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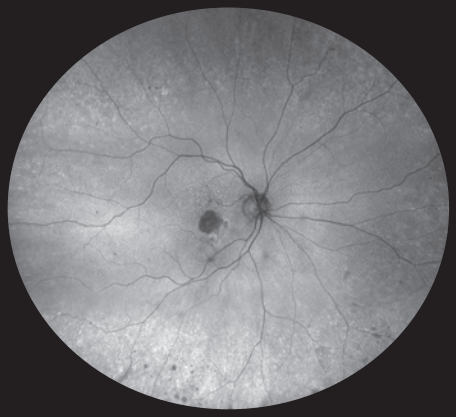

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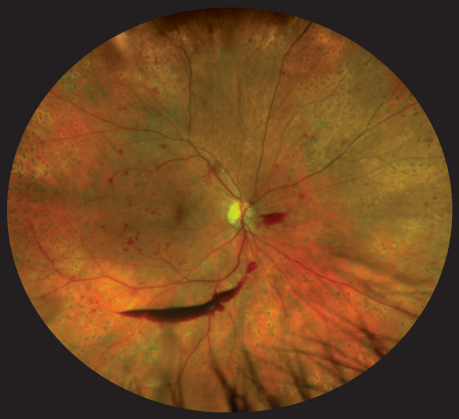

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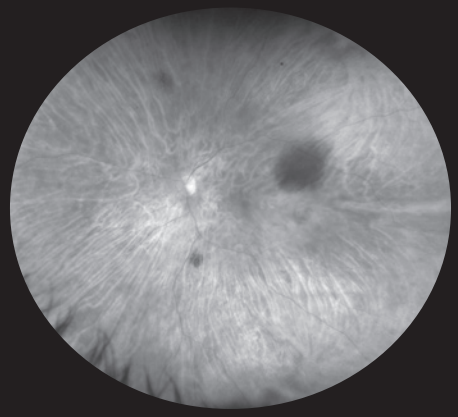

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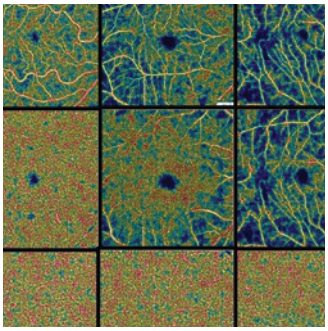

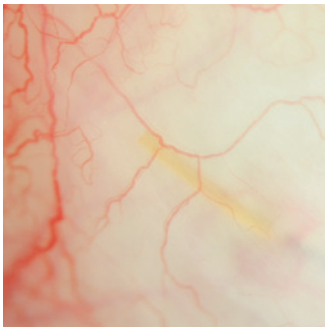

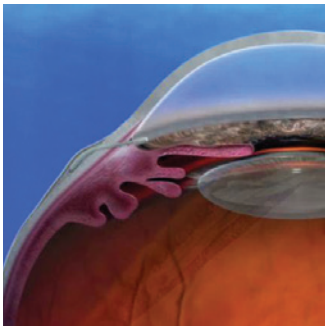

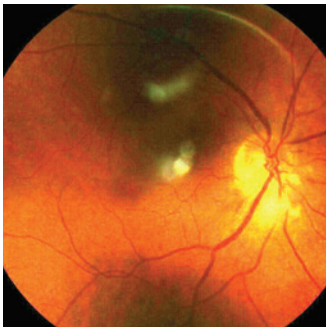

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OCT-Angiography

Insight into macular vascular changes seen in retinitis pigmentosa using OCT-A

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RETINITIS pigmentosa (RP) is defined as a group of rare, hereditary retinal diseases that result in progressive loss of photoreceptors. Patients typically present with nyctalopia and progressive loss of peripheral vision.[1] For many years, the focus of RP has been on understanding the pathophysiology of the disease and identifying the various structural abnormalities that manifest throughout the disease progression, including arteriole attenuation, waxy optic nerve pallor, bone spicule formation, posterior subcapsular cataracts and macular mottling.

Optical coherence tomography angiography (OCT-A) is a new, innovative, non-invasive imaging modality that allows for advanced imaging and analysis of the macular vascular changes associated with RP that have not been previously reported. These findings have provided additional insight into the pathophysiology behind the disease, suggesting involvement at the level of the inner retina. We present three cases of RP at varying stages to highlight the changes in macular vascular density throughout the retinal and choroidal layers as the disease progresses.

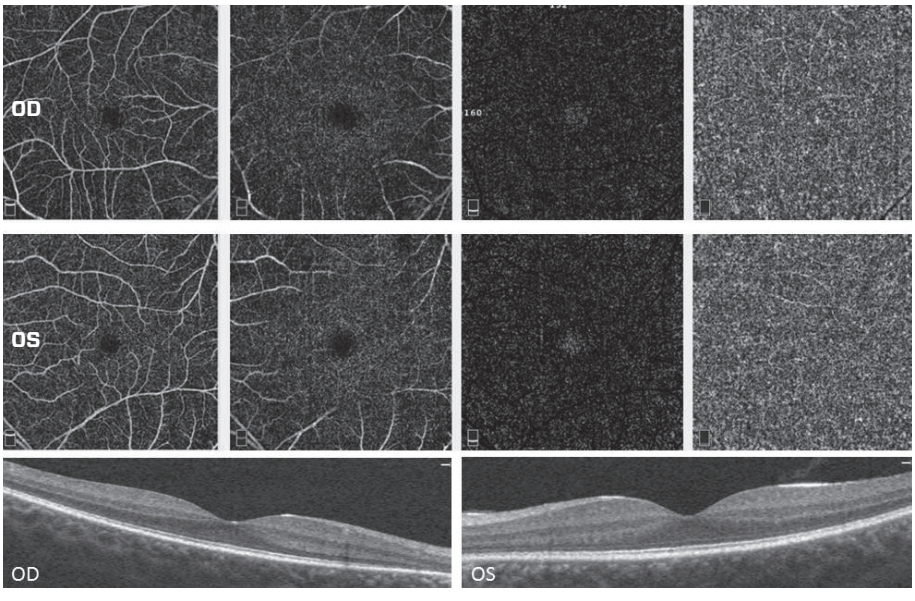
CASE REPORT 1

An 18-year-old African American male presented with a history of unknown retinal dystrophy, presumed RP. Two years previously, a prior doctor had suspected RP based on mild clinical signs but was unable to confirm without electroretinography. The patient had no complaints of decreased night vision or peripheral vision. After probing, the patient reported a slight delay in visual recovery after looking at bright lights. The patient denied a family history of RP. His systemic history was unremarkable and he was not taking any medications.

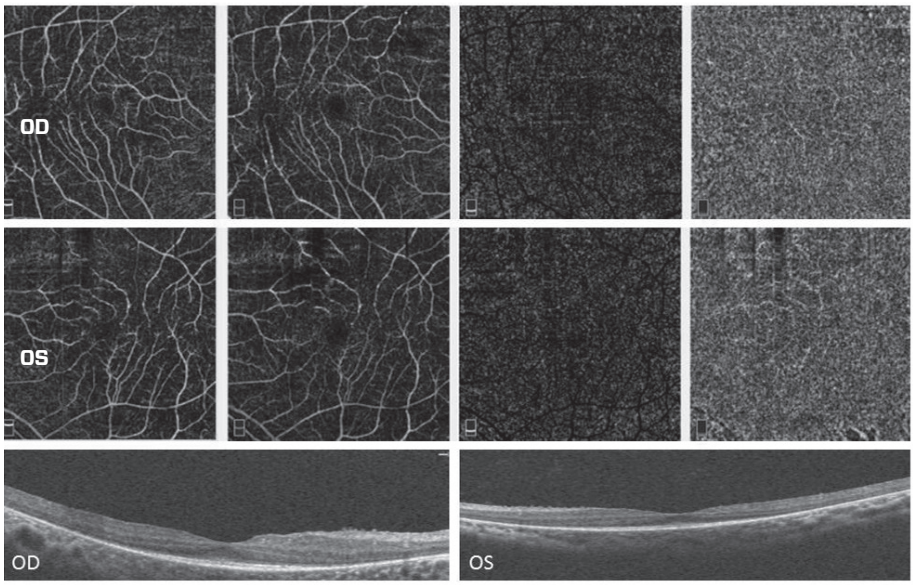
Best corrected visual acuities were 6/6 OD, OS. Pupils, confrontations, extraocular motility and colour vision were found to be normal. Intraocular pressure measured 11 mmHg OD, OS. Anterior segment findings were unremarkable, with no posterior subcapsular cataracts. Both eyes exhibited similar findings on fundus evaluation. The optic nerves were pink and healthy, C/D ratio was 0.3, with no waxy pallor. The macula was intact, with no haemorrhaging, oedema or mottling. Retinal vasculature demonstrated slight vessel attenuation. In addition, there was mild bone spicule formation in the periphery and mid-periphery.

SD-OCT of the macula appeared healthy with no apparent structural abnormalities. Vascularisation of the retinal layers was visualised and segmented using OCT-A. In addition, objective quantification of vessel density was evaluated for each eye using the AngioVue software.

Analysis of the angiograms revealed decreased retinal vascular perfusion and capillary density in both the superficial capillary plexus (SCP)



▲ Figure 1. OCT angiography and SD-OCT of the right and left eye of a patient with mild retinitis pigmentosa



▲ Figure 2. OCT angiography and SD-OCT of the right and left eye of a patient with moderate retinitis pigmentosa

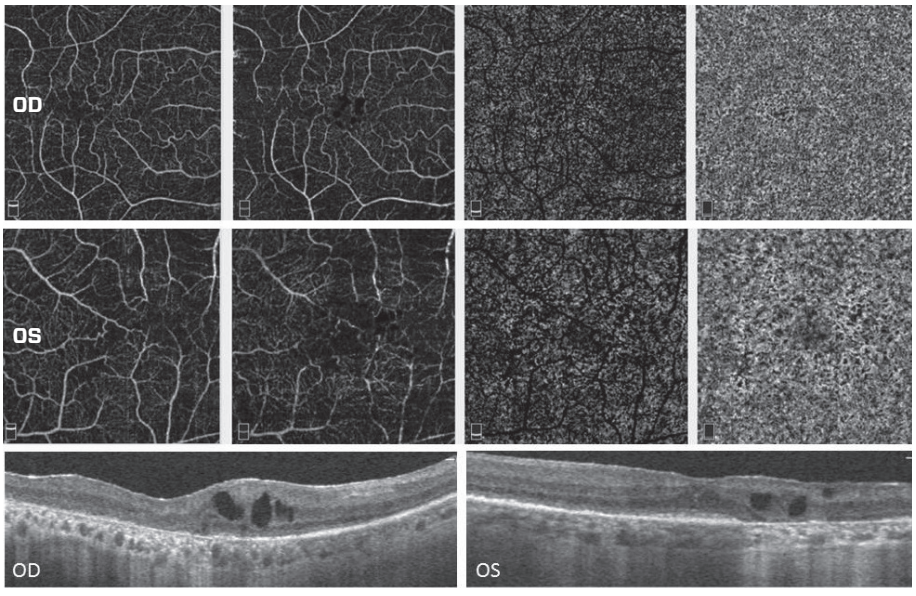
and deep capillary plexus (DCP) with no apparent abnormality at the choriocapillaris. Careful evaluation of the vessel density maps revealed more significant loss at the level of the SCP than the DCP (Figure 1).

Despite the relatively quiescent nature of the fundus appearance and SD-OCT, OCT-A was able to detect and localise irregularities in vascular flow within the inner retina in this patient with mild disease.

CASE REPORT 2

A 27-year-old Hispanic male presented with the chief complaint of diminution of vision in both eyes and a history of RP. His systemic history was unremarkable and he was taking no medications. Best corrected visual acuities were 6/7.5- OD, OS. Pupils, confrontations, extraocular motility and colour vision were found to be normal. Intraocular pressure was measured to be 14 mmHg OD and 15 mmHg OS. Anterior segment findings were unremarkable, with no posterior subcapsular cataracts. Posterior segment findings of both eyes revealed mild pallor of the optic nerves with 0.3 round C/D ratio. The macula was intact, with no haemorrhaging, oedema or mottling. A mild epiretinal membrane was present in the macula right eye, greater than left eye. The retinal vessels exhibited mild vessel attenuation. The periphery was flat and intact with bone spicule retinal pigment epithelial clumping in all quadrants.

Significant findings on the SD-OCT included epiretinal membrane and slight disruption of the photoreceptor integrity line in both eyes. OCT-A revealed an enlarged foveal avascular zone with abnormally low vascular density in the superficial and deep capillary plexus with more significant involvement of the deep capillary plexus with no apparent abnormality seen at the level of the choroid (Figure 2). With moderate RP, as seen with this patient, the DCP appears to be more significantly involved than the SCP, although both complexes are severely compromised.[2]



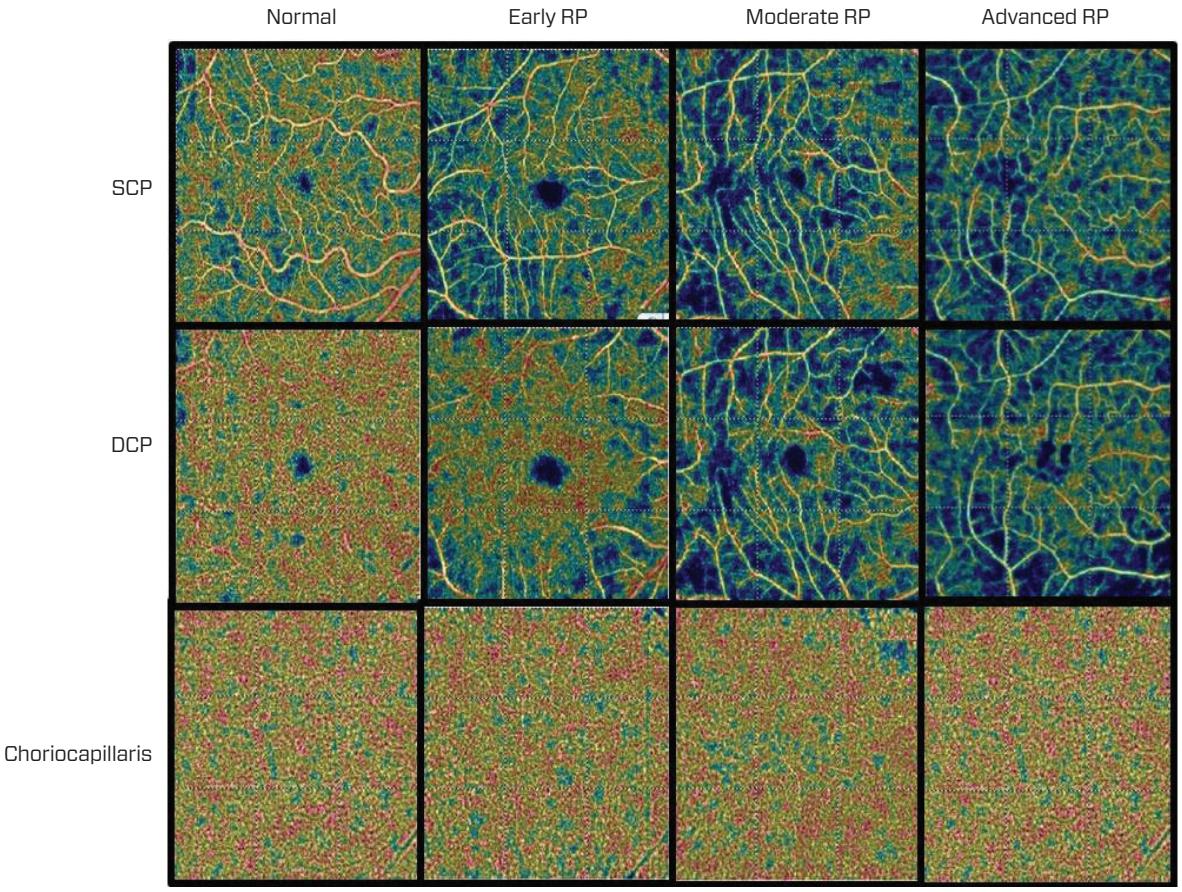
▲ Figure 3. OCT angiography and SD-OCT of the right and left eye of a patient with advanced retinitis pigmentosa

CASE REPORT 3

A 56-year-old Hispanic male presented with a chief complaint of blurry vision and decreased peripheral vision in both eyes. The patient had been diagnosed with RP 20 years prior in Cuba. His systemic history was unremarkable and he was taking no medications. The patient reported a family history of RP and diabetes mellitus type 2.

Best corrected visual acuities were 6/18 OD and 6/15 OS. Extraocular motility was full; however, confrontation fields were significantly reduced in all quadrants in both eyes. Pupils were normal with no APD. The patient failed the HRR colour vision screening in both eyes.

Continued page 4



▲ Figure 4. OCT angiography showing the macular capillary density of the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris of various stages of retinitis pigmentosa (RP) compared to those of a normal patient

OCT-Angiography

From page 3

Intraocular pressure was measured to be 14 mmHg OD, OS. Anterior segment findings revealed mild meibomian gland disease, pinguecula, trace amount of pigment on the corneal endothelium, and PC IOL with 1+ diffuse PCO in both eyes. Significant posterior segment findings of both eyes included: waxy pallor of both optic nerves with 0.2 C/D ratio, retinal vascular attenuation, pigmentary changes and RPE mottling of the macula, and bone spicule RPE clumping in the periphery in all quadrants.

SD-OCT showed mild macular oedema with cystic pockets of fluid in both eyes, but visual acuity was only mildly affected due to preservation of the photoreceptor integrity line and ellipsoid zone at the fovea. OCT-A showed decreased vascular density in the SCP and DCP with the left eye affected more than the right eye. Mild changes were observed at the level of the choriocapillaris, but most of the change was observed in the SCP and DCP with the DCP more severely impacted than the SCP (Figure 3). The OCT-A density maps confirmed that the severity of disease correlated with reduction in vascular density within the inner retinal SCP and DCP, with reduction in DCP directly related to visual function.

Discussion

Retinitis pigmentosa is the term used to designate a group of inherited retinal disorders characterised by progressive loss of photoreceptors and retinal dysfunction resulting in deterioration of central vision.[1] RP is characterised by classic symptomatology and clinical findings including nyctalopia, visual field constriction, bone spicule pigmentation and abnormal full-field electroretinograms. RP affects the photoreceptor-RPE cell metabolic complex and begins with a loss of the rod photoreceptors as evidenced by the initial involvement of the equatorial and peripheral retina.

Over time, the cone photoreceptors become involved, resulting in progressive visual loss. Histopathological studies have identified shortening of the photoreceptor outer segments as the earliest identifiable finding in RP.[2] Typical clinical features of RP include peripheral retinal bone-spicule deposition, optic nerve pallor and retinal vessel attenuation. Loss of normal retinal vasculature is believed to be due to photoreceptor degeneration.[3]

Abnormalities within the retinal vasculature as well as changes in ocular blood flow have been implicated in the pathogenesis of RP. In fact, fluorescein angiography and indocyanine green angiography have illustrated the abnormal retinal and choroidal vasculature in RP noting increased dye transit time, narrowed vessel lumen and reduced dye concentration.[4] In addition, electoretinogram shows increased arteriovenous transit time and reduced blood flow velocity.[5]

Since the advent of OCT, it has become the standard for assessing anatomical abnormalities via high resolution tomographic images. OCT is able to accurately assess the photoreceptor segments and thicknesses of retinal layers in RP patients and has shown a decrease in foveal thickness, interruption of the IS/OS junction, and reduction in choroidal thickness.[5] Correlations between the retinal structure and visual acuity have been identified in affected patients.

Historically, RP has been characterised as a disease of the photoreceptors with loss of the outer retinal cells. However, new research is identifying disorganisation and damage to the inner retina including death of the retinal ganglion cells. Outer retinal involvement can occur as a result of chronic apoptosis of the ganglion cells and disorganisation of the inner retina.[6-8]

OCT-A is a recently developed, non-invasive, contrast-free technique for imaging the retinal and choroidal microvasculature. The technique uses the movement of red blood cells in the retinal vasculature to create an image of retinal blood flow. This allows for segmentation and evaluation of all retinal layers and capillary networks. Analysis of OCT-A images in RP patients has confirmed the aforementioned involvement of the inner retinal layers in the pathogenesis of RP.

It has been documented that photoreceptor damage leads to changes in the inner retinal tissue including the retinal ganglion cells. Despite varying hypotheses regarding the morphological changes to the inner retina, a direct correlation has been found between ganglion cell thickness and macular function in RP patients. Furthermore, it appears that the multi-focal electroretinogram is negatively affected by apoptosis of the ganglion cells.[9]

The resolution provided by OCT-A has provided outstanding visualisation of the SCP and DCP vascular networks within the inner retina and has been able to identify varying features that cannot be distinguished by classical fluorescein angiography. The superficial vascular plexus is located in the ganglion cell layer and in the nerve fibre layer. The deep vascular plexi are located in the inner nuclear layers and external plexiform layer.

OCT-A illustrates different morphological features of the retinal blood supply for the two plexi.[10] The vascular supply of the superficial plexus is characterised by multiple linear structures having a centripetal distribution converging towards the fovea. Secondary vessels arise from the main vessels forming a web-like pattern. The calibre of the vessels is uniform throughout the scan. The deep plexus comprises an interwoven pattern of vessels that surround the foveal avascular zone in numerous horizontal and radial interconnections. The calibre of the vessels is also uniform throughout the scan.[11,12]

OCT-A in patients with RP demonstrates alterations in the normal vasculature within the superficial and deep retinal layers as well as throughout the choroid. The SCP and DCP vessel densities are reduced in patients with RP.[9] It has been postulated that this reduction in blood flow occurs early in the disease process and leads to eventual ischaemia, retinal vessel damage and cell death involving both the inner and outer retinal space. Furthermore, vessel density abnormalities at the level of the DCP appear to be directly related to macular function and visual potential.

Analysis of the three patients presented in this article suggests that severity of disease correlates with degree of reduction in vascular flow as seen on the segmented angiograms as well as with diminution in the vessel density map (Figure 4). Because OCT-A is able to identify and quantify loss of normal retinal vasculature in RP patients, it should be used to monitor disease progression in affected patients. Vascular changes may precede functional changes as seen on visual field testing and may thus play a pivotal role in staging and categorising the disease.

OCT-A provides excellent insight into the microvascular changes occurring throughout the retina and choroid and allows for additional insight into the pathophysiology behind the disease. It appears that alterations in the vascular density and pattern of flow seen on angiogram correlate with disease severity. OCT-A may exhibit signs of disease earlier and should be utilised to provide timely management of affected patients. ▲

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XEN Gel Stent glaucoma treatment system

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THE XEN Glaucoma Treatment System is a new option for patients with refractory glaucoma. This minimally-invasive device drains aqueous into the subconjunctival space, a procedure long-considered the gold standard for glaucoma surgery.

Previously, this could be achieved only with invasive operations such as trabeculectomy or insertion of a glaucoma drainage device, which carry not-insignificant risks. The XEN aims to provide a safer and more predictable way of achieving subconjunctival filtration. In doing so, the XEN expands the role of minimally-invasive glaucoma surgery (MIGS) across the spectrum of glaucoma and has the potential to revolutionise the way refractory glaucoma is treated.

Treatment system

The XEN Glaucoma Treatment System consists of the XEN Gel Stent and the XEN Injector. The XEN Gel Stent is a soft, flexible, hydrophilic tube composed of porcine-derived collagen that has been shown to have good biocompatibility.[1]

Cross-linked with glutaraldehyde to prevent degradation, the XEN creates a permanent outflow pathway between the anterior chamber and the subconjunctival space. The XEN is 6 mm long and has an inner lumen diameter of 45 µm. These dimensions have been selected based on the Poisseuille equation (which predicts flow based on tube length, internal diameter and fluid viscosity) to prevent hypotony.

Surgical technique

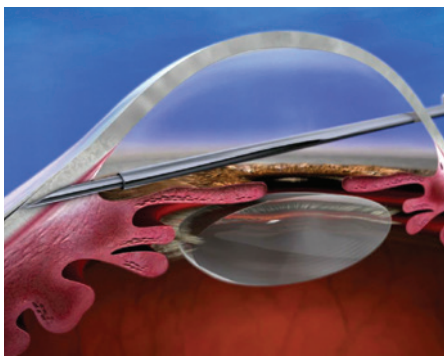
The XEN is performed under local anaesthetic in a 15-minute operation. Typically performed as a stand-alone procedure, the XEN can also be combined with cataract surgery for patients with both refractory glaucoma and visually-significant cataract. The implant is inserted using a preloaded injector via an *ab interno* approach through a 1.2 mm clear corneal incision, exiting the sclera 3 mm from the limbus in the superonasal quadrant. There is no conjunctival incision or suturing required, leading to a safer procedure and faster post-operative recovery.

Like other filtration surgery, anti-metabolites are administered prior to insertion to prevent subconjunctival scarring. While the procedure looks simple, it is technically demanding and must be well-executed to achieve optimum results and prevent complications. However, once mastered, the XEN represents the safest, fastest and least-invasive method of creating a new outflow pathway to the subconjunctival space.

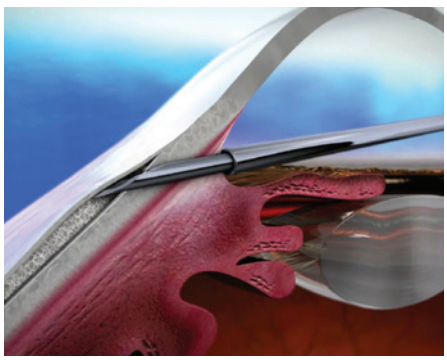
Indications

The XEN Glaucoma Treatment System is indicated for the management of refractory glaucoma, including primary open-angle glaucoma, pseudoexfoliative glaucoma and pigmentary glaucoma, which is unresponsive to maximum tolerated medical therapy. The XEN can be performed as a primary procedure[2] or in eyes where previous surgical treatments, such as other MIGS devices or trabeculectomy, have failed.

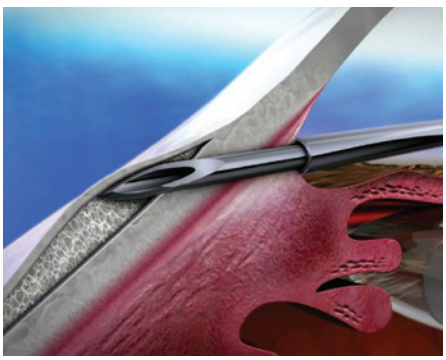
As the XEN is minimally-invasive and has a good safety profile, it



▲ Figure 1. The XEN injector is passed through a clear corneal incision, across the anterior chamber, and advanced through the sclera into the subconjunctival space



▲ Figure 2. Magnified view showing advancement of the injector into the subconjunctival space



▲ Figure 3. Magnified view showing rotation of the bevel in the subconjunctival space

can be considered earlier in the disease process than trabeculectomy. Additionally, because the XEN drains to the subconjunctival space it has greater IOP-lowering efficacy than other MIGS procedures and is therefore also suitable for cases with significant IOP elevation and more advanced disease.

The XEN is contraindicated in active neovascular glaucoma or if there is intraocular silicone oil, vitreous in the anterior chamber, or an anterior chamber intraocular lens. The procedure should not be performed if there is significant conjunctival scarring or an existing glaucoma drainage device in the target quadrant. The safety and effectiveness of the XEN has not been established in congenital or infantile glaucoma.

Post-operative management

The XEN creates a bleb that is typically low, diffuse and comfortable. Post-operative recovery is much faster than trabeculectomy with little blurring of vision, minimal restriction on physical activity and less need for intensive topical steroids. Fewer post-operative visits are required compared to trabeculectomy and there is no need for suture removal or lysis. While complications such as malposition, occlusion or rarely, erosion can occur, these can typically be prevented with good surgical technique. As the XEN requires bleb management and occasionally needling, the procedure is best performed by glaucoma surgeons who are experienced in bleb management.

Evidence

The efficacy and safety of the XEN has been evaluated in the APEX study, a prospective, multi-centre, 24-month study of 215 patients in 14 countries with mild-to-moderate primary open angle glaucoma and no history of intraocular surgery. Patients underwent either the XEN procedure alone or in combination with cataract surgery.

In a preliminary report, there was an average reduction in IOP of 7.6 ± 4.8 mmHg to a mean of 13.8 mmHg at 12 months.[3] This was associated with a reduction in IOP-lowering medications from 2.6 ± 1.1 at baseline to 0.6 ± 0.8 at 12 months. There were no cases of bleb leak and only one patient (0.5 per cent) developed symptomatic hypotony requiring injection of viscoelastic. There was no difference in efficacy between the XEN as a stand-alone procedure or in combination with cataract surgery. The 24-month results are due to be published this year. Other smaller studies have shown similar results.[4–6]

The success rates of XEN compare favourably with gold-standard trabeculectomy. In a multi-centre, retrospective interventional cohort study, there was no detectable difference in failure rate between stand-alone XEN insertion or trabeculectomy with mitomycin C.[7]

Future of glaucoma surgery

The XEN represents a major advance in the surgical management of glaucoma. It combines the efficacy of subconjunctival filtration with the safety and fast recovery of minimally-invasive glaucoma surgery. While there will always be a place for trabeculectomy in selected patients, particularly those with very advanced disease, for the majority of patients with refractory open-angle glaucoma the XEN provides an attractive alternative. ▲

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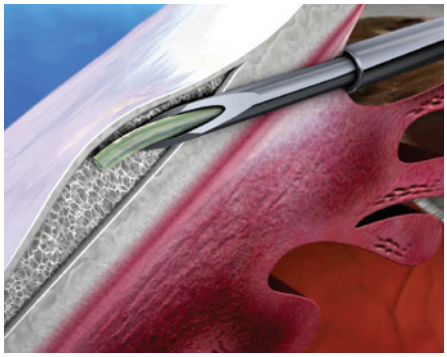
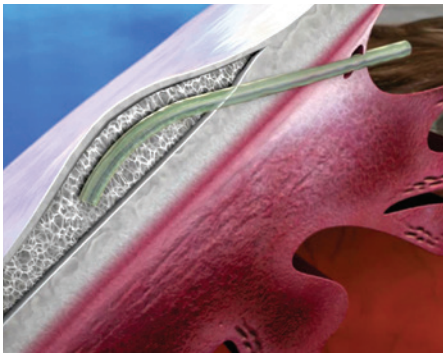
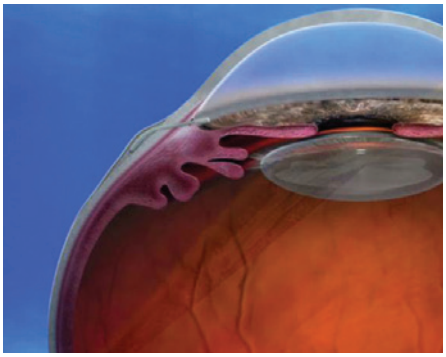


▲ Figure 4. Deployment of the XEN Gel Stent into the subconjunctival space



▲ Figure 5. The XEN Gel Stent *in situ* draining aqueous from the anterior chamber to the subconjunctival space



▲ Figure 6. Globe cross section with XEN Gel Stent in place.

CASE REPORT

XEN Gel Stent as an alternative to trabeculectomy

Dr Nathan Kerr
MBChB MD FRANZCO

Royal Victorian Eye and Ear Hospital
Centre for Eye Research Australia

Eye Surgery Associates, Melbourne

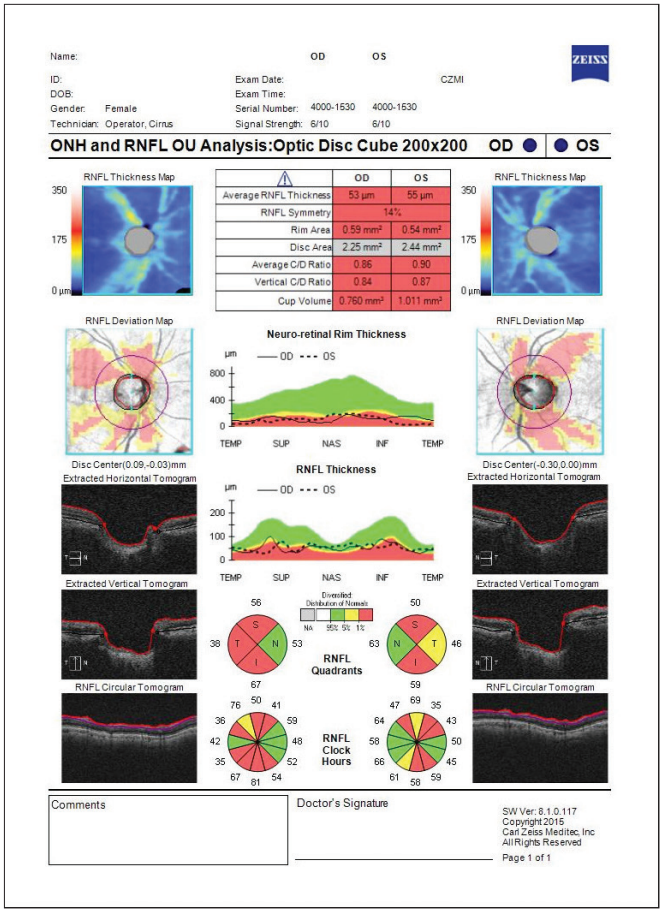
A 57-YEAR-OLD Caucasian woman with open-angle glaucoma refractory to medical and laser treatment was referred to me by her optometrist for a second opinion and to discuss alternatives to trabeculectomy.

The patient had a history of primary open-angle glaucoma diagnosed seven years previously and had presenting intraocular pressures in the mid 20s. Her central corneal thickness was reduced at 533 microns in her right eye and 540 microns in her left eye. There was a family history of glaucoma affecting her mother who was diagnosed in her late 60s. Her mother was treated with topical medications and reportedly suffered field loss but not blindness.

The patient's general health was good and she was not regularly taking any medications.

Despite treatment with bilateral selective laser trabeculoplasty (SLT) by her original ophthalmologist and good adherence with three topical ocular hypotensive medications, her intraocular pressures remained in the high teens. Her ophthalmologist noted a Drance haemorrhage in her left eye and advised that trabeculectomy was required.

Having read the information sheet, the patient was worried about the risks, slow recovery and time-off required from her work as a gardener, and was interested in seeking an alternative. Her friend in the United States had undergone the XEN Gel Stent procedure with good results and the patient was interested to know if she was a candidate for the procedure.



▲ Figure 1. OCT shows thinning of the retinal nerve fibre layer.

Examination

On examination her best-corrected visual acuity was 6/6 in each eye. Her conjunctiva was white and healthy. Both anterior chambers were deep and quiet and her angles were open on gonioscopy. Intraocular pressures measured by Goldmann applanation tonometry were 16 mmHg in her right eye and 18 mmHg in her left eye. There was no pseudoexfoliation or cataract in either eye. Dilated fundoscopy revealed cup-to-disc ratios of 0.9 with thinning of the neuroretinal rim both superiorly and inferiorly in each eye. There was a resolving Drance haemorrhage in her left eye.

Optical coherence tomography (OCT) showed marked thinning of the retinal nerve fibre layer in each eye (Figure 1) and automated perimetry showed early field loss with slow progression

Surgical treatment of refractory glaucoma without conjunctival incisions or suturing

in each eye on guided progression analysis (Figures 2A and 2B).

We discussed the patient's diagnosis and our shared goal of preventing vision loss from glaucoma. Given the patient's age, presenting pressures, reduced corneal thickness, family history of glaucoma, and development of a Drance haemorrhage at 18 mmHg, we discussed the need to achieve an IOP in the low double digits which can realistically be achieved only with subconjunctival filtration surgery.

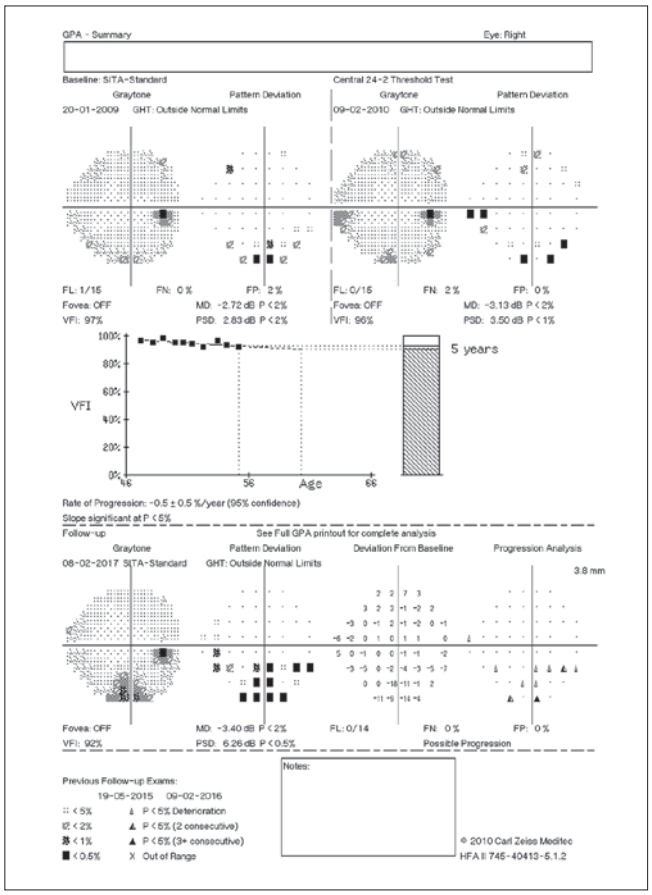
While trabeculectomy is the current accepted gold standard, we discussed the option of a XEN Gel Stent as an alternative. The XEN has a favourable safety profile and offers a much less invasive operation and faster post-operative recovery. For many patients it can delay or prevent the need for invasive surgery. The patient was carefully counselled on the risks and benefits and elected to proceed with the XEN Gel Stent.

Surgical course

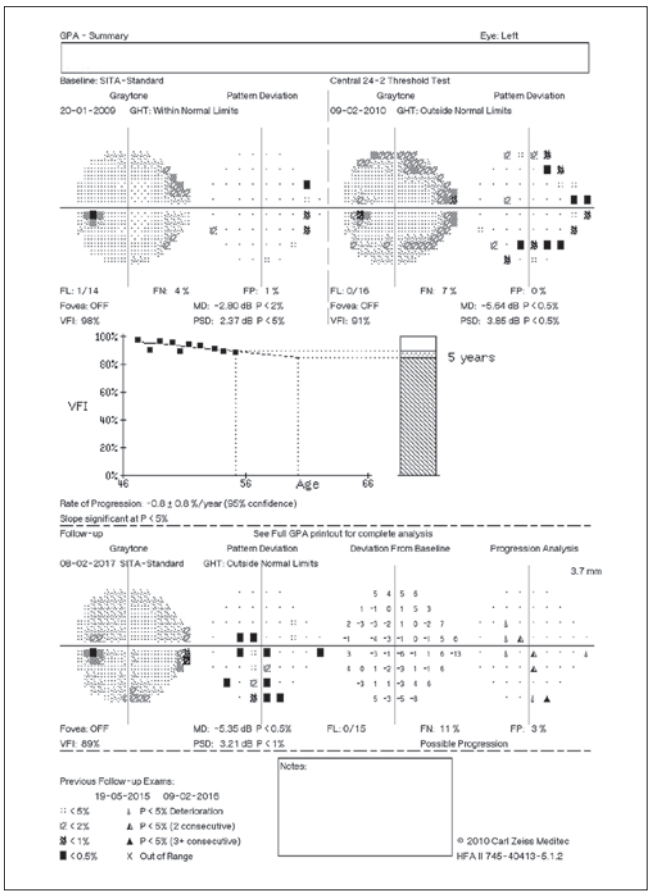
In the operating room under a peribulbar block, I marked the planned exit point for the XEN Gel Stent. To control subconjunctival fibrosis, I injected mitomycin C posteriorly and swept it away from the limbus to prevent the development of an avascular bleb. I made a 1.5 mm clear corneal incision and a single side port to stabilise the eye. I injected acetylcholine to constrict the pupil and protect her crystalline lens. Then I filled the anterior chamber with viscoelastic before checking and hydrating the XEN before implantation.

The injector was passed across the anterior chamber and through the sclera into the subconjunctival space at exactly my markings. I rotated the bevel of the needle toward 12 o'clock to ensure a superior bleb. I then deployed the stent carefully into the subconjunctival space before checking for correct length and position using a gonioprism.

Continued page 10



▲ Figure 2A. Humphrey visual field guided progression analysis, right eye



▲ Figure 2B. Humphrey visual field guided progression analysis, left eye

XEN case report

From page 9

Lastly, I removed the viscoelastic with bimanual irrigation and aspiration, checked for the development of a bleb, and hydrated the wounds before administering intracameral antibiotic to prevent infection. At the end of the procedure I placed a pad and shield over the eye and prescribed topical steroids every two hours and antibiotics four times a day.

The patient was instructed to discontinue glaucoma medications in the operated eye, to avoid heavy lifting or straining, keep the eye dry, and wear a shield at night for the first week.

An appointment was scheduled for the following day and the patient was given my mobile number to call in case of emergency.

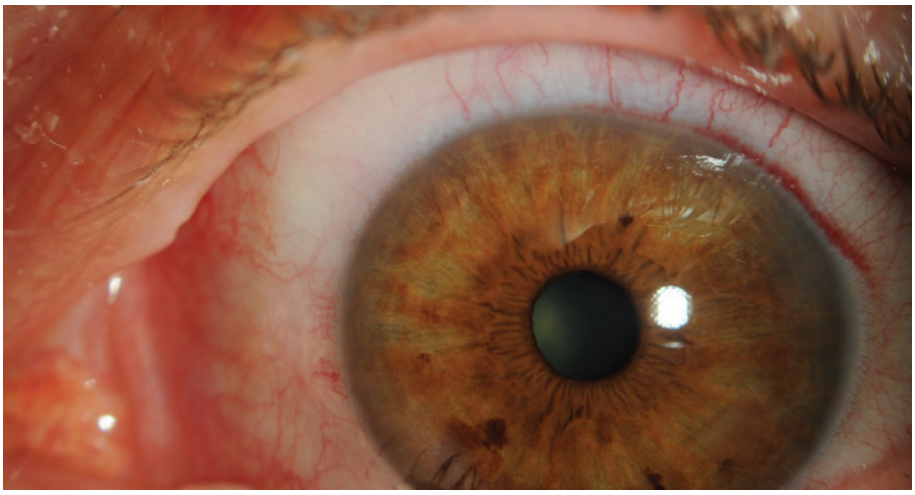
Outcome

At the day 1 post-operative visit, the patient's visual acuity was 6/9 in the operated eye and her intraocular pressure was 7 mmHg without sequelae. Her anterior chamber was deep and there were no macular folds or choroidal effusions. The XEN was well-positioned and there was a low diffuse bleb and no leak (Figures 3A and 3B).

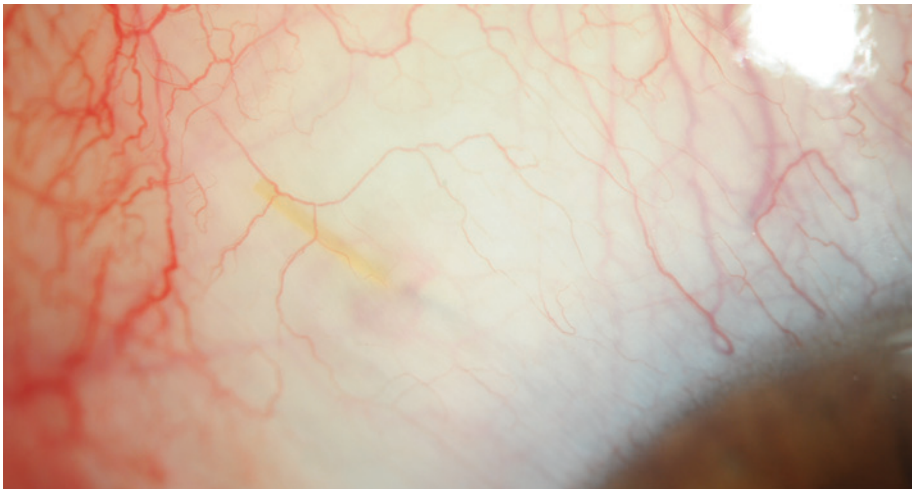
At one week post-operatively, her visual acuity had returned to 6/6 and her intraocular pressure was 10 mmHg. Antibiotics were discontinued at one week and steroids tapered over the next three months. At three months the patient is off all eye-drops and her visual acuity is 6/6 and IOP 9 mmHg. The fellow eye has been scheduled for surgery.

Discussion

The XEN Gel Stent represents a major advancement in the treatment of refractory glaucoma. It provides intraocular pressure levels approaching those of trabeculectomy, in a fast, minimally-invasive operation with a good safety profile and rapid post-operative recovery.[1] Unlikely trabeculectomy there are no conjunctival incisions or suturing required, which is appealing from a patient perspective.



▲ Figure 3A. Slitlamp photography of the XEN Gel Stent in position



▲ Figure 3B. Low diffuse bleb associated with the XEN Gel Stent

While numerically low pressures are common, hypotony is rare.[2] Accordingly, its favourable safety profile enables the XEN Gel Stent to be offered at an earlier stage of disease and in many patients it can avert or delay the need for invasive surgery.[3] If additional pressure reduction is required, medical therapy can be restarted and the procedure does not preclude further operations such as trabeculectomy or glaucoma drainage device insertion from being performed.

Patients should be monitored closely post-operatively. Optimal outcomes require bleb management including needling and therefore the procedure is best performed by surgeons experienced in bleb management.

As with all subconjunctival procedures that form a bleb, there is a small risk of bleb-related complications. However, compared to trabeculectomy, the morphology of the XEN bleb is different, tending to be low and diffuse. Like any stent, there is a small risk of occlusion or exposure; however, this is rare and can generally be averted with proper technique and placement. ▲

1. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, et al. Efficacy, safety, and risk factors for failure of standalone *ab interno* gelatin microstent implantation versus standalone trabeculectomy. *Ophthalmology* 2017. doi: 10.1016/j.ophtha.2017.05.004.
2. Sheybani A, Dick HB, Ahmed IIK. Early clinical results of a novel *ab interno* gel stent for the surgical treatment of open-angle glaucoma. *J Glaucoma* 2016; 25: e691–696.
3. Kerr NM, Wang J, Barton K. Minimally invasive glaucoma surgery as primary stand-alone surgery for glaucoma. *Clin Exp Ophthalmol* 2017; 45: 393-400.

Rank order of IOP medications

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A SYSTEMATIC review published by Li et al[1] in the journal of the American Academy of Ophthalmology included 20,275 participants from 114 randomised controlled trials (RCT). The aim of the RCTs was to determine the effectiveness of single topical medical treatment using four medication classes (excluding miotics) when compared with placebo or another single active topical medical agent.

To be included in this systematic review, at least 60 per cent or more of the participants in each trial needed to be diagnosed with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Studies were excluded if combination treatment or surgical intervention was utilised; there were fewer than 10 participants in each group and/or fewer than 28 days of follow-up after randomisation.

All medical treatments were more effective than placebo in lowering IOP. At three months, the mean reductions in IOP, ranked from the most to the least-effective topical agent, are listed in Table 1.

As shown in Table 2, prostaglandin analogues were more effective in lowering IOP when compared to other drug classes. There was no statistically significant difference in efficacy between the different prostaglandin analogues, including bimatoprost, travoprost, latanoprost or tafluprost.

Levobunolol was more effective when compared to other beta-blockers. The mean difference in IOP between timolol 0.5% or timolol < 0.5% was small and not statistically significant. Interestingly, brimonidine was more effective at lowering IOP than apraclonidine and its performance was better than carteolol, betaxolol and levobetaxolol, which are beta-blockers. Unoprostone and betaxolol were the least effective in lowering IOP.

Rank order
1. Bimatoprost 0.03%
2. Latanoprost
3. Travoprost
4. Bimatoprost 0.01%
5. Levobunolol
6. Tafluprost
7. Timolol
8. Brimonidine
9. Carteolol
10. Levobetaxolol
11. Apraclonidine
12. Dorzolamide
13. Brinzolamide
14. Betaxolol
15. Unoprostone

▲ Table 1. Ranking from most-effective to least-effective

Medication class	Preparations	Mean reduction in IOP (mmHg) at 3 months (95 per cent CI)
Prostaglandin analogues	Bimatoprost 0.03%	5.77 (5.04 – 6.50)
	Latanoprost 0.005%	4.85 (4.24 – 5.46)
	Travoprost 0.004%	4.83 (4.12 – 5.54)
	Bimatoprost 0.01%	4.74 (1.91 – 3.19)
	Tafluprost 0.0015%	4.37 (2.94 – 5.83)
	Unoprostone 0.15%	1.91 (1.51 – 2.67)
Beta-blocker	Levobunolol 0.25%	4.51 (3.85 – 5.24)
	Timolol 0.25%, 0.5%, 0.1%	3.70 (3.16 – 4.24)
	Carteolol 1%	3.44 (2.42 – 4.46)
	Levobetaxolol 0.5%	2.56 (1.52 – 3.62)
	Betaxolol 0.25%, 0.5%	2.24 (1.59 – 2.88)
Alpha 2 agonist	Brimonidine 0.2%	3.59 (2.89 – 4.29)
	Apraclonidine 0.5%	2.52 (0.94 – 4.11)
Carbonic anhydrase inhibitors	Dorzolamide 2%	2.49 (1.85 – 3.13)
	Brinzolamide 1%	2.42 (1.62 – 3.23)

▲ Table 2. Mean reduction (including 95 per cent confidence interval) in IOP in mmHg for all IOP-lowering medical treatments included in the study

The study ranks the relative efficacy of IOP-lowering medications and therefore can be used to guide clinical decision-making for medical treatment of POAG. However, it should not be considered a solitary reference for choice of medication that should be used for treatment of POAG.

The following factors must be considered when prescribing medical therapies, including mode of action, adverse effects, contraindications, the patient's systemic health conditions, existing risk factors, extent of damage present and current rate of progression, predicted life expectancy, level of compliance and financial burden of treatment.

Prostaglandin analogue

Prostaglandin analogue is usually selected as the first line medical treatment of POAG due to its superior efficacy when compared to other medication classes, convenient once-daily dosing and hence better tolerability and compliance and minimal systemic contraindications. The topical adverse effects include conjunctival hyperaemia, periorbital skin pigmentation, hypertrichosis, iris pigmentation and heterochromia.

In addition, there have been reports of patients who developed anterior uveitis after receiving latanoprost. Although the risk is small, it should be used with caution in patients with co-existing intraocular inflammation including uveitis due to the risk of developing cystoid macular oedema (reversible), and in patients with a history of herpetic infection due to the increased risk of reactivation of herpetic eye disease.

Beta blockers

Beta-blocker is the next best IOP lowering medication in terms of efficacy. When compared to prostaglandin analogues, it has a short onset of action (30 minutes) and is therefore beneficial for rapid IOP reduction such as in acute angle closure attack. However, beta-blocker has more systemic contraindications and higher risk of adverse effects when compared to prostaglandin analogues.

Non-selective beta-blocker acts on beta-1 and beta-2 receptors while cardioselective beta-blocker acts on beta-1 receptors. Blockage of beta-2

Continued page 12

Clinical Quiz

Associate Professor Mark Roth

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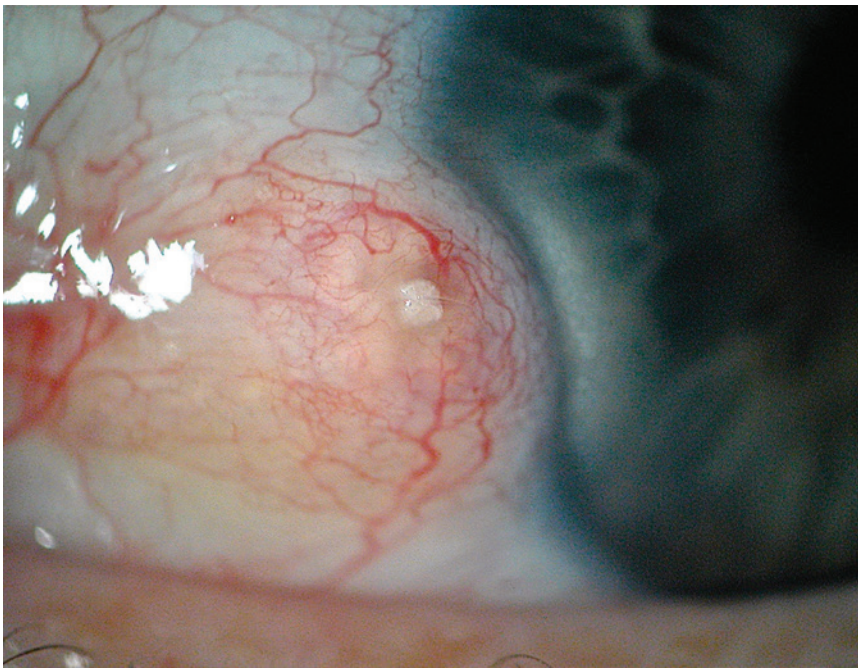
NEWENCO FAAO OAM

A 48-YEAR-OLD, Caucasian woman presents with a long-standing, large, right inferiotemporal, oval, conjunctival lesion. The lesion is 6 mm in diameter and 3 mm thick, with associated dilated blood vessels. There is a yellow-white corneal line adjacent to lesion and one prominent follicle and hair in the centre of the mass. The patient is asymptomatic.

What is your diagnosis?



▲ Conjunctival lesion Image: Associate Professor Mark Roth

Answer page 24

IOP medications

From page 12

receptor is problematic in patients with asthma and chronic obstructive pulmonary disease. Selective beta-blockers may also cause bradycardia, hypotension and hypoglycaemia.

Alpha 2s and CAIs

Alpha-2 agonists are contraindicated in patients taking monoamine oxidase inhibitor. Carbonic anhydrase inhibitors (CAI) are contraindicated in patients with sulfonamide allergies and patients with corneal graft and endothelial dystrophies as they may exacerbate corneal decompensation. Both CAIs and alpha-2 agonist require two to three times daily dosing, which reduces compliance.

Limitations

IOP is the primary and most common outcome to quantify the effectiveness of topical medical therapies in the literature. IOP is the only known modifiable risk factor for treatment of glaucoma and IOP reduction correlates with preservation of visual field. The extent of damage to the optic nerve head, the rate of retinal ganglion cell atrophy and degree of neuroretinal rim degeneration cannot be calculated and quantified easily.

The effect of the medication on the patient's quality of life is even more difficult to quantify and requires long-term follow-up. In contrast to IOP, visual field is a more meaningful outcome measure to quantify the effectiveness of treatment because it correlates with the patient's quality of life such as driving. However, only 20 per cent of randomised controlled trials included in the systemic review reported visual field as an outcome measure.

The extrapolation of visual field result is also difficult due to the heterogeneity associated with different reporting methods and relatively short follow-up time of three months. It will be interesting to see studies which have visual field results as an outcome when evaluating the effectiveness of topical IOP-lowering medication.

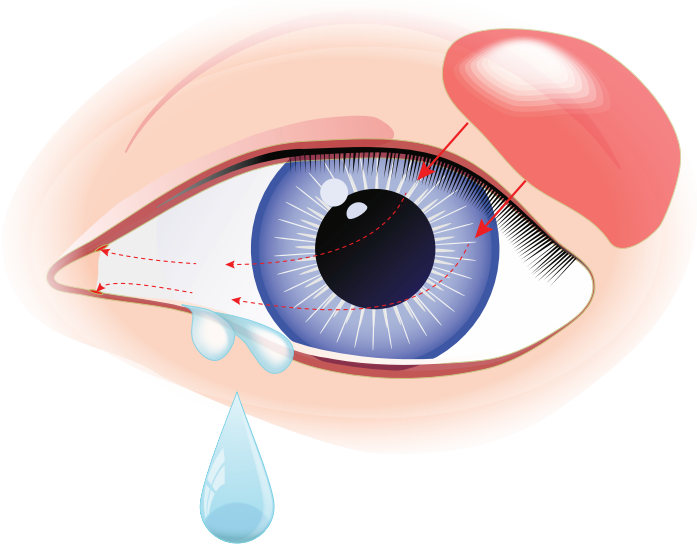
It is worth noting that this study does not consider the role of fixed/unfixed combination agents in the treatment of POAG. Combination agents are generally used when single agents are inadequate for reaching the target IOP. They may be considered as first-line treatment when the extent of existing glaucomatous damage is profound. Fixed combination therapy is more cost-effective and offers the convenience of once or twice-daily dosage which maximises compliance and adherence. Fewer drops also mean reduced exposure of the ocular surface to preservatives and less risk of toxicity.

It has been published that fixed combination of latanoprost 0.005% and timolol 0.5% is statistically more effective in lowering IOP when compared to monotherapy.[2] However, there is no clear evidence demonstrating the superiority of fixed combination agents. Therefore, it will be interesting to see where combination agents fit in the rank order of topical IOP-lowering medications for the treatment of POAG. The other fact to keep in mind is that unlike single active agents, the dosing regimen and treatment times of fixed combination agents cannot be optimised. ▲

1. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma. *Ophthalmology* 2016; 123: 1: 129-140.
2. Polo V. Treatment of glaucoma with the fixed combination of latanoprost 0.005% and timolol 0.5%. *European Ophthalmic Review* 2009; 3: 2: 33-36.

A sight for sore eyes

Clinical guidelines for managing dry eye in Sjögren's patients



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AS PART of the Sjögren's Syndrome Foundation's initiative to develop clinical guidelines for practitioners, a panel of eye-care professionals and consultants was formed to determine consensus guidelines for managing dry eye associated with Sjögren's syndrome. Foulks et al published their recommendations in the April 2015 issue of *The Ocular Surface*. These clinical guidelines are based primarily on the 2007 report of the International Workshop on Dry Eye (DEWS), as well as evidence from key peer-reviewed publications. The level of evidence determined the strength of the recommendation.

Sjögren's syndrome

Sjögren's is an autoimmune disease, primarily affecting the exocrine glands of mucous membranes, resulting in dry eye and dry mouth, often with additional muscoskeletal disturbance and damage to other body systems.

Dry eye is one of the most quality-of-life and activity limiting problems in Sjögren's syndrome. Symptoms include discomfort and fluctuation of vision. The researchers recommend the use of four specific questions to evaluate the severity of symptoms:

- How often do your eyes feel dryness, discomfort or irritation?
- Would you say it is often or constantly?
- When you have eye dryness, discomfort or irritation, does this impact your activities, for example, do you stop or reduce your time doing them?
- Do you think you have dry eye?

A patient reporting 'yes' to any of these questions warrants further investigation.

Diagnostic tests

The researchers note that in each patient, the clinician must determine whether the dry eye is due to aqueous production deficiency, excess evaporation, or combined mechanisms. Because the sequence of evaluation can influence the results of the subsequent tests, they recommend performing the tests from least invasive to more invasive.

Direct observation without any manipulation of the eyelids, tear film, or ocular surface should be performed first. Direct observation includes using the specular reflection to observe the tear meniscus (is it scanty?) and the tear lipid layer (is it coloured?) These observations alone help to show if an aqueous deficiency or meibomian dysfunction or both are present.

The phenol red thread test is then performed, prior to instilling dye and taking care not to induce reflex tearing. The Schirmer 1 test is tricky to interpret except in severe dry eye, as it can induce reflex tearing and instilling anaesthesia may change the tear volume. The phenol red thread test may be an alternative.

Instillation of topical fluorescein should be followed by measurement

Continued page 14

Sjögren's patients

From page 13

of the tear film break-up time (TFBUT). Corneal staining should be recorded 1.5–3 minutes after fluorescein instillation. Conjunctival staining with fluorescein can be assessed using the yellow Wratten filter, or by instilling lissamine green and making observations after three minutes.

MANAGEMENT APPROACHES

Communication

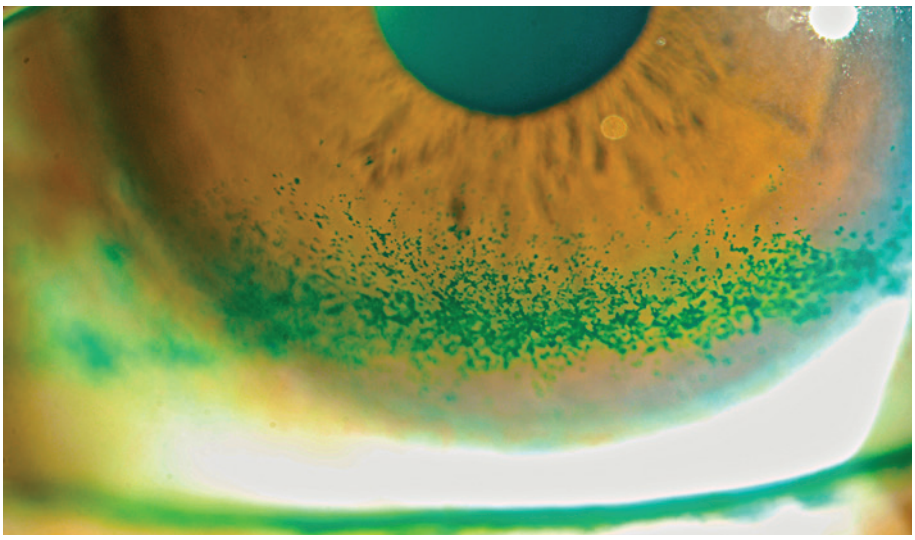
The researchers emphasise the importance of communication between the practitioner and patient regarding the nature of the disease, aggravating factors and goals of treatment. Given the multiple contributing causes of dry eye, the patient should consider dry eye therapy as part of their overall health management.

Mild, episodic dry eye can be managed with modification of the patient's environment and activities of daily living. These include: avoiding systemic medications that can reduce tear secretion, maintaining eyelid margin hygiene, avoiding very dry or windy environments and limiting certain tasks associated with reduced blink rate. When these preventive measures are inadequate, there is a logical sequence of therapies that can be used.

Lubricants

Tear volume replacement with ocular lubricants is the first line of therapy for dry eye in Sjögren's disease. Among the wide variety of formulations using carboxymethylcellulose and hydroxymethylcellulose, the researchers concluded that none is clearly superior.

Given the toxicity of preservatives to the ocular surface, preservative-free unit dose vials are recommended when tear supplements are used more than four to six times a day. Ophthalmic ointments may be used before bedtime to provide relief of dry eye symptoms and enable sleep. Typically, thicker preparations have a longer residence time but are more likely to blur vision, although newer agents containing hyaluronic acid may disrupt this constraint.



▲ Figure 1. 45-year old female with Sjögren's syndrome. Inferior corneal lissamine green staining punctate and coalesced pattern. Image: Associate Professor Mark Roth

Therapeutics

Moderate-to-severe ocular surface disease often requires the use of anti-inflammatory therapies. Studies have shown topical corticosteroids are effective in decreasing clinical signs and symptoms. However, the possible complications associated with long-term use such as cataracts, intraocular pressure spikes and infection, limit their use to short-term or pulse therapy. The researchers recommend a two- to four-week course for cases inadequately controlled with other therapies.

Topical cyclosporine (Restasis or compounded) has been shown to increase tear production, and improve signs and symptoms in patients with chronic aqueous-deficient dry eye. No significant side-effects have been reported, and long-term safety of topical cyclosporine has been confirmed in the literature.

Systemic therapy

Traditional treatments for posterior blepharitis and meibomian gland dysfunction include hot compresses and lid hygiene. In more recalcitrant cases, the researchers recommend the use of topical antibiotics or low dose oral tetracyclines to decrease bacterial colonisation of the lid margins. Omega 3 essential fatty acids supplements are also considered to have anti-inflammatory effects.

The evidence of their use in treating dry eye is growing, and at 1000-1500 mg per day for three months, it is considered a low-risk dietary supplement.[1] Foulks et al[2] recommend that patients taking more than 3000 mg per day omega 3 supplements should do so only under a physician's care.

Contact lenses

Large-diameter rigid, gas-permeable lenses are recommended to control severe ocular surface damage, when other treatments are insufficient. Therapeutic scleral contact lenses

in Sjögren's patients serve to protect the ocular surface from the eyelids and environment, relieve discomfort and improve quality of vision. Retention of a fluid reservoir over the cornea and lack of corneal touch are key elements to the therapeutic effect of scleral lenses.

Further options

Once the inflammatory component of dry eye is controlled, occlusion of the lacrimal puncta using plugs can be considered. This can be performed on a temporary or permanent basis. Those unresponsive to intensive lubricant and anti-inflammatory therapy may require use of topical autologous serum. This is typically dosed four times daily, and can be used in conjunction with other therapies. The most severe cases of dry eye may consider partial closure of the interpalpebral fissure, using botulinum toxin injections or surgical options, to reduce surface exposure.

Eye-care practitioners frequently encounter patients with dry eye symptoms. Although most patients complaining of dry eye do not have Sjögren's, it should be considered as a possible aetiology, particularly when it is associated with inflammation, difficulty in management, dry mouth, arthritis or other systemic evidence of inflammation or autoimmune disease. The researchers strongly encourage clinicians to refer patients with suspected Sjögren's disease to a rheumatologist for systemic disease diagnosis and management. ▲

1. Deinema LA, Vingrys AJ, Wong CY, et al. A randomized, double-masked, placebo-controlled clinical trial of two forms of omega-3 supplements for treating dry eye disease. *Ophthalmology* 2017; 124: 43-52.
2. Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. *Ocul Surf* 2015; 13: 2: 118-132.

FDA approves first treatment for GCA

THE US FOOD and Drug Administration (FDA) has approved subcutaneous tocilizumab for the treatment of giant cell arteritis (GCA) in adults. The drug is marketed as Actemra by health-care company Hoffmann-La Roche.

The decision follows the results of a double-blind, placebo-controlled study which involved 251 patients with GCA. Researchers looked for sustained remission from the disease from week 12 to week 52.

It was found that a greater proportion of patients receiving subcutaneous tocilizumab along with standardised prednisone regimens achieved sustained remission compared to patients receiving placebo with standardised prednisone regimens.

The standard of care for patients with GCA is steroid therapy; however, prolonged courses of steroids often are required, leading to substantial steroid-associated complications.

The FDA granted the application for Actemra a 'Breakthrough Therapy' designation and a 'Priority Review'.

www.fda.gov

Manage lid-disease before trabeculectomy

TO AVOID bleb-related infection (BRI), lid disease should be managed prior to trabeculectomy surgery, a study has found. Researchers conducted a clinical study of BRI following trabeculectomy surgery. The study involved documenting historical data review from patients' records, self-reported questionnaires specific to ocular surface symptoms and a repeated detailed clinical examination of the lid, ocular surface and tear film.

Twenty-eight cases and 31 controls were assessed. Researchers found that the overwhelming risk factor for development of BRI was chronic blepharitis. No increased risk was identified with the antimetabolite used during trabeculectomy surgery or the type of conjunctival reflection adopted for surgery. Neither age nor dry eye was identified as a risk factor.

An increased risk of BRI was identified in eyes with chronic blepharitis. To minimise the risk of infection following trabeculectomy surgery, it may be advisable to manage lid disease in patients prior to performing trabeculectomy surgery, or offer an alternative treatment such as a shunt.

Br J Ophthalmol 2016; Oct 18 (Epub ahead of print)

New study of infectious conjunctivitis

THE FIRST patient has been enrolled in a phase 3 clinical trial for SHP640, a combination broad-spectrum antiseptic and corticosteroid being evaluated for treating infectious keratitis in adults and children.

According to an announcement by the biopharmaceutical company Shire, international clinical trial sites are expected to open in the third quarter of 2017.

SYNCHRONIZE, the phase 3 trial, will include four multicentre, randomised, double-masked, placebo-controlled studies, with two for adenoviral conjunctivitis and two for bacterial conjunctivitis.

Shire plans to enrol more than 2,700 patients to investigate the efficacy and safety of SHP640 in adenoviral and bacterial conjunctivitis.

SHP640 is a broad-spectrum antiseptic (povidone-iodine, 0.6%) and anti-inflammatory steroid (dexamethasone, 0.1%) combination. The treatment regimen being studied for SHP640 is one drop, four times per day, for seven days.

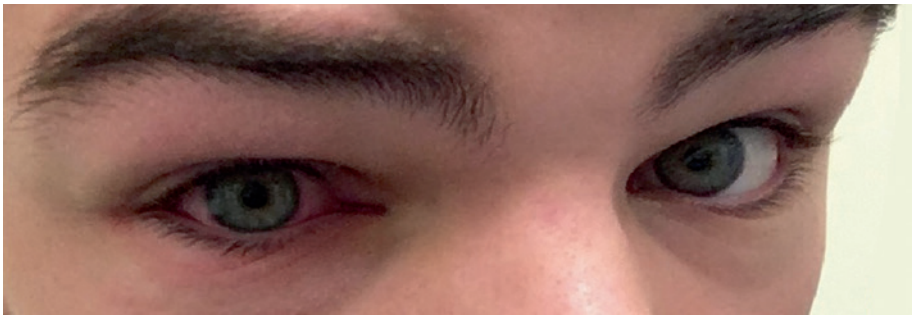
www.shire.com

Meningococcal conjunctivitis

MenW is rising

Wesley Teoh
Medical Student (MBBS V)

Monash University, VIC



▲ Figure 1. Patient presents with painful watery right eye

INFECTIOUS conjunctivitis is a commonly presenting complaint to health professionals globally.[1] Most conjunctivitis presentations are viral in origin, self-limiting and require only topical palliative therapy such as lubricants. We present a case of non-invasive primary meningococcal conjunctivitis (PMC) identified on retrospective Gram-stain and culture diagnosis.

Australia is currently experiencing a rise in the notifications of *Neisseria meningitidis* serogroup W (MenW).[2] In 2014, there were 17 notified cases of MenW. That number rose to 34 in 2015 and 110 in 2016.[3] Although the most common presentation of MenW is septicaemia, localised disease also occurs, including septic arthritis, epiglottitis, pneumonia and pericarditis.[2,3] Although rare, especially in adults, PMC is potentially vision and life-threatening.[4,5] This report reminds health professionals of the current meningococcal W outbreak in Australia and the possible consequences of PMC.

CASE REPORT

A 19-year-old Caucasian male presented to a metropolitan emergency department (ED) in Victoria, having experienced pain and copious watery discharge from his right eye for six hours. He complained of a unilateral red eye, mild visual disturbance and foreign body sensation which worsened on removal of contact lenses which had been in place for two weeks.

He had experienced a coryzal (catarrhal inflammation of the mucous membrane in the nose) illness a week prior to his presentation, which had resolved. He had no meningism (symptoms similar to those of meningitis but not caused by meningitis), fever, rashes or other symptoms. Apart from hypermetropia (he wore monthly contact lenses), he had no past medical history. He was an active cyclist and university student who lived with his family.

On examination, unaided Snellen visual acuity was 6/6 bilaterally, with mild peri-orbital swelling and global scleral injection in the right eye. Slitlamp examination revealed widespread chemosis, significant epiphora, marked hyperaemia, a minor anterior chamber reaction (0.5+ of cells) and follicular response in the affected eye. Multiple corneal punctate epithelial erosions were present. There was no periauricular lymphadenopathy and vital signs were normal. His left eye was unremarkable.

Due to the severity of his chemosis, a swab was sent for Gram-stain and culture. The intensity of conjunctival chemosis and other signs indicated that the pathology was not related to contact lens wear, but this could not be entirely ruled out. The patient was discharged on topical lubricants with presumed viral conjunctivitis.

Five days later, the patient was recalled to the emergency department and admitted because the culture grew *Neisseria meningitidis* serotype W (sensitive to ceftriaxone, chloramphenicol, ciprofloxacin and penicillin). The patient was completely asymptomatic at this time. His haematology and biochemistry results were normal. He commenced topical chloramphenicol 0.5% every two hours and 2 g intravenous ceftriaxone twice daily. Contact tracing and chemoprophylaxis with 500 mg ciprofloxacin was initiated and the health authorities were notified.

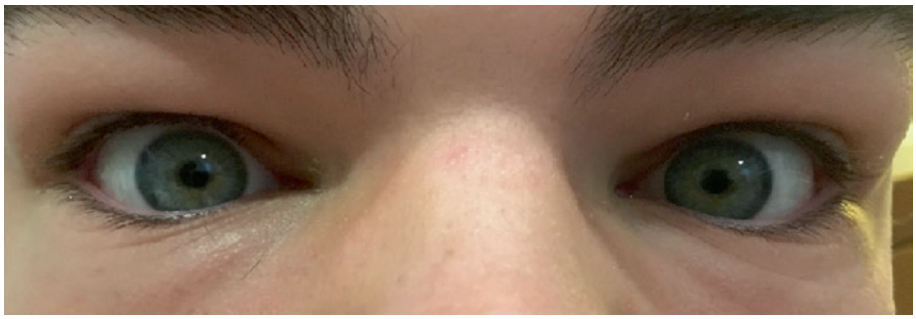
The patient was discharged following normal ophthalmic review and blood cultures, after receiving two days of intravenous ceftriaxone. He continued topical chloramphenicol for a further five days.

Discussion

Neisseria meningitidis is an uncommon but potentially dangerous cause of bacterial conjunctivitis.[6] PMC is extremely rare in adults, with only 20 cases reported before 1990.[4] Even in children, it is an uncommon cause of bacterial conjunctivitis, accounting for only two per cent of cases in a review of 1,030 children with acute bacterial conjunctivitis.[7] Meningococcal conjunctivitis can be divided into primary (exogenous) and secondary (endogenous) disease, where the latter is a complication of systemic meningococcal disease.[6,7]

PMC typically presents abruptly with associated burning sensation, irritation, epiphora and yellow-green purulent

discharge from the affected eye, similar to *Neisseria gonorrhoeae*.[5] Low fevers are present in 24 per cent of PMC cases and enlarged regional lymph nodes in 14 per cent.[4] Our patient presented atypically and mimicked epidemic viral conjunctivitis. However, one case report in the ophthalmology literature reported a similar case with a retrospective culture diagnosis.[4]



▲ Figure 2. Patient following two days of intravenous ceftriaxone and five days of topical chloramphenicol

There are 13 *Neisseria meningitidis* serogroups: A, B, C, W and Y most commonly cause disease.[3] Until recently, serogroup B (MenB) was the most common cause of invasive meningococcal disease in Australia, accounting for 63 per cent to 88 per cent of annual notified cases from 2006 to 2015.[3] However, in 2016 there were 110 notified MenW cases, surpassing MenB (92 cases).[3] MenW also appears to have a higher case fatality rate than disease caused by other serogroups.[3]

There are currently three types of meningococcal vaccines available in Australia: meningococcal C conjugate vaccine, multicomponent meningococcal B vaccine and quadrivalent (A, C, W, Y) meningococcal conjugate vaccines.[3] It is important to note that there is no single vaccine which covers all five common serogroups.

With the recent rise of MenW, the quadrivalent meningococcal vaccine is now being funded in Victoria, Queensland, New South Wales and Western Australia in 2017 for adolescents aged 15-19 years.[3] Readers should consult the respective state or territory health department website for further details.

Humans are the only natural hosts of *Neisseria meningitidis* and about one in 10 is an asymptomatic carrier.[8,9] It is a normal flora of the oropharynx but not of the eye.[10] Prevalence and duration of carriage vary over time and in different populations and age groups, with peak carriage rates (> 20 per cent) occurring in adolescents.[3] Most meningococcal cases in Australia tend to occur during early spring or winter.[3] Meningococcal bacteria are transmitted in respiratory droplets and the risk of transmission increases with prolonged close contact with those infected.[3]

Meningococcal disease tends to affect people who are immunocompromised (from age, disease or treatment), asplenic, experiencing recent or current viral upper respiratory tract infection or live in crowded conditions.[3] The literature has also cited the extended wear of contact lenses to be a risk factor for microbial keratitis, especially with Gram-negative organisms.[11,12,13] Although not specific to conjunctivitis, this finding raises the possibility of an increased risk of microbial conjunctivitis in our patient who had had his contact lenses in place for two weeks.

Possible local complications of PMC include corneal ulceration, iritis, keratitis and subconjunctival haemorrhage.[5,7] It can cause blindness and progress to systemic disease (18 per cent), being fatal in 13 per cent of those with systemic disease.[7] There is limited information in the international literature regarding PMC and it raised several questions regarding appropriate treatment of the patient.

Patients treated solely with topical antibiotics have a 19-fold increased risk of developing systemic disease compared to those treated with topical and systemic antibiotics.[7] Doctors should consult their local infectious diseases physician or hospital guidelines for specific treatment options. This report reminds us of the current MenW outbreak in Australia and raises awareness of the possibility of atypical presentations of this disease.

Optometrists in particular should consider this in any atypical anterior eye presentation and consider conjunctival swabbing as part of their work-up. ▲

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Therapeutic NEWS of note

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Consequences of declines in measles vaccinations

Even a small decrease in the measles vaccination rate could lead to a three-fold increase in cases, a study has concluded.

Researchers looked into the public health and economic impact of 'vaccine hesitancy', which is defined as a 'delay or refusal to accept vaccination based on personal beliefs despite availability.'

Using Center for Disease Control data to simulate measles, mumps and rubella (MMR) vaccine coverage for US children aged from two to 11 years, researchers estimated the number of measles cases and associated costs that would occur with declining vaccine coverage due to non-medical reasons.

At baseline, MMR vaccine coverage was 93 per cent, and the prevalence of non-medical exemptions was two per cent. This would yield 48 measles cases annually in this age group across the USA. However, if vaccine coverage dropped by five per cent, the estimated number of measles cases would increase to 150, costing the public sector an additional $2.1 million.

The researchers concluded that even minor reductions in childhood vaccinations, driven by vaccine hesitancy, will have substantial public health and economic consequences. In effect, when people opt out of vaccination, they are not just making a personal choice, they are affecting their community as a whole. Because vaccine hesitant parents tend to live in clusters, it makes the potential of large outbreaks much more likely.

JAMA Paediatrics July 24, 2017. doi:10.1001/jamapediatrics.2017.1695.

Vision loss in Indigenous Australians

The National Eye Health Survey has found that vision loss is 2.8 times more prevalent in Indigenous Australians than in non-Indigenous Australians.

Researchers conducted a nationwide, cross-sectional, population-based survey of Indigenous Australians aged 40 years or older and non-Indigenous Australians aged 50 years and older. Trained examiners conducted standardised eye examinations, including visual acuity, perimetry, slitlamp examination, intraocular pressure and fundus photography.

Overall, the prevalence of vision loss in Australia was 6.6 per cent: 6.5 per cent in non-Indigenous Australians and 11.2 per cent in Indigenous Australians.

In Indigenous Australians, the leading causes of vision loss were uncorrected refractive error (60.8 per cent), cataract (20.1 per cent) and diabetic retinopathy (5.2 per cent).

The study authors concluded that improvement in eye health care in Indigenous communities is required. The leading causes of vision loss —uncorrected refractive error and cataract—are readily treatable.

Ophthalmology 2017 Jul 6. doi: http://dx.doi.org/10.1016/j.ophtha.2017.06.001

Anti-VEGF for diabetic retinopathy remains a strong option

While it's too early to suggest that health-care providers should eliminate the use of lasers for the treatment of proliferative diabetic retinopathy, recent research has shown anti-VEGF injections to be a strong option for some patients.

'Is it time to retire your laser?' asked Adam Glassman of the Jaeb Center for Health Research, in an editorial in *JAMA Ophthalmology*. 'There are now two large, randomised clinical trials that show the benefits of anti-VEGF treatment compared with panretinal photocoagulation,' Glassman wrote. The trials are the Diabetic Retinopathy Clinical Research Network Protocols and the CLARITY study, which reported successful outcomes with the use of anti-VEGF injections compared with panretinal photocoagulation treatment, the standard treatment for many years.

'Anti-VEGF was a more effective treatment for preserving visual function and reducing complications that can accompany proliferative diabetic retinopathy,' Glassman wrote. 'Despite the promising results of the clinical trials, the barriers for wide-spread use of anti-VEGF agents persist.'

Glassman said compliance was a barrier. In the Protocol S trial, 12 per cent of participants in the anti-VEGF group failed to complete all visits through two years, and nine per cent of the aflibercept group in the CLARITY trial were also lost to follow-up. A second barrier noted by Glassman was cost, although the use of bevacizumab (Avastin) was mentioned as a cost-effective alternative.

JAMA Ophth 2017; Jul 1; doi: 10.1001/jamaophthalmol.2017.1652.

Efficacy of phacoemulsification

Phacoemulsification (phaco) as a solo procedure lowers intraocular pressure and reduces patient dependency on glaucoma medications.

Researchers conducted a retrospective review including 32 studies and 1,826 subjects with comorbid cataract and primary open angle glaucoma who underwent phaco and its effect on IOP and the required amount of topical glaucoma medications.

Researchers found a 12 per cent, 14 per cent, 15 per cent and nine per cent reduction in IOP from baseline at six,

12, 24 and 36 months, respectively, after phaco. A mean reduction in glaucoma medications of 0.57, 0.47, 0.38 and 0.16 was noted per patient at six, 12, 24 and 36 months after phaco, respectively.

The IOP-lowering effects appear to last at least 36 months, with gradual loss of the initial effect noted after two years, according to researchers.

A large variance in IOP reductions after phaco, ranging from 1.2 per cent to 29.4 per cent, was also observed. The researchers suggested that the difference may be the result of surgical variations or by differences in patient characteristics between as well as within the studies.

The review implies that if phaco can temporarily reduce the medication burden on patients, it may open a window during which there is a reduced risk of glaucoma surgical failure.

J Glaucoma 2017; 26: 6: 511–522. doi: 10.1097/IJG.0000000000000643

Disinfecting your tonometer

Sodium hypochlorite (diluted bleach) offers effective disinfection against adenovirus and herpes simplex virus (HSV) for tonometers, a report by the American Academy of Ophthalmology states.

Literature searches were conducted in the PubMed and the Cochrane Library databases for original research investigations. After exclusion criteria were applied, 10 laboratory studies remained for this review.

The infectious agents covered in the assessment were adenovirus 8 and 19, HSV 1 and 2, human immunodeficiency virus 1, hepatitis C virus, enterovirus 70, and variant Creutzfeldt-Jakob disease.

All four studies of adenovirus 8 concluded that after sodium hypochlorite disinfection, the virus was undetectable, but only two of the four studies found that 70% isopropyl alcohol (alcohol wipes or soaks) eradicated all viable viruses.

All three HSV studies concluded that both sodium hypochlorite and 70% isopropyl alcohol eliminated HSV. Ethanol, 70% isopropyl alcohol, diluted bleach and mechanical cleaning all lack the ability to remove cellular debris completely, which is necessary to prevent prion transmission.

It was also determined that disinfectants can cause tonometer tips to swell and crack by dissolving the glue that holds the hollow tip together. The cracks can irritate the cornea, harbour microbes or allow disinfectants to enter the interior of the tonometer tip.

The report recommends the use of sodium hypochlorite against adenovirus and HSV but encourages clinicians to regularly check their tonometers for signs of damage.

Ophthalmology 2017; Jul 11. doi: http://dx.doi.org/10.1016/j.ophtha.2017.05.033

For children, low dose atropine is better than high dose

Low-dose atropine showed equal efficacy in slowing myopia progression in children and had fewer side-effects than higher doses, according to a large meta-analysis of published studies.

Researchers reviewed 720 studies that included 3,137 children younger than 18 years; 268 were Asian, 201 were Caucasian. Studies with high, moderate and low-dose atropine (0.01%) were included, and while efficacy was not dose-dependent, side-effects were shown to be positively correlated with concentration.

The pooled data showed significantly less progression of myopia with all doses of atropine compared with control groups, but no correlation was found between dose and treatment effect. Ethnicity also had no impact on the effect of treatment.

A total of 308 adverse events occurred in 2,425 patients in the atropine groups (12.7 per cent). The difference with control groups was statistically significant. The most common effects were photophobia, poor vision at near and allergy, and their incidence significantly increased with dose escalation.

The study authors recommended the use of the lowest dose of atropine (0.01%) for therapy, but called for clinical trials with that dose.

However, the authors also suggested that combined approaches, including outdoor activities, orthokeratology, bifocals and possibly stem cells, might be necessary to better prevent the progression of myopia.

JAMA Ophthalmol 2017; 135: 6: 624-630. doi: 10.1001/jamaophthalmol.2017.1091.

Contact lenses risk no higher in children

The number of adverse effects in contact lens wearing patients under the age of 18 years is no higher than in adults, according to a review published in *Optometry and Vision Science*.

Authors of the research review collated data from a range of studies to estimate the incidence of complications in patients younger than 18 years. The analysis focused on signs of corneal infiltrative events measured against ‘patient years’ of soft contact lens wear.

In three large prospective studies representing between 159 and 723 patient years of soft contact lens wear in patients eight to 14 years, the incidence of corneal infiltrative events was low: 136 per 10,000 years.

Data from a large retrospective study showed similarly low rates of corneal infiltrative events: 97 per 10,000 years in eight- to 12-year-olds (based on 411 patient years of wear) and 335 per 10,000 years in 13- to 17-year-olds (based on 1,372 patient years of wear). None of the prospective studies reports any cases of microbial keratitis.

One retrospective study found no cases of microbial keratitis occurred in eight- to 12-year-olds (411 patient years) and an incidence of 15 per 10,000 patient years in 13- to 17-year-olds (1,372 patient years), which is no higher than the incidence of microbial keratitis in adults wearing soft contact lenses on an overnight basis.

Although they emphasised the need for further research, the authors concluded that the overall data support the safety of prescribing contact lenses for children.

Optom Vis Sci 2017; 94: 6: 638–646. doi: 10.1097/OPX.0000000000001078

Did cataract surgery cause this patient's NAION?

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CASE REPORT

A 78-YEAR-OLD Caucasian male presented for a cataract evaluation. The patient reported that his right eye seemed worse than his left eye. The patient was scheduled for cataract extraction of the right eye. His ocular history was significant for cataracts and blepharoplasty. His medical history was significant for Alzheimer's disease with moderate dementia.

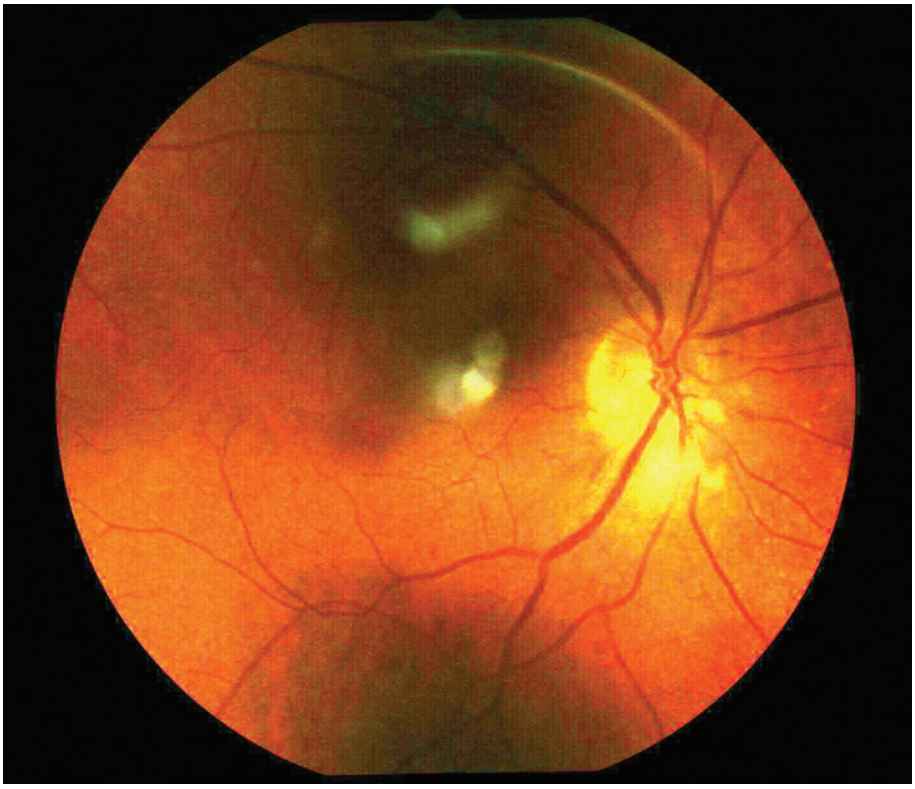
At the initial visit, the patient's best corrected acuities were 6/45-2 in the right eye and 6/20+2 in the left eye. Pupil testing was unremarkable and his eye movements were full, as were confrontation fields. His intraocular pressures (IOPs) were 13 mmHg in both eyes. Slitlamp examination of the right eye revealed grade 2+ nuclear sclerotic and grade 2+ posterior subcapsular cataracts. The left eye exhibited grade 2+ nuclear sclerotic and grade 1+ posterior subcapsular cataracts. All other anterior structures were unremarkable. The posterior examination of both eyes revealed maculae that were flat and dry, optic nerves were perfused with a cup-to-disc ratios of .45 x .45 and the peripheral retinas were flat and intact. The patient underwent successful phacoemulsification cataract surgery with a posterior chamber IOL in the right eye.

The patient's one-day post-operative examination was unremarkable. Post-operative medications included prednisolone acetate 1%, moxifloxacin 0.5% and ketorolac 0.5% four times a day in the right eye. Uncorrected acuities were 6/18-1 in the right eye and 6/18+2 in the left eye. IOPs were 17 mmHg right eye and 16 mmHg left eye. The right eye anterior chamber was deep with trace cells, posterior chamber IOL was stable, surgical incisions were intact and there was no Siedel sign.

The patient was then scheduled for left eye cataract surgery the following week.

As the patient was being checked into surgery the following week, he reported that the vision in his right eye seemed to be better but he was unable to see anything in his superior visual field. On further questioning, his wife reported that he had noticed a spot in his vision prior to his first cataract extraction but they had not thought anything of it and attributed it to his cataracts.

Because of this new complaint, the left eye surgery was cancelled and the patient was re-evaluated. His right eye acuity was 6/21 with pinhole 6/12. The IOP was 11 mmHg in the right eye. Pupils were equal, round, reactive to light with no relative afferent pupillary defect. Confrontation fields suggested a superior field defect in the right eye. Anterior segment findings were unremarkable. Fundus examination revealed inferior-nasal optic disc oedema and no haemorrhages (Figure 1). The computerised visual field exhibited a superior altitudinal defect. The left eye visual field was unremarkable.



▲ Figure 1. Fundus examination revealed inferior-nasal optic disc oedema and no haemorrhages

Although the patient denied any jaw claudication, scalp tenderness or temple pain, we proceeded to order an erythrocyte sedimentation rate and C-reactive protein (CRP) test to rule out temporal arteritis. Laboratory results showed an elevated ESR at 62 mm/hr and a normal CRP at 4.2 mg/L.

We started the patient on 60 mg oral prednisone daily and scheduled a temporal artery biopsy. The temporal artery biopsy was negative for inflammation. The oral prednisone was discontinued and the patient was diagnosed with non-arteritic anterior ischaemic optic neuropathy (NAION). The patient was then scheduled for cataract extraction of his left eye. The patient underwent successful cataract extraction of the left eye with no complications.

Discussion

This case report highlights the importance of listening to our patients and the rare association of cataract extraction and non-arteritic anterior ischaemic optic neuropathy.

Anterior ischaemic optic neuropathy can present in two forms: arteritic (AAION) and non-arteritic (NAION).[1,2] Although the exact mechanism is still unclear, it is thought that NAION is a result of acute ischaemia to the optic disc.[1-3] NAION is characterised by a sudden, painless decrease in vision with optic disc oedema and visual field defect.[1,3] The most common visual field defect is an altitudinal defect. However, other common visual field defects may include central, centrocecal, arcuate or a generalised depression.[1]

The patient may also present with reduced visual acuity, dyschromatopsia, afferent pupillary defect, peripapillary splinter haemorrhages and a small or crowded disc, also referred to as a disc at risk.[4,5] Other risk factors include sleep apnoea, diabetes mellitus, hypertension and hypercholesterolaemia.[4] In addition, the use of phosphodiesterase-5 inhibitors and amiodarone have been associated with the development of NAION.[5]

A less commonly cited association with NAION is cataract extraction. The association with cataract surgery is rare but it is also one of the most visually devastating complications.[6] Past studies have shown that there is an increased risk of NAION with cataract surgery that is greater than the overall incidence of NAION.[7] The incidence of NAION following cataract extraction is estimated to be one case per 2,000 whereas studies suggest that the overall incidence of NAION is 2.3 to 10.2 cases per 100,000 in individuals over the age of 50 years.[7,8,9]

However, a more recent study suggests that the increased incidence may reflect the use of retrobulbar and peribulbar anaesthesia as well as intracapsular and extracapsular surgical techniques. More modern surgical methods using phacoemulsification and topical anaesthesia have a prevalence and incidence of NAION after cataract surgery comparable to that of the general population.[9] Additionally, this study found no evidence suggesting that patients who have experienced NAION in one eye have an increased risk of NAION following a non-complex cataract surgery in the fellow eye.[9]

Although new evidence suggests that concern for NAION in the fellow eye following cataract surgery may be unwarranted, it is still important to educate our patients about the associated risks. Currently, there is no treatment for NAION. Surgical intervention with optic nerve sheath decompression has been shown to be ineffective and possibly harmful.[10,11,12] Other strategies to improve recovery by improving perfusion to the nerve have been attempted. Aspirin, vasodilators, systemic steroids and intravitreal steroids have been trialled but none has been proved to be effective.[12]

During the patients pre-operative visit there were no signs of ischaemic optic neuropathy. The patient explained to us that he noticed the decrease in vision after the initial visit, prior to his first eye cataract surgery, and attributed the change in his vision to the cataracts. However, after right eye cataract surgery, he became more aware of the visual field defect in his right eye and brought it to our attention prior to the surgery in his left eye.

In this case the NAION was not related to the cataract surgery but when consulting our patients with a history of NAION who are interested in undergoing cataract surgery, we should educate them on the associated risks and reassure them that risk of NAION in the fellow eye is low.[9] Ultimately, it is the patient's decision to undergo cataract surgery but it is our responsibility to be aware of associated risks and provide guidance to our patients. ▲

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Three steps for third nerve palsy: pupil, palsy and patient

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AN 89-YEAR-OLD man with poorly-controlled diabetes presented with complaints of constant diplopia for the past few days. The patient's right lid had partial ptosis and his extra ocular motility in that eye was limited in adduction, supraduction and infraduction.

This was all consistent with incomplete third nerve palsy. Neuroimaging was obtained through the patient's primary care physician but the study was inadequately directed. Nevertheless, no evidence of aneurysm or subarachnoid haemorrhage was seen. Two weeks later, the patient returned for follow-up with now complete ptosis and no movement in any of the previously mentioned gazes.

When a patient presents with a suspected palsy of cranial nerve three, it is imperative that the clinician knows all of the appropriate steps that need to be taken. There is almost no case where this condition does not suggest some underlying pathology that is either morbid or even mortal.

A recent study found causes of a third nerve palsy to be microvascular (42 per cent), trauma (12 per cent), neoplasm (11 per cent), post-surgery (10 per cent) and aneurysm (six per cent).[1] Be aware that given an individual patient's unique presentation, the risk of aneurysm may be much higher or lower in any given situation.

Microvascular diseases, such as diabetes and hypertension, should be of concern if they are causing neurological deficits but an aneurysm-causing compression on cranial nerve three is a cause of grave concern. The 30-day mortality for patients with subarachnoid haemorrhages caused by cerebral aneurysm rupture is as high as 45 per cent.[2] Knowing the proper approach for this condition is paramount for any eye-care practitioner.

Step 1: Look at the PUPIL

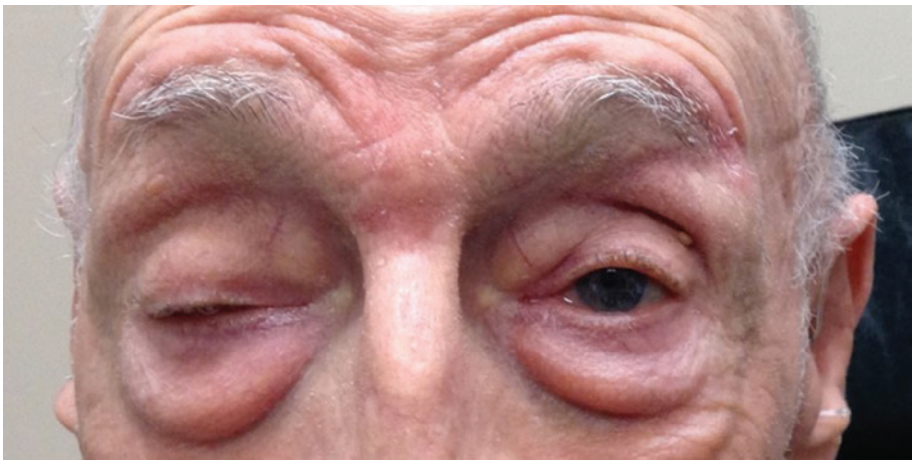
The earlier mentioned patient had his pupils thoroughly examined for reaction to light directly, indirectly, and an afferent pupillary defect was searched for; the same testing was done when the patient returned two weeks later. On both visits, it was thoroughly confirmed that both pupils were briskly reactive to light directly and indirectly, and that there was no afferent pupillary defect in either eye.

Thus, he had 'pupil sparing'. Pupil testing is an important way to determine the amount of suspicion there should be for a suspected aneurysm causing third nerve palsy. The 'rule of the pupil' is widely taught as the best way to determine if an aneurysm should be suspected.

Pupil fibres superficially travel with cranial nerve three and are vulnerable to compression from an aneurysm of the posterior communicating artery. These fibres are relatively immune to ischaemia from vascular infarct. However, this rule should apply only in cases of complete third nerve palsy.

Lee et al describe situations where the 'rule of the pupil' cannot be applied. If a patient has an incomplete third nerve palsy, which the authors describe as at least one extra ocular muscle having some function left or an incomplete ptosis, then the rule can no longer be applied and the patient should be worked up for a possible aneurysm. Additionally, third nerve palsies in conjunction with other non-ocular, neurological symptoms should no longer have the rule applied. In addition, evidence of aberrant regeneration means that the rule cannot be applied.[3]

If complete third nerve palsy is present, then the rule can be cautiously applied to determine if an aneurysm should be suspected. If the pupil reacts poorly to light, the patient



▲ Figure 1. Ptosis in complete third nerve palsy.

should be immediately evaluated for an aneurysm. However, Kissel et al determined that it is not enough to look only for presence of pupillary light reaction.[4] If there is partial internal dysfunction of the pupil with greater than 1 mm of anisocoria or diminished light reaction, then the suspicion of aneurysm should be high.

Step 2: Look at the PALSY

Patients with complete third nerve palsy without pupil involvement have a low risk of harbouring an intracranial aneurysm. If the palsy is incomplete or partial, then the patient should be suspected of having a developing aneurysm regardless of the pupillary state. Patients with partial third nerve palsy can have a pupil that is initially normal in function. Any partial third nerve palsy must be emergently evaluated for aneurysm regardless of pupillary state.

If a patient falls into any of the previously mentioned categories where an aneurysm is suspected, then neuroimaging needs to be done. To be on the safe side, even complete third nerve palsy with absolutely no pupil involvement may be best served by ruling out an intracranial aneurysm. Although extremely rare, it has been published that pupillary involvement may not appear in the case of an aneurysm until four months after initial paresis.[4]

The most common place for an aneurysm causing a third nerve palsy is on the posterior communicating artery, because the nerve runs parallel to this artery. The most sensitive and reliable non-invasive method of detecting an aneurysm is computerised tomography angiography and should be the first test that is requested. However, if the patient is pregnant or is a child, they should not be exposed to the radiation and magnetic resonance angiography is the next best option.[5]

Non-invasive scans may be performed or interpreted incorrectly. It is imperative to explain to a radiologist all thoughts on potential aetiologies so that the neuroimaging may be properly directed. Still, errors can be made. If the nerve and artery are anatomically far apart in a patient, then a very large aneurysm may be required to cause compression.

Conversely, if the artery and nerve are anatomically close together in a patient, then a very small aneurysm which may be missed on non-invasive imaging may result in palsy. In cases where an aneurysm is strongly suspected and non-invasive scans provide no evidence of such, digital subtraction angiography is required.[6]

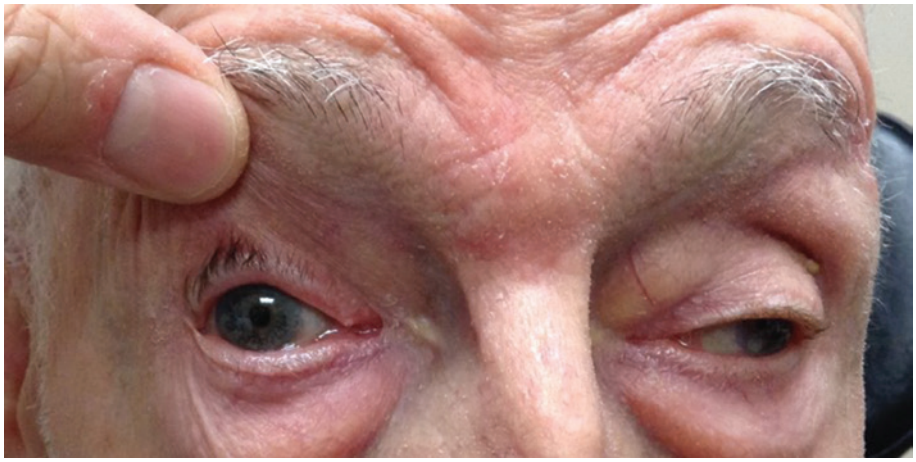
Step 3: Look at the PATIENT

Age and related medical conditions are important when assessing patients with third nerve palsy. Microvascular palsies are uncommon in younger patients and alternative aetiologies should be considered in patients younger than 50 years. While older age and the presence of ischaemic vascular diseases such as diabetes, atherosclerosis, hypercholesterolaemia and hypertension, favour microvascular aetiology, they are not protective against an aneurysm. Microvascular aetiology should not be strongly suspected in patients not having ischaemic vascular diseases.

In a study conducted by Watanabe et al, on patients with cranial nerve three or four palsies caused by diabetes, about 70 per cent of these patients had other diabetic complications elsewhere in the body.[7] A microvascular aetiology warrants referral to the patient's primary care physician because hypertension, diabetes or high cholesterol that may be damaging a cranial nerve is probably affecting other organ systems elsewhere in the body. It may also be prudent to recommend erythrocyte sedimentation rate and C-Reactive Protein testing, since giant cell arteritis (GCA) can cause pupil sparing third nerve palsy that would mimic a microvascular aetiology.[8]

Improvement of microvascular palsy should be seen over time and the condition should resolve nearly completely. However, if there is no improvement over time, then a different aetiology should be considered. Presumed microvascular palsy may progress throughout one week and be unimproved at two weeks. However, microvascular palsy will not get progressively worse over the course of two weeks. Patients with presentation and risk factors characteristic of microvascular palsy can still have alternative causes, such as neoplasm, inflammation, GCA and brain stem infarction.[9]

An aetiology for the earlier mentioned patient was determined most likely to be microvascular due to his type 2 diabetes. The patient was taking insulin four times a day, was on maximum metformin therapy, and his medical records revealed blood sugar values that fluctuated from around 400 and dipped down to about 40. The patient was also being medically managed for hypertension and high cholesterol. The patient's primary care physician was alerted and recommended to follow tighter diabetic control. The patient was informed that he should wear a patch over his affected eye to relieve the diplopia and that his condition should resolve within three months. Within several weeks, his palsy recovered.



▲ Figure 2. Pupil test determines a suspected aneurysm causing third nerve palsy

Continued page 24

Third-nerve palsy

From page 23

Conclusion

If a patient presents with third nerve palsy, three steps should ensure that the patient receives the appropriate care needed to rule out any cases of aneurysm aetiology and that other aetiologies are properly managed. If an aneurysm is suspected, urgent hospital evaluation with appropriate neuroimaging is required. If aneurysmal cause is completely ruled out and there are microvascular risk factors, then patients should have these systemic diseases managed by the appropriate practitioners, while keeping other aetiologies in mind.

Acknowledgement

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Clinical Quiz

From page 12

DIAGNOSIS: Large conjunctival dermoid

Conjunctival dermoid can occur as an isolated lesion, as in this case, or it can be a component of Goldenhar syndrome.

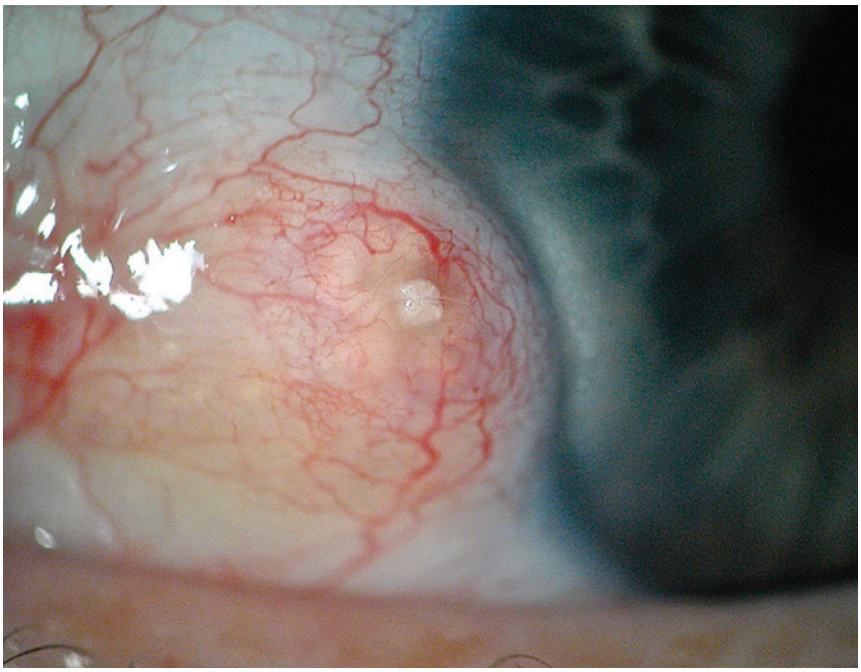
Dermoids can appear in various sizes as a yellow-white limbal mass, usually inferotemporally but can appear in other meridians. The size can range from 2 mm to 15 mm in diameter, and 0 to 10 mm in thickness. Fine white hairs often protrude from the lesion as well as a yellow-white lipid line in the adjacent corneal stroma.

Larger dermoids can cause ocular surface irritation and astigmatism. Histopathologically, dermoid is lined by stratified squamous epithelium and deep to the epithelium is dense collagenous tissue.

Management

Smaller, asymptomatic lesions can be observed and monitored. Alternatively, surgical removal can be considered. Reasons for surgical removal include: secondary astigmatism, encroachment on visual axis, ocular surface irritation, dellen formation and cosmetic reasons.

For excision a combination of lamellar keratoplasty, amniotic membrane and stem cell replacement can be employed. ▲



▲ Conjunctival lesion Image: Associate Professor Mark Roth

Jerry A Shields and Carol L Shields. *Eyelid, Conjunctival and Orbital Tumors: An Atlas and Textbook*, 3rd edition. Wolters Kluwer 2016.

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