for example, ocular hypertensive vs primary open angle glaucoma) may not be a sound strategy.

Exp Eye Res 23 Jun 2016;149:40-47. doi: 10.1016/j.exer.2016.06.012 (Epub ahead of print).

Surprise! Pterygium in low UV index areas

A Canadian study has found that in a geographic area with low ultraviolet light index, the frequency of epithelial neoplasia seen in excised pterygium specimens was higher than expected. The rate was 2.33 per cent.

Of 215 pterygium specimens received at the Henry C Witelson Ocular Pathology Laboratory, McGill University, Montreal, ocular surface squamous neoplasia was identified in five. Four patients were women and one was a man, and age did not appear to influence the results.

All five lesions were classified according to the Armed Forces Institute of Pathology recommendations. Conjunctival intraepithelial neoplasia I was seen in three cases, and conjunctival intraepithelial neoplasia II and III were each seen in one case.

'Our frequency rates were close to rates reported in Sydney and even higher than in Florida, regions that are known to have higher yearly exposures to UV rays than Montreal,' the authors wrote.

The relatively high rate of dysplasia in a low ultraviolet light index area challenges the main cause of this disease in our population. The authors suggested that all pterygium samples should be sent for histopathological evaluation, even in areas with low ultraviolet light index.

Saudi J Ophthalmol 2016; doi:10.1016/j.sjopt.2016.02.007.

There's the rub

A study published in *Clinical and Experimental Optometry* has shown the adverse effects of eye-rubbing before and after contact lens insertion.

To examine the prevalence of 'removal-relief' rubbing and its potential consequences, rubbing histories were recorded for contact lens wearing normal and keratoconic patients as well as for normal non-contact lens wearers. Analogue scaled responses were used to identify and compare abnormal rubbing habits.

Researchers found that contact lens wearing patients, both with and without keratoconus, reported significantly more rubbing before contact lens insertion ($p < 0.05$) compared to non-contact lens wearers. Eye-rubbing after contact lens removal ('removal-relief' rubbing) was found to be significantly more prevalent among contact lens-wearing keratoconic patients compared to contact lens-wearing non-keratoconic patients ($p < 0.001$ in both cases).

The author concludes that rubbing-related trauma occurring before contact lens insertion may predispose the cornea to wound healing activities and greater levels of adverse response to contact lens wear. Such adverse responses could predispose the cornea to greater trauma, which occurs in response to rubbing on removal of contact lenses.

Strong counselling to avoid eye rubbing is often not an adequate form of management for a significant number of patients with keratoconus. Evidence of relapses indicates the need for better and more frequent methods of counselling for keratoconus patients.

Clin Exp Optometry 2016; 99: 4: 366-372. doi: 10.1111/cxo.12343.

Retinal dystrophy: diagnosis and treatment

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INHERITED RETINAL dystrophy (IRD) is now the leading cause of severe, irreversible vision loss in adults of working age in the United Kingdom, following recent advancements in the treatment of diabetic eye disease.[1]

IRD is a heterogeneous group of genetic disorders resulting in premature death of photoreceptors and/or retinal pigment epithelium. Other mechanisms, such as retinoschisis, can occur.

Different patterns of photoreceptor loss result in different phenotypes: retinitis pigmentosa begins with rod degeneration, and cone dystrophy with cone degeneration. In cone-rod dystrophy, both types of photoreceptors are involved. This article briefly covers diagnosis, genetic diagnosis and treatments of retinal dystrophy. One caveat: the field is moving rapidly so this article may be rendered out of date almost immediately after publication.

Diagnosis

Diagnosis of IRD depends on thorough history and examination including:

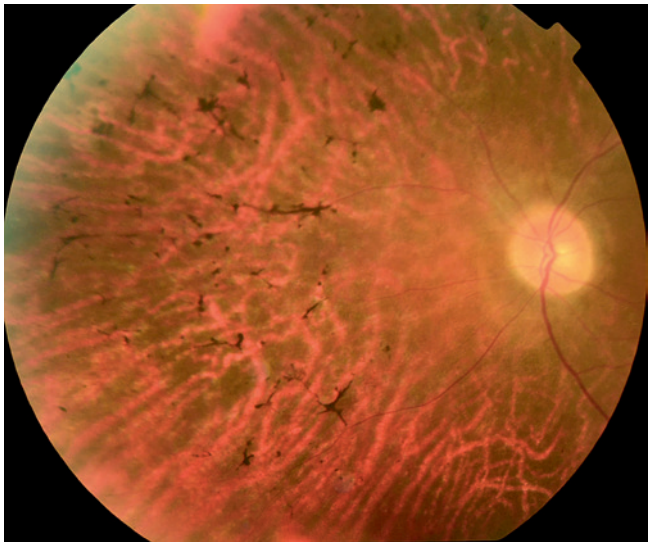
- Comprehensive history including presence of nyctalopia (night blindness) and medication history
- Family ophthalmic history
- Best corrected visual acuity
- Assessment of anterior eye including anterior chamber angles to assess suitability for pupil dilation
- Measurement of intraocular pressure
- Dilated retinal examination including non-contact fundus lens examination (78 D optimal)
- Examination of the retinal periphery with indirect binocular ophthalmoscopy.

Ancillary testing includes:

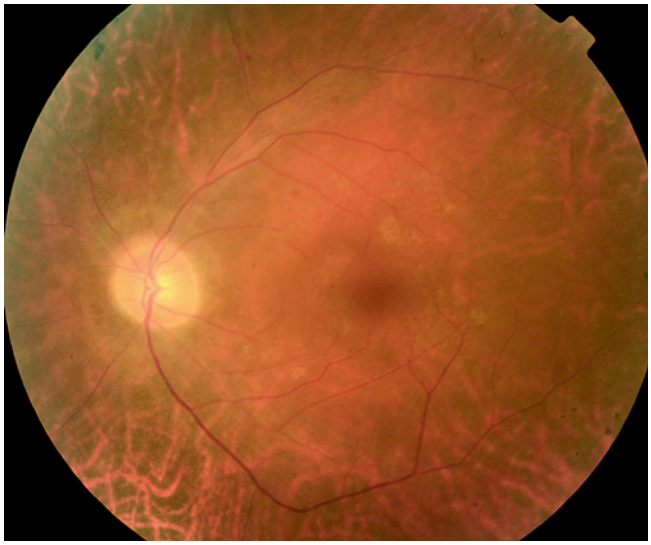
- Documentation of retinal status with retinal photography (Figures 1 and 2)
- Assessment of visual field with automated threshold perimetry, both monocularly and binocularly (Figure 3)
- Retinal autofluorescence imaging (Figure 4)
- Macular OCT to help detect the pattern of photoreceptor loss and macular abnormalities (cystoid macular oedema, atrophy or schisis) (Figure 5)
- Electroretinography (ERG) to measure function of rods and cones within the widespread retina. Multifocal ERG to measure macular function.

Figures 1-5 show the left eye of a 56-year-old male with a clinical diagnosis of retinitis pigmentosa. Gene testing has not been performed.

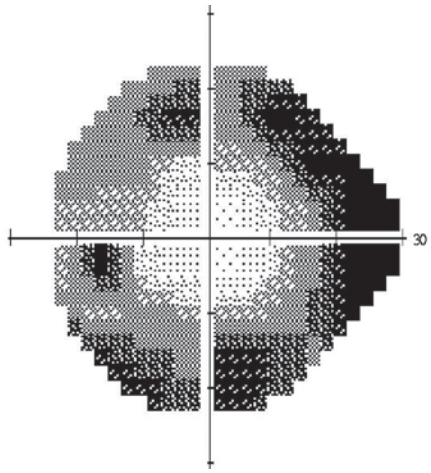
Diagnosis of IRD is made holistically, taking into account history, clinical findings, ERG findings and gene testing when performed.



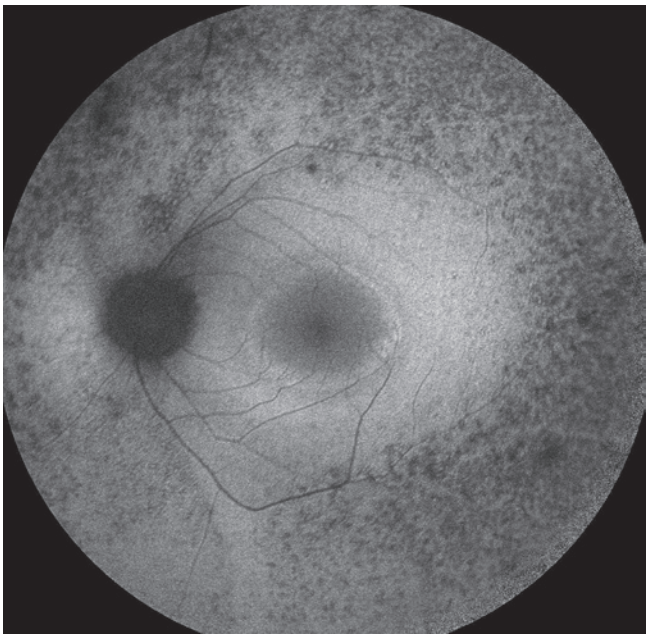
▲ Figure 1. Colour fundus photograph of posterior pole demonstrating disc pallor, attenuated vessels and peripheral intraretinal pigment migration



▲ Figure 2. Colour fundus photograph of nasal retina demonstrating RPE thinning and intraretinal pigment migration



▲ Figure 3. Automated perimetry demonstrating field constriction



▲ Figure 4. Fundus autofluorescence demonstrating multiple small hypoautofluorescent peripheral lesions and a ring of hyperautofluorescence in the macula

IRD is not diagnosed solely on the basis of retinal pigmentation or abnormal ERG. In some patients, repeat ERG may be necessary after several years to confirm the condition is progressive.

Genetics

Autosomal dominant, autosomal recessive, X-linked, mitochondrial, multi-gene related and syndromic patterns of inheritance have been described. Close to 300 genes and loci have been identified as related to IRD to date,[2] with an estimated future total of more than 500 responsible genes. Gene testing may be offered to patients over the age of 18 years, particularly for family planning purposes.

Patients need to be counselled that gene testing is 'negative', that is, a single responsible gene mutation is identified and responsible for the eye disease in at least 50 per cent of patients. Gene testing produces complex clinical, personal and financial outcomes and must be undertaken only in association with genetic counsellors.

Treatment

The only current treatment studied in a randomised clinical trial is vitamin A supplementation.[3] This treatment is controversial; it has associated risks of teratogenicity during pregnancy and idiopathic intracranial hypertension, and may be offered only in consultation with physicians. Vitamin A supplementation is not recommended in patients with ABCA4 mutations.[4]

Future treatments of IRD focus on replacing missing elements of the visual pathway from photoreceptors to occipital cortex and may be considered gene-dependent or gene-independent.

Gene-dependent treatments

Gene-dependent treatment replaces or repairs the patient's abnormal gene. Classical gene therapy replaces defective genes using viral vectors which carry the normal gene. Gene therapy is most suited to conditions with a null mutation, where the problem is due to absent normal protein.

The first classical gene therapy treatment was for Leber's congenital amaurosis type 2, due to abnormality of the RPE 65 gene located on chromosome 1.[5,6]

Treatment results in improved visual function but unfortunately, the degeneration progresses. More recently, a phase I/II clinical study using classical gene therapy for choroideraemia has shown improvement in visual function,[7] but long-term results in dystrophy progression are not yet available.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a new method of gene repair, rather than replacement. CRISPRs are the hallmark of a bacterial defence system which forms the basis of the CRISPR-Cas9 genome editing technology.

In brief, abnormal DNA is cleaved *in situ* and the cell's DNA repair mechanism repairs the cleaved DNA using a guide normal DNA molecule. CRISPR has been used to delay retinal degeneration in a rat model of IRD.[8] *In vitro* human retinal cells have been shown to be capable of DNA repair using CRISPR technology.[9] CRISPR technology is new and rapidly advancing but there are no current human trials recruiting.

Gene-independent treatments

Gene-independent treatments include growth factors, stem cells, optogentics and retinal prostheses (bionic eye).

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Retinal dystrophy

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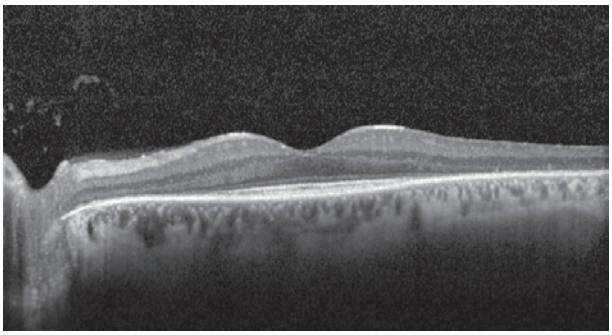

▲ Figure 5. Optical coherence tomography demonstrating extensive parafoveal photoreceptor loss

- **Growth factors**

This approach utilises growth factors which are known to be important in retinal health and disease to support residual photoreceptors. Trials of ciliary neurotrophic growth factor delivered by encapsulated cells in an intraocular implant demonstrated safety and suggested improvement in vision in patients with retinitis pigmentosa,[10] but not in CNGB3 achromatopsia.[11] Rod-derived cone viability factor, in which abnormalities are the cause of cone loss in patients with retinitis pigmentosa, shows promise as a treatment to support abnormal cones.[12]

- **Stem cells**

This approach aims to replace missing retinal cell types. Pluripotential stem cells have been recently isolated from fibroblasts obtained during skin biopsy. These cells can be differentiated as retinal progenitor cells, retinal ganglion cells and retinal pigment epithelium *in vitro* using specific growth factors. Pluripotent stem cells may have gene editing performed on them using CRISPR technology prior to differentiation to specific retinal cell types. Differentiated cells are injected into the subretinal space during vitrectomy or can be injected into the vitreous cavity with a single intravitreal injection. Phase I/II clinical trials are underway in Best disease[13] and retinitis pigmentosa.[14,15]

- **Optogenetics**

This approach bypasses diseased photoreceptors and relies on the incorporation of molecules which respond to light (channelrhodopsin, halorhodopsin or melanopsin) into healthy inner retinal cells. Incorporation of channelrhodopsin into On-bipolar and rod-bipolar cells, or halorhodopsin into On- and Off-retinal ganglion cells allows both on- and off-responses to light stimuli. A phase I/II gene therapy trial of channelrhodopsin-2 in retinitis pigmentosa is underway.[16]

- **Bionic eye**

This approach relies on the use of implants which can respond to light and send stimuli to the patient's remaining visual pathway. Implants can be epiretinal, subretinal, suprachoroidal, in the optic nerve, in the lateral geniculate nucleus and in the occipital cortex. This approach relies on neuroplasticity as patients adapt to using the implant.

Pre-clinical studies are underway for a suprachoroidal implant at the Royal Victorian Eye and Ear Hospital[17] and an occipital implant at Monash University.[18]

Conclusion

Rapid progress is being made in understanding the genetic basis of IRD. Although new treatments are in development which aim to replace or repair defective genes or to support or replace defective tissues, they are not yet available to offer to patients in routine clinical care. ▲

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Atropine for amblyopia

The case for pharmacologic penalisation of the sound eye

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AMBLYOPIA is a neuro-developmental disorder resulting from abnormal visual experience early in life that affects 2-3 per cent of children.[1,2] Vision development becomes compromised because of the presence of an amblyogenic factor, that is, constant unilateral strabismus, anisometropia or obstruction of the ocular media.

The first step in the treatment of amblyopia is correction of significant refractive error. When present, typical prescribing protocols, based on a cycloplegic refraction, provide the full correction of anisometropic, astigmatic and myopic refractive error, with the goal of providing equally clear retinal images. The amount of hyperopic correction is dependent on whether the child also has an esotropia, and any reduction in hyperopia (cutting the plus usually by not more than +1.50 D) is made symmetrically to both eyes.[3]

Wearing such an optical correction has been shown, over time, to have a bona fide treatment effect on amblyopia beyond the visual acuity (VA) improvement obtained from simply eliminating optical blur.[3-5]

Vision loss that is still present following a minimum of 16-18 weeks of optical treatment alone usually warrants some form of penalisation of the sound eye.

Historically, patching has been the most widely used form of penalising; however, patching can have psycho-social drawbacks and compliance can be problematic. An alternative treatment is pharmacologic penalisation of the sound eye using 1% atropine sulfate eye-drops.

This review highlights the current evidence base for pharmacologic penalisation of the sound eye with atropine to treat unilateral amblyopia. Patient selection, treatment protocols, expected treatment outcomes, treatment time course, adverse effects, follow-up considerations, and patient/parent education are discussed.

Pharmacology

Atropine, a belladonna alkaloid, is as an anticholinergic drug. In the eye, atropine blocks the responses of the ciliary muscle and the iris sphincter to cholinergic stimulation, thereby producing cycloplegia and mydriasis, respectively. Atropine has a slower onset and more prolonged effect than cyclopentolate or tropicamide. The time to maximum cycloplegia takes several hours and can persist for 14 days or longer.

Atropine is contraindicated for eyes with shallow anterior chambers because of the risk of precipitating angle closure glaucoma. There is mild stinging associated with the instillation of the drops and local allergic (hypersensitivity) reactions are occasionally seen. Systemic side-effects include dryness, flushing of skin, fever, tachycardia, confusion, unusual behaviour and irritability.

Use of 1% atropine for amblyopia treatment

When used for amblyopia treatment, the atropine drop is administered to the sound eye with the goal of the resultant cycloplegia causing sufficient blur so that fixation switches from the sound eye to the amblyopic eye.

The extent of blur and whether it is present at near only or at both distance and near, depends on the child's refractive error and whether the child is wearing his/her full refractive correction. A hyperopic child wearing a full correction will be blurred only at near, whereas one wearing a partial correction will be blurred at both distance and near.

Historically, atropine penalisation has been advocated for mild to moderate amblyopia (6/24 or better VA) based on the premise that the amount of blur induced by the atropine would be likely to be insufficient to cause a shift in fixation preference in amblyopic eyes with 6/30 or worse VA.

In 1997, a survey of the Pediatric Eye Disease Investigator Group (PEDIG) investigators found that three per cent prescribed atropine as the primary treatment modality for amblyopia and 41 per cent prescribed it when patching proved unsuccessful.[6] Without rigorously conducted studies, treatment for amblyopia had been based mainly on observation and clinical impression, and patching was the mainstay of treatment.

Since then, the PEDIG has reported findings from numerous randomised clinical trials and prospective observational studies, the Amblyopia Treatment Studies (ATS), which clinicians can turn to for guidance in developing sound treatment protocols for their practices.[7]

The first PEDIG clinical trial for amblyopia that evaluated atropine compared VA outcomes in children aged from three to younger than seven years of age with moderate

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Atropine for amblyopia

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amblyopia (6/12 to 6/30) who had been randomised to either daily administration of 1% atropine in the sound eye or at least six hours of daily patching.[6]

Both treatment groups had similar improvements in amblyopic eye VA at six months and the treatment effect did not vary by age, cause of amblyopia or depth of amblyopia. Both treatments were well tolerated, with parents reporting a slightly higher degree of acceptance for atropine treatment (Table 1).[8] Surprisingly, a shift in fixation preference from the atropinised sound eye to the amblyopic eye was not essential for VA improvement.[9,10]

Amblyopia Treatment Index Subscale Scores by Treatment Group*

ATI Subscale		Median Score‡ on ATI: Patching	Atropine	P Value
Adverse Effects	3 to < 7 yo	2.25	2.20	p = 0.002
	7 to <13 yo	2.25	2.31	p = 0.45
Difficulty with compliance	3 to < 7 yo	2.20	1.80	p < 0.001
	7 to <13 yo	2.60	2.00	p < 0.001
Social stigma	3 to < 7 yo	3.00	2.00	p < 0.001
	7 to <13 yo	2.33	2.00	p < 0.001

* Adapted from Table 4 in Holmes JM et al. Impact of patching and atropine treatment on the child and family in the Amblyopia Treatment Study. *Arch Ophthalmol* 2003; 121; 11: 1625-1632 and from data presented in Felius J, et al. Evaluating the burden of amblyopia treatment from the parent and child's perspective. *J AAPOS* 2010; 14: 389-395.

‡ 1 to 5 rating scale; higher number indicates more difficulty

▲ Table 1. Acceptance of treatment regime by patients reported in ATS studies [8,15]

A subsequent randomised clinical trial compared less frequent (weekend only) administration of 1% atropine drops to daily atropine as an initial treatment for three-year-old to seven-year-old children with moderate amblyopia.[11] VA improvement was 2.3 lines in both groups at the four-month outcome visit. Those who had shown VA improvement at the four-month visit continued on treatment.

At the time of study completion, approximately 50 per cent in both groups had amblyopic eye VA of either 6/8 or better, or VA within one line or equal to that of the fellow eye; 80 per cent reached their maximum VA improvement by four months; some showed continued improved for up to 10 months.

Prescribing a plano lens to the sound eye to augment the effect of atropine by creating blurred distance vision in addition to increased blur at near has also been evaluated in a randomised trial.[12] Prescribing a plano lens did not substantially improve amblyopic eye VA compared with prescribing weekend atropine alone; however, more patients (40 per cent) achieved 6/7.5 or better VA in the added plano lens group than in the atropine alone group (29 per cent). Amblyopic eye VA improved at least three lines in approximately 50 per cent of the participants. Atropine has also been shown to be an effective treatment for children with severe amblyopia of 6/30 to 6/120.[9]

Clinical implications

For moderate amblyopia in children 3 to < 7 years of age:

- Atropine penalisation (one drop in the non-amblyopic eye) has a similar treatment effect as two hours and six hours of prescribed patching; thus, it can be considered for first-line amblyopia treatment or for patching failures.
- Daily atropine administration is not necessary; a twice-per-week schedule is also effective; daily administration has not been shown to result in larger improvements or quicker results.
- There is no evidence that atropine needs to be administered only on weekend days or that the days need to be sequential.
- Atropine penalisation can be effective in treating both moderate and severe amblyopia, and amblyopia in children older than seven years of age.

Reverse amblyopia and measuring sound eye VA

Although some children in the aforementioned clinical trials had apparently reduced sound eye VA at follow-up visits, there were no cases of persistent reverse amblyopia, where VA measured more than one line worse than baseline, after discontinuation of atropine.[9,10,12] Initially, reverse amblyopia was suspected in some children but it was then determined that in most of these cases the sound eye VA had not been assessed through the full hyperopic correction.

Atropine can uncover hyperopia additional to that found with cyclopentolate drops at the initial refraction. Therefore, it is important to determine if the atropinised sound eye has any uncorrected hyperopia, and when present, to measure sound eye VA through the full hyperopic prescription at follow-up visits. Nevertheless, it is important to monitor sound eye VA during atropine penalisation therapy because there are reported cases of reverse amblyopia in the literature.[13,14]

Atropine side-effects

The most common ocular adverse effect associated with atropine treatment in the aforementioned studies was light sensitivity, with reports varying from seven per cent to 29 per cent, albeit rarely sufficient to lead to a change in treatment.[9,12,15] Systemic reactions were rare and in most instances these children were switched to daily 5% homatropine.[6,11,12] Although we are not aware of any studies substituting 1% cyclopentolate, it is possible this shorter-acting cycloplegic eye-drop could be similarly effective if administered daily.

Use in older children

There is currently no known age cut-off in terms of visual plasticity and thus the potential for successful amblyopia

treatment. While amblyopia is more responsive to treatment in younger children, many older children have marked improvements in VA.[16]

In a clinical trial of seven-year-old to younger than 13-year-old children with moderate amblyopia, VA improvements were found to be comparable for those who were randomised to two hours of patching compared with those randomised to weekend-only atropine.[17]

Reading requirements during school days should be considered for older children who are being treated with atropine, particularly when their sound eye has hyperopic refractive error that is under-corrected.

Summary

Atropine penalisation for amblyopia is an alternative treatment to patching for children with moderate amblyopia and has also been shown to be effective for some patients with severe amblyopia. Two days per week is typically an effective dose. Light sensitivity can be easily managed with sunglasses and a brimmed hat when outdoors; systemic reactions are rare. Overall, parents and children generally find atropine penalisation to be an acceptable treatment method and often prefer it to patching. In addition to using atropine as a first-line treatment for amblyopia, it should be considered for patching failures.

CASE REPORT

ML, an active pre-schooler, presented at four years and nine months of age. He had been prescribed glasses to be worn full-time and patching of his right eye for five hours per day at the age of two years; however, his glasses were broken and patching had been abandoned because of an allergic reaction to adhesive patches and non-compliance with a 'Pirate Pete' eye patch.

Pertinent clinical findings were a cycloplegic refraction of RE +8.00 DS and LE +9.50 DS, with best-corrected VA of 6/9 and 6/45 in the right and left eyes, respectively.

In regard to patient management, the importance of full-time glasses wear was emphasised, and given the history of non-compliance with patching, twice weekly 1% atropine penalisation was prescribed.

Amblyopic eye VA improved from 6/45 to 6/30 at the three-month review and then to 6/21 at the six-month review. ML is still on treatment with the aim of his showing further improvement at the next review. ▲

Atropine penalisation clinical pearls

- Monitor for reverse amblyopia; permanent severe reverse amblyopia is rare but possible
- Test VA of sound eye through full plus at follow-up visits; retinoscopy to determine if residual plus
- Make sure atropine has been discontinued for two full weeks before diagnosing reverse amblyopia
- Discuss with parents and provide a written instruction sheet that includes the following:
  - Administration of drops to which eye; the 'medicine' goes in the good eye
  - Parent should wash hands before and especially after drops
  - Safe storage out of reach of children
  - Potential adverse ocular effects of mild stinging and redness after initial instillation; light sensitivity when dilated
  - Sunglasses and a brimmed hat recommended for outdoor activities
  - List of potential systemic side-effects and instructions on what to do if they occur
  - Parents inform school that child is on atropine penalisation treatment; likewise inform other health-care providers, particularly if child visits a hospital emergency room

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Remember: examine the optic nerve head

Alex Petty

BOptom(Hons)

Tauranga, New Zealand

A classic example of a patient needing services for one issue and having an unrelated condition diagnosed

CASE REPORT

A 62-YEAR-OLD English woman of Indian descent presented to my practice as she had been noticing flashes in the temporal periphery of her vision of the left eye for the previous month. These flashes were occurring only in the evening and more so when she rotated her head to the left. There was no history of trauma and she was not noticing any floaters, blind spots in her vision or decreased acuity.

The patient had emigrated from the United Kingdom several years before and remembered that at her previous eye test she had been told one of her eyes looked a little unusual; however, treatment was not discussed. She got by using a pair of over-the-counter +2.00 reading glasses.

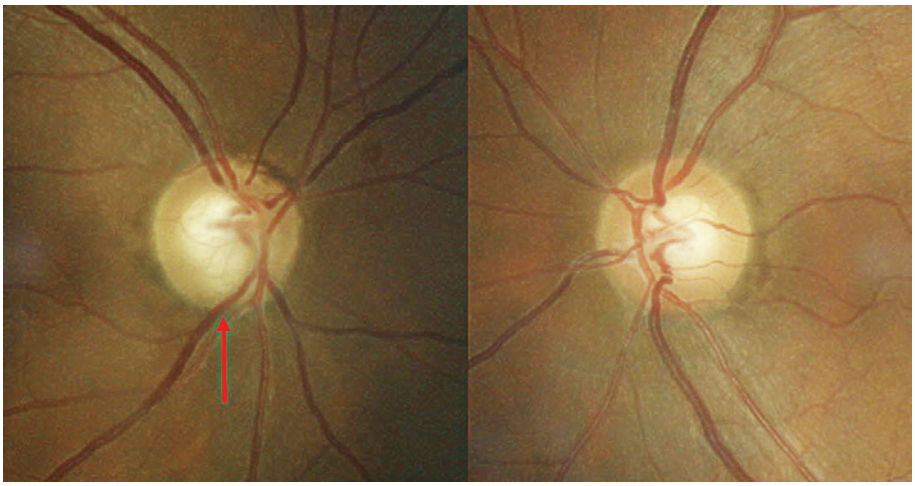
Our patient's general health was fine, although she did have some deafness from a severe bout of chicken pox when she was in her 30s. She had no diabetes or high blood pressure and she took no regular medications. As far as she knew, no-one in her family had any eye issues.

Suspecting a posterior vitreous detachment, I carried out a pre-dilation work-up. Unaided visual acuity was 6/5 in each eye with a refraction showing R +0.50/-0.50 x 35 (6/5), L +0.50/-0.50 x 95 (6/5), add +2.25. Pupils were equal, round and regular and no afferent defect was present. Ocular motility revealed no restrictions and in my chair the patient reported no flashes or discomfort on left gaze. The anterior eye was unremarkable with open angles (AC/C ratio of 0.6 with Van Herrick estimation) and clear cornea and crystalline lens. There was no obvious iris trans-illumination. Tonometry revealed some intraocular pressure asymmetry with R 25 mmHg, L 21 mmHg. Her corneae were on the thin side at R 512 µm and L 519 µm.

Following dilation with 1% tropicamide in both eyes, the mobile posterior vitreous face could be seen in the left eye although no free pigment was noticeable behind the crystalline lens. The retina was intact in each eye with no holes, tears, blood or traction seen, and there were no obvious vitreous floaters close to the retina. A diagnosis of posterior vitreous detachment in the left eye was made and the patient was reassured and given warnings in case her symptoms changed.

Optic nerve

Examination of the optic nerves during this posterior investigation revealed the unusual appearance that was alluded to in the history. Asymmetry was present between the two eyes with the right eye's inferior neuro-retinal rim appearing notched and pale (Figure 1). The left eye, in contrast, was relatively normal with a medium size and a 0.45 cup/disc ratio. The patient was asked to return for a glaucoma work-up the following week.



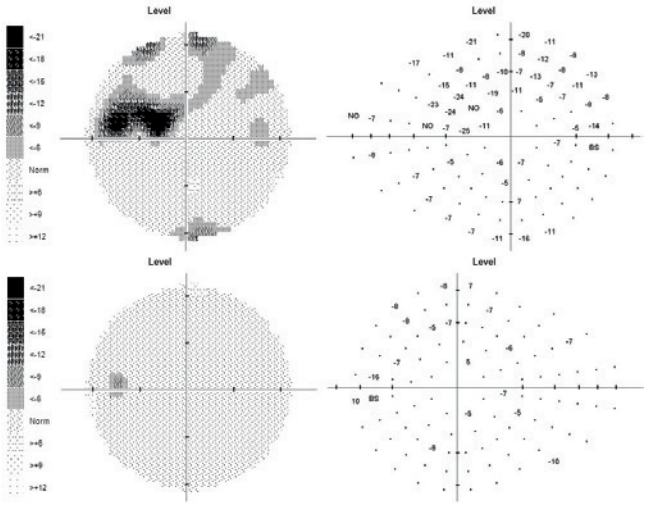
▲ Figure 1. Right and left optic nerves. The red arrow highlights the location of the inferior rim thinning in the right eye. No nerve fibre layer defect is noticeable with red-free viewing.

After further questioning on our patient's return, she admitted that she noticed tingling at the tips of her fingers from time to time. She mentioned that she had had some blood loss during her chicken pox illness; however, this was likely to have been related to her skin lesions and was not relevant.

Intraocular pressures were again higher in the right eye (R 23 mmHg, L 18 mmHg) Goldmann applanation. Gonioscopy showed normal open angle structures and no sign of any pseudo-exfoliative material or pigment.

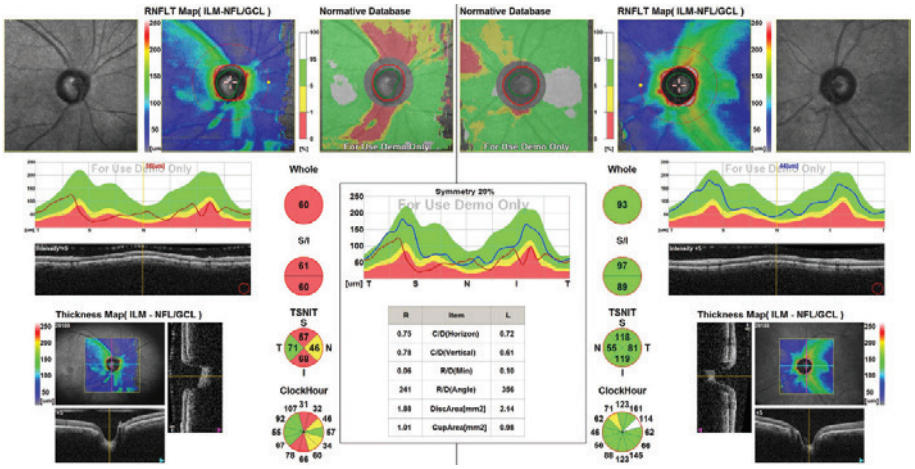
Visual field testing was performed well by the patient (Medmont M700 Glaucoma Test) and unsurprisingly, showed a superior arcuate field defect. The right inferior field and the left field were relatively normal (Figure 2).

OCT testing (Nidek RS-3000) was carried out and confirmed an inferior retinal nerve fibre layer (RNFL) defect in the right eye. Surprisingly, the superior RNFL in the right eye is also flagged as being markedly thin (Figure 3). The left eye RNFL was within normal limits.



▲ Figure 2. Visual field plots of the right eye (top) and left eye (bottom) showing the superior arcuate defect in the right eye

Analysis of the ganglion cell layer (GCL) showed an expected defect of the inferior macula (Figure 4); however, the superior macula GCL was relatively normal. Given that the superior rim of the right ONH appeared healthy and the inferior visual field was normal, this brings into question the validity of the flagged superior RNFL loss in this eye. The left eye GCL was within normal limits.



▲ Figure 3. OCT showing thinning of the RNFL superiorly and inferiorly in the right eye

After consideration of these findings and the patient's risk factors, a diagnosis of unilateral primary open-angle glaucoma in the right eye was made. The patient was concerned about the prospect of life-long topical glaucoma medication as she had apparently reacted to eye-drops in the past. As a result, she was referred for consideration of selective laser trabeculoplasty (SLT).

Discussion

This case is a classic example of a patient needing our services for one issue and having an unrelated condition diagnosed in the process. It highlights the importance of being on the look-out for other signs of ocular disease when carrying out routine investigations.

This patient had a number of risk factors for glaucoma:[1] advancing age, higher IOP in one eye, thin corneae and potential Raynaud's disease.

It is unclear in the literature if people of Indian descent are more or less likely to develop POAG, although according to one group, glaucoma was responsible for 12 per cent of the blindness in Hyderabad, India,[2] a figure similar to that in the UK and USA.[1]

Raynaud's disease is a condition which is characterised by cold fingers and toes, loss of skin colour in these areas and a prickly feeling or stinging pain during recovery. In Raynaud's disease, arteries to the extremities go into vasospasm when exposed to cold or stress, narrowing and temporarily limiting blood supply. It is thought that this decreased perfusion could suggest a vascular disorder compromising blood flow to the optic nerve and increasing the risk of glaucoma.

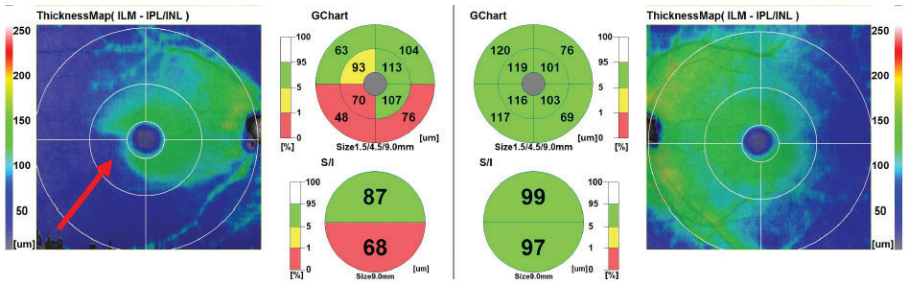
Other conditions with poor ocular perfusion include sleep apnoea, migraine headaches and patients with a nocturnal drop in blood pressure. Patients with these conditions may also have a higher risk of glaucoma.[3]

When making the initial diagnosis of glaucoma, as practitioners we have to be careful to consider other

Continued page 24

Examine the optic nerve head

From page 23



▲ Figure 4. OCT macula analysis of the ganglion cell layer shows thinning inferiorly in the right eye. Note the wedge defect of this layer in the colour representation as shown by the red arrow.

masquerade conditions. Compressive optic neuropathy, ocular ischaemic syndrome, anterior ischaemic optic neuropathy and even methanol poisoning may cause glaucoma-like cupping of the optic nerve head.[4]

This patient has a number of clinical signs of glaucoma: a notched optic nerve head, a higher IOP in the eye, thin corneae, visual field changes in the expected location and OCT scanning confirming RNFL loss and ganglion cell layer loss. In this case, it is highly unlikely another condition is responsible.

When considering treatment options, it is useful to be mindful of the patient's stage in life. Glaucoma is a condition that requires treatment for life and it carries significant financial and social burdens for the patient. Our patient is in her early 60s and may have another three to four decades of life ahead of her.

It is important her treatment gives her the best chance of retaining her vision in the future. Laser treatment such as SLT can be useful as an initial treatment for POAG as it is equally efficacious as the typical front-line glaucoma medication latanoprost, decreasing intraocular pressure by around 30 per cent.[5] SLT treatment also avoids the risks of non-compliance with medical treatment. Research with electronic eye-drop monitoring revealed only 76 per cent to 86 per cent eye-drop compliance in glaucoma patients, and evaluation of prescription claims showed patients had glaucoma eye-drops available to use 69 per cent of the time.[6]

SLT is not a magic bullet as it is well known that the IOP-lowering effect of SLT decreases over time. The mean survival time (time taken for 50 per cent of eyes to no longer have pressure reduction of ≥ 20 per cent) is around two years,[7] although some patients may still retain good pressure control after five years.[8]

In the end, the patient opted to start with medical treatment (Xalatan nightly to both eyes) for her POAG, despite being offered SLT by the ophthalmologist in order to avoid allergy. Apparently the prospect of a laser was more confronting than the idea of using eye-drops each night. She was to be followed up in our clinic after two months to assess her pressure control.

Summary

With optometry's increasing scope of practice, it is important for practitioners to remain highly vigilant when examining even routine cases. All optometrists should be comfortable detecting, diagnosing and managing glaucoma. Management may include referral to other optometry or ophthalmology colleagues who regularly treat glaucoma, commencing the patient on medical treatment yourself, or recommending SLT treatment as a first-line therapy in order to avoid eye-drops and increase compliance. Be comforted that patients with POAG will not go blind overnight but they will require your care and expertise for many years into the future. ▲

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PBS Information: Authority required for the treatment of wet age-related macular degeneration, diabetic macular oedema and central retinal vein occlusion. Refer to PBS schedule for full Authority Required information.
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Common: retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia. Others: see full PI. **DOSAGE AND ADMINISTRATION*:** 2 mg aflibercept (equivalent to injection volume of 50 µL). EYLEA is for intravitreal injection only. The interval between doses injected into the same eye should not be shorter than one month. Advice on treatment initiation and maintenance of therapy specific to each patient population is described in the section below. Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. There is limited information on the optimal dosing interval and monitoring interval especially for long-term (e.g. > 12 months) treatment. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued. *For wet AMD:* Treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. Long term, it is recommended to continue EYLEA every 2 months. Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes. The dosing interval can be extended up to every 3 months. *For CRVO:* Treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. *For BRVO:* Treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. *For DME:* Treatment is initiated with one injection per month for five consecutive months followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. *For myopic CNV:* EYLEA treatment is initiated with one injection of 2 mg aflibercept (equivalent to 50 µL). Additional doses should be administered only if visual and/or anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease. **DATE OF PREPARATION:** Based on PI dated July 2016. Approved PI available at http://www.bayerresources.com.au/resources/uploads/PI file10294.pdf or upon request from Bayer Australia Ltd, ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073.

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