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As 2012 ended and we ushered in the Snake in 2013, it is also the time of the year that we review our achievements in the year before and plan our goals for 2013. 2012 marked the second year of the Residency Program at SNEC and the start of the SingHealth Eye ACP. Many lessons were learnt in the setting up of the Residency program and we can only learn from our experiences to continually strive to better ourselves and our program so that the next generation will be better than us. The SingHealth Eye ACP strives to coordinate SNEC’s three pillars more effectively ie. clinical service, education and research. It is often nigh impossible to match these in one’s schedule in real life as it is expected of us to produce excellent clinical work most of the time. But to also factor in teaching (to all levels!) and research. Despite the challenges, I’m also heartened and relieved to know, on comparing with others, that SNEC is still actually rather special. Our huge clinical volume is the driving force for research and produces the wonderful material for teaching. It is without doubt that our residents are well exposed to the vast range of ophthalmic problems our population experiences.

Teaching is multi-faceted. We often think of teaching as the process of how we impart our skills and experiences. But education is probably the better word. Wikipedia defines it as “a form of learning in which knowledge, skills, and habits of a group of people are transferred from one generation to the next through teaching, training, research, or simply through autodidactism. Generally, it occurs through any experience that has a formative effect on the way one thinks, feels, or acts.”

Teachers need to be taught and updated, hence we have the Continuing Medical Education (CME), conferences and various faculty development options to improve our methods of teaching. This newsletter continues to serve its role in the dissemination of knowledge so that our colleagues continue to be highly competent and kept abreast of developing changes in ophthalmology. We hope you will continue to enjoy reading our articles.

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Electrophysiology refers to the study of electrical properties of biological cells and tissues in the body. It measures the voltage change or electric currents generated by the cells, these are predominantly neural cells in the retina and optic nerve. In ophthalmology, it is useful as it provides us with an objective measure of retinal, optic nerve or cortical function.

There are three main groups of tests:
1) Electroretinogram (ERG)
2) Visual evoked Potential (VEP)
3) Electro-oculogram (EOG)

From each, we can determine various retinal and cortical functions:

<table>
<thead>
<tr>
<th>TEST</th>
<th>TISSUE TEST</th>
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<tbody>
<tr>
<td>Electro-oculogram</td>
<td>Retinal pigment epithelium</td>
</tr>
<tr>
<td>Electroretinogram</td>
<td></td>
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<tr>
<td>- Full-field ERG</td>
<td></td>
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<tr>
<td>A wave</td>
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<tr>
<td>B wave</td>
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<tr>
<td>- Pattern ERG</td>
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<tr>
<td>- Multifocal ERG</td>
<td></td>
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<tr>
<td>Visual evoked potential</td>
<td></td>
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<tr>
<td>Flash VEP</td>
<td>Entire visual pathway</td>
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<tr>
<td>Pattern VEP</td>
<td>(retina/nerve/tract/cortex)</td>
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To determine the clinical profile of children referred to the SNEC-SERI visual electro-diagnostic laboratory, we analysed the data from 421 children who underwent electrophysiological tests between 2003-2011.

The majority of children were referred by paediatric ophthalmologists, followed by retinal and neuro-ophthalmologists.

The commonest reason for referral was for evaluation of poor vision (46%), followed by assessment for suspected retinal dysfunction (36%). Other reasons included assessment for optic nerve or cortical problems (9%), exclusion of functional visual loss (2%) and others which included evaluation for potential drug toxicity and assessment for visual potential.

The reason for referral was different when the children were divided into different age groups. Monitoring of drug toxicity (particularly vigabatrin) and visual potential evaluation were more common in those younger than 2 years of age. Figure 2 demonstrates that the older children were largely referred for the evaluation of poor vision of unknown causes as well as for potential retinal disease, with particular emphasis on dystrophies.
The underlying cause of visual impairment could be identified in the majority (Figure 3). These are listed in Table 1 with retinal dystrophy accounting for the most of the diagnoses.

![Figure 3: Type of diagnosis](image)

<table>
<thead>
<tr>
<th>Type of diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone or cone-rod dystrophy</td>
<td>65 (15%)</td>
</tr>
<tr>
<td>Rod-cone dystrophy</td>
<td>57 (13%)</td>
</tr>
<tr>
<td>Photoreceptor dystrophy</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>CSNB</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Retina dysfunction</td>
<td>60 (15%)</td>
</tr>
<tr>
<td>- Cone</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>- Rod</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>- Photoreceptor</td>
<td>44 (11%)</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>31 (7%)</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>28 (6%)</td>
</tr>
<tr>
<td>Post-retinal</td>
<td>38 (9%)</td>
</tr>
<tr>
<td>Normal</td>
<td>91 (19%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>25 (6%)</td>
</tr>
</tbody>
</table>

Table 1: Type of diagnosis

The following two case studies illustrate how the electrophysiology can aid in the diagnosis and management of these children.

**CASE STUDY 1**

A 12 year-old Indian boy presented with poor vision which was noticed by the parent since early childhood. His visual acuities were 6/120 and count fingers for the right and left eyes respectively. They denied any family history of eye problems.

There was bilateral RPE mottling at the macula, that corresponded with dark areas that were detected on autofluoresence (Figure 4). It was uncertain if he had a maculopathy or a more extensive photoreceptor problem. Electrophysiology was performed.

![Figure 4: Fundus photographs](image)

The PERG was flat, and there was a decreased response, affecting cones more than rods, on ffERG (Figure 5). Central responses were depressed on mFERG (Figure 6). These findings were suggestive of a cone-rod dystrophy with maculopathy.

![Figure 5: Pattern and full-field ERG- case 1](image)
CASE STUDY 2

A 8 year old Indonesian boy presented with visual acuities of 6/24 after correcting for myopia of -11DS. He had a fine nystagmus but intraocular examination was unremarkable. He did not have nystagia nor photophobia.

The ERG showed a flat scotopic response, and an electronegative maximal response, with a broadened photopic a-wave (Figure 7). These findings were typical of congenital stationary night blindness (CSNB) and he was referred to the low vision clinic for rehabilitation.
Combined phaco vitrectomy is a widely used and accepted procedure for managing eyes with co-existent cataract and retinal pathology. Often the phaco-IOL is “prophylactic” because worsening of the nuclear sclerotic cataract is inevitable after vitrectomy, especially with the use of gas or silicone oil for tamponade.

When performing combined surgery, the phacoemulsification must be done well in order to facilitate the vitrectomy. Corneal edema, retained viscoelastic, miosed pupils or retained soft lens matter at the end of cataract surgery can impede the surgical view and compromise the success of the subsequent vitrectomy. Using a scleral tunnel instead of a clear corneal tunnel can be useful in these cases as the wound is more secure and less likely to obscure intraoperative retinal visualization. Dr Wong explained that his preference was to perform the vitrectomy and membrane peeling before inserting the intraocular lens as the aphakic state maximizes the view for the vitrectomy. He advised that the IOL should be inserted before fluid gas exchange because this may be more difficult in the presence of a gas filled posterior segment.

Dr Wong’s preference is to perform the cataract surgery at the same time as the vitrectomy routinely in phakic eyes with macular holes, epiretinal membranes, vitreomacular traction and myopic macular schisis. He also added that this can also be considered in phakic eyes with “uncomplicated” proliferative diabetic retinopathy (eg: Vitreous hemorrhage in the absence of significant tractional retinal detachment).

There have been several reports that show that combined phaco vitrectomy is an extremely successful procedure with minimal complications. And that the complication rates were no worse than vitrectomy alone. Good post-operative IOL stability and centration, with faster visual recovery and rehabilitation can be achieved without the need for a second surgery. However, it is not without complications and case selection is important.

These cases describe potential complications during combined phaco/IOL – vitrectomy surgery.

The first case had undergone combined phacovitrectomy for a macula hole. At the end of the surgery, a 3-piece IOL was inserted into the bag. During the post-operative follow-up, the macular hole was successfully closed, however the optic of the IOL was noted to be anteriorly displaced with pupil capture (Figure 1).

Optic capture after combined surgery has been reported in the literature. Smith et al reported an iris capture rate of 8.6% after phacovitrectomy for primary retinal detachment. Rahman reported a 8.95% iris capture rate after phacovitrectomy with gas tamponade for a mixture of indications. Katsu reported a 12% iris capture rate after phacovitrectomy for complications of diabetic retinopathy. The risk of this complication can be reduced by using a 3 piece IOL instead of a 1 piece IOL and Rudinsky reported in his case series a 7.7% iris capture rate with single piece IOL compared with no cases with a 3 piece IOL. The most common underlying reason would be that of the effect of the gas filled posterior segment exerting an anterior displacement of the IOL optic.

The next possible problem with combined phacovitrectomy is the post-operative refractive outcome. Often, patients with macular conditions have thickened foveas. He described a case of a macular pucker causing a central retinal thickness of 701um. Based on the preoperative biometry, the IOL was selected so as to achieve a refractive target of -0.55D. On the postoperative day 1, the autorefraction showed a result of -0.5/-1.00x110. However at 2.5 months after the surgery, the central retinal thickness had settled to 454um, resulting in a myopic shift to -2.50/-1.50x100 (Figure 2).
Is Combined Phaco-IOL Vitrectomy Always a Good Idea?

Biometry may not be accurate in patients with retinal conditions that affect macula or foveal thicknesses as the axial length measurement may then be measured short than the axial length should be. On option is to use biometry of the other eye which may be adequate in conditions like macular involved retinal detachments where the visual outcome is guarded. However accuracy of biometry is absolutely vital, particularly if visual outcome is expected to be good.

It has been reported that a myopic shift ranging from -0.36 to -0.46D can occur after gas tamponade. Myopic shifts may be more significant in patients with longer axial lengths (>24.5mm); worse preoperative visual acuity (<5/200); and preoperative foveal detachments. However it does not appear to be influenced by the use of gas during surgery. Furthermore if phacoemulsification cataract surgery is done as a second procedure sequentially after the vitrectomy, the refractive outcomes are similar to non-vitrectomised eyes. Therefore when refractive accuracy is important in a particular patient, sequential surgery may provide the more accurate result, especially if premium IOLs like toric lenses are used.

There is also a higher risk of iris neovascularisation associated with phacovitrectomy. Various authors have shown that lens removal during vitrectomy results in a higher incidence of iris neovascularisation and rubeotic glaucoma. This may be related to the removal of the lens barrier which allows vascular growth factors to migrate from the posterior segment to the anterior segment more easily. Chung et al also reported that combined surgery in diabetics resulted in a neovascular glaucoma rate of 15.4% compared with sequential surgery which did not have any cases of neovascular glaucoma in their case series. However, eyes left phakic after diabetic vitrectomy had a higher reoperation rates. Others reported no difference between combined and sequential surgery. Some case series even reported that iris neovascularisation was lower in the combined phaco-vitrectomy group.
However, Dr Wong highlighted the biggest issue with doing combined surgery is the preoccupation with the insertion of the intraocular lens at the same sitting. This can, in some cases, result in suboptimal outcomes. He illustrated this point with a case of retinal detachment treated with primary vitrectomy. The patient subsequently redetached and a gas cataract developed. A second surgery in the form of phacovitrectomy with IOL implantation and encirclage was then performed. Unfortunately, the retina redetached as a consequence of inferior proliferative vitreo-retinopathy (Figure 3). In addition, a dense posterior capsular opacity developed together with posterior synechiae, limiting the view for examination. This combined with silicone oil emulsification and anterior capsular fibrosis can significantly affect visualization if further surgery is required.

If further surgery was to be performed, the intraocular lens and the capsule would have to be removed to facilitate visualization during surgery.

Sequential surgery with vitrectomy done after phaco/IOL may be an option in cases requiring non-urgent vitrectomy in the presence of an early or non-visually significant cataract. For example in cases with epiretinal membrane in the presence of cataract the patient can have cataract surgery first and sometimes they maybe satisfied with the visual improvement and subsequent vitrectomy may not be required. Cases of diabetic retinopathy with fluctuating vitreous hemorrhage can also be offered the option of just cataract removal alone first.

Alternatively, sequential surgery can be done with cataract surgery after the vitrectomy. The predominant advantage would be greater accuracy of the biometry, and no risk of iris capture and posterior synechiae.

However, in eyes with complicated retina pathologies, lensectomy may be required. These eyes would best be left aphakic after the first surgery. The patient can be visually rehabilitated with aphakic contact lenses or secondary IOL implation (anterior chamber IOL or iris/scleral fixated IOL) after the retina condition has stabilized. The posterior or anterior capsular rim can be preserved during lensectomy so that the secondary posterior chamber IOL can be placed in the sulcus. This is a good option when retinal pathology is not too complex.

However in complex cases or cases with significant post operative inflammation, there may be extensive posterior synechiae with poor pupil dilation and iris trauma when attempting to implant a secondary IOL. Severe capsular fibrosis and contraction can also worsen the situation if it results in ciliary body traction causing hypotony.

In conclusion, although combined phaco vitrectomy is an acceptable and elegant procedure, there are potential problems in some scenarios. The cataract surgery must be done well to minimized corneal haze and maintain pupil dilation and clear posterior capsule. Case selection is crucial. In eyes with more complex retinal pathology it is more important to focus on treating the retina disease first, and addressing the lens issues later.
Ptosis surgery is one of the most common procedures performed by the Oculoplastics department at the Singapore National Eye Centre (SNEC). We have been auditing our results since the 1990s in an attempt to determine our ptosis surgery outcomes in an objective way. However, previous audits had various limitations including subjective bias in the measurements of parameters such as marginal reflex distance 1 (MRD1), absence of pre- and post-operative photography, lack of assessment of other parameters other than post-operative MRD1 and failure to look at patient satisfaction.

In 2009, we started a prospective ptosis audit to collect data in a robust and reliable manner, as well as to overcome the shortcomings of previous audits. The audit form was further refined, with the current audit form finalized in 2010. Changes made to the form ensured less observer bias and that all necessary data was captured. The form was also made more concise and easier for the observer to fill up. In addition, there was more emphasis on patient subjective grading with a re-definition of the numerical grading scale to allow for a more standardized comparison of patient satisfaction. It also had a column to remind doctors to ensure patients’ pre- and post-operative (one and three months post-operative) photographs were taken (Figures 1 to 4). Photography enabled us to objectively critique our own work, clarify any doubts we may have about the clinical results, and mitigate against inter-observer differences in MRD1 reading and the effect of Hering’s law in asymmetric cases (Figures 5 and 6). The figures have no caption. Need a statement with each figure. Please show the different measurements that were made on the photographs with the appropriate arrows.

Data captured by the finalized form included patient demographics, aetiology of ptosis (congenital or acquired), mechanisms of ptosis (aponeurotic, myogenic, neurogenic, mechanical due to mass effect or recurrent), and history of previous eyelid or ptosis surgery. Preoperative measurements of MRD1 and levator function (LF) were recorded. Indications for surgery (e.g., occlusion of visual axis, amblyopia, abnormal head posture, cosmetic reasons) were noted. Surgical data included the type of anesthesia (local or general), type of surgery (levator repair, levator resection or brow suspension), and for the latter, type of material used (autologous or alloplastic). We also noted whether the surgeon performing the operation was a consultant or trainee, and whether there was any intention for under- or over-correction.

Postoperatively, MRD1 measurements were documented, and symmetry was graded according to the following: symmetrical (equal MRD1 in both eyes), mild asymmetry (≤1 mm difference in MRD1 between both eyes), moderate asymmetry (>1 mm but ≤2 mm difference in MRD1 between both eyes) and obvious asymmetry (>2 mm difference in MRD1 between both eyes). Lid contour was graded as good or dissatisfactory; lid crease as symmetrical, asymmetrical or accessory. Any complications such as exposure keratopathy, wound granuloma, wound dehiscence, infection, leg scar, or forehead scar were recorded. We also noted the need for post-operative readjustment within 2 weeks, and the reason for readjustment (e.g., to address lid height under-correction, over-correction, lid contour or lid crease).
Using this new form, we evaluated our results from January to December 2010. 158 patients had surgery done with a mean follow-up of 3.1 months (range 1-10 months). 29 patients had less than one month follow up and were considered defaulters and not evaluated. Among the 30 patients with congenital ptosis, levator resection (n=17, 56.7%) was the most commonly performed procedure, followed by brow suspension (n=10, 33.3%) and levator repair (n=3, 10.0%). One hundred and twenty-eight patients had acquired ptosis, of which majority underwent levator repair (n=123, 96.1%), while 4 had levator resection (3.1%) and 1 had brow suspension (0.8%).

Majority of the patients (n=112, 86.8%) did not require ptosis re-adjustment, which was done within 2 weeks of surgery. Of the 17 (13.2%) who did, 12 were for lid height under-correction, 4 for lid height over-correction and 1 for unacceptable lid contour. A high proportion (91.9%) of our patients had an improvement in MRD1 post operatively. However 34.0% had post-operative MRD1 of less than 2mm, although many of these “failure” cases were considered successful based on post-operative photographs and patient satisfaction grading. These cases and their clinical photographs were looked at individually, and reasons for less than expected increase in MRD1 included variability of MRD1 reading especially in presence of severe dermatochalasis and Hering’s law in bilateral but asymmetric ptosis. Hence 91.9% would be a conservative estimate, and the percentage of patients having increase in MRD1 post-operatively would in fact be higher.

In terms of lid height symmetry, most patients had symmetrical lid height (n=76, 59.4%) or mild asymmetry (n=39, 30.5%). Only a small proportion of patients had moderate asymmetry (n=10, 9.8%) or obvious asymmetry (n=3, 2.3%). Hence, approximately 90% of patients had lid height asymmetry less than 1mm. Symmetry was significantly correlated with patient’s satisfaction grading (Pearson’s r = -0.283, p=0.001). A high percentage (99.1%, n=114) of patients had good lid contour. Assessment of the lid crease revealed symmetry in 75.2% (n=85) of patients, asymmetry in 23.9% (n=27), with 1 patient (0.9%) having an accessory crease. Complications occurred in 3 (2.3%) of the study patients, which included 1 case of wound dehiscence in a child post brow suspension which was addressed with good result, 1 case of conjunctival prolapse where repair of the conjunctival prolapse and ptosis readjustment was performed with good outcome, and 1 case of upper lid hematoma which was drained on the first post-operative day with resolution of the hematoma.

The mean score for subjective patient grading was 7.8, with 29.1% (n=43) giving a grade between 9-10, 55.4% (n=82) between 7-8, 14.2% (n=21) between 5-6, and 1.3% (n=2) giving a grade less than 5. Average subjective patient grading was 7.8. Approximately 85% of patients gave a subjective satisfaction grading of at least 7 on the scale of 1 to 10. Please clarify….is 1 = v satisfied or is 10 = v satisfied.

In summary, our centre has achieved good results in ptosis surgery in terms of subjective and objective outcomes for our patients. We found that patient satisfaction with ptosis surgery was not dependent on MRD1 alone, and symmetry played an important role in subjective patient grading. Our study is the first prospective ptosis surgery audit in an Asian population. With the continuation of this audit in years to come, it will allow us to generate clinical outcomes in a robust manner and allow for more reliable benchmarking with major centres elsewhere.
A PHACO POTPOURRI

Presented by Dr Ronald Yeoh on 21 March 2012 | Written by Dr Annabel Chew

Dr Ron Yeoh presented 3 topics relating to phacoemulsification surgery – namely viscoelastic removal, lens touch cataract and decentered intraocular lens (IOL).

VISCOELASTIC REMOVAL

It is important to remove viscoelastic between the IOL and the posterior capsule so that the IOL can sit on the posterior capsule to reduce the risk of IOL rotation. This is especially important for toric IOL and toric multifocal IOLs. Furthermore retained viscoelastic can lead to raised intraocular pressure, capsular block syndrome, and development of posterior capsular opacification.

To ensure complete removal of the viscoelastic, it is necessary to remove the viscoelastic posterior to the IOL, anterior to the IOL and under the cornea. In order to enable adequate clearance of the viscoelastic between the IOL and the posterior capsule, the irrigation and aspiration (IA) probe can be placed behind the IOL. To achieve this, the IOL can be nudged gently and tilted anteriorly. Aspiration should be performed gently, taking care to orientate the port of the IA probe upwards. After that, the IOL should be repositioned and centred in the bag. Occasionally, residual viscoelastic may present itself from the angles; balanced salt solution (BSS) can be done to flush the remaining viscoelastic out.

If the posterior capsule is engaged into the port of the IA probe while aspirating, one should stop aspirating, maintain the position and activate the reflux by kicking the foot pedal to the left, or pinch the aspiration tubing to release the posterior capsule. Greater care must be taken in the presence of zonular dehiscence.

It should be noted that rarely, aqueous misdirection can occur intraoperatively, during which fluid is trapped behind the capsular bag. The posterior capsule fails to distend posteriorly despite infusion. In these eyes, aspirating the viscoelastic behind the IOL should be avoided, as there is a high risk of posterior capsular rupture.

LENS TOUCH CATARACT

After vitreous surgery, the majority of patients will develop nuclear sclerotic cataracts after 1 to 2 years. Surgeons need to be aware of this possibility when performing cataract surgery in post-vitrectomy eyes. It would be wise to manage these cases as for posterior polar cataracts, i.e. performing hydrodelamination instead of hydrodissection, and doing the phacoemulsification slowly, with reduced settings.

Anterior segment photographs of both eyes showing cataracts from a single patient; the picture on the right shows a waterlogged, lens-touch cataract.
However, lens touch cataracts can also develop as a complication of intravitreal injection during which the needle may have touched the lens or “scratched” the posterior capsule. Characteristically, this would be followed by rapid cataract formation within 1 to 7 weeks. Typically, a glistening appearance from waterlogging through the posterior capsular rent can be seen. As there is an increasing number of intravitreal injections performed worldwide, usually without akinesia; these lens touch cataracts may be seen more frequently. D’Amico reported 7 lens injuries out of 582 intravitreal injections performed (0.7%); Jonas reported 3 lens injuries out of 5000 intravitreal injections performed (0.06%).

**DECENTERED IOL**

IOL decentration is uncommon. Decentration can occur in the presence of an eccentric rhexis, capsular bag fibrosis or phimosis and zonular dehiscence. No active management is required if the lens is a monofocal IOL; the IOL is not significantly decentered from the visual axis and the best corrected visual acuity is not significantly affected. With regards to the decentered multifocal IOL, intervention is usually not required if the innermost optical ring can be seen within the undilated pupil. If intervention is deemed necessary, the decision would be between re-positioning the IOL and exchanging the IOL. In the absence of capsular support, the method of placing an IOL safely and securely should be carefully considered.. Anterior vitrectomy may be required if vitreous is present in the anterior chamber.,

Re-positioning the IOL can be difficult if the capsular bag is fibrosed and the anterior and posterior capsular surfaces may be stuck together. The IOL can be mobilized by injecting viscoelastic into the capsular bag, and then a Sinsky hook can be used to free the haptics from capsular adhesion to enable adequate centration of the IOL. If the adhesion is too strong and the IOL cannot be safely dislodged, it may be necessary to cut the optic into half so as to enable removal of each half through the main wound more easily. A 3-piece IOL can then be placed into the sulcus if there is adequate anterior capsular support.

If the decentration is due to a localized area of capsular fibrosis, the area of fibrosis can be dissected with a pair of intraocular scissors to enable the capsular bag to re-open with viscoelastics so that we can rotate the IOL back into position. Sometimes the area of fibrosis is beneath the anterior capsule and can be removed by peeling it off the anterior capsule without having to cut the anterior capsule.

The multifocal IOLs can be centered with the help of miostat and the use of Purkinje images.

A well centred rhexis is important for good lens centration, and the femtosecond laser maybe helpful with better rhexis creation.

References:
MOEISIN: A CRITICAL REGULATOR OF CORNEAL FIBROSIS

Presented by Prof Roger W. Beuerman on 4 April 2012 | Written by Dr Arvind Gupta

Corneal fibrosis is the third leading cause for blindness worldwide. Fibrosis is the end result of many forms of insults to the cornea. Keratocytes, specialized corneal fibroblasts, residing in the corneal stroma are transformed into myofibroblasts at the time of trauma and are eventually responsible for the occurrence of fibrosis. Currently, the treatment for fibrosis causing blindness revolves around different forms of corneal transplants. Hence, there is a need to develop a more specific therapy targeting the regulation of occurrence of corneal fibrosis.

After the initial insult to the cornea, a diverse array of cytokines are produced which are responsible for the rearrangement of the cytoskeleton of keratocytes thereby enabling them to have changes in motility, adhesion, architecture and increased expression of cytoskeleton regulators. Transforming Growth Factor-β (TGF-β) has been found to be one of the most important cytokines regulating the occurrence of fibrosis.

SMADs are transcription factors that transducer various extracellular signalling factors and function mainly by activating various target genes. SMAD 2 and 3 are preferentially induced by TGF-β and thus are involved in the pathogenesis of the corneal fibrosis.

Erzin-radixin-moeisn (ERM) proteins are a family of ubiquitous actin-binding proteins with high amino acid homology (80-85%). They act both as linkers between the actin cytoskeleton and plasma membrane and as signal transducers in responses involving cytoskeletal remodelling. Thus, they can regulate the cytoskeleton, control cellular shape and motility and modulate signalling pathways.

EXPERIMENT WITH MOUSE MODEL:

A central 2mm hole was trephined centred on the animal's cornea till a depth of half the thickness of the stroma. The disc of epithelium and stroma was removed. One of the eyes was used for the experiment while the other eye was used as control. The mice were sacrificed at the day 1, 3 and 5. Various experiments concluded the following:

- Post-injury, α-SMA and moesin are co-expressed in the stromal keratocytes and their concentrations gradually increase in at the site of stromal injury
- TGF-β1 induces the α-SMA expression in the corneal stroma
- Topical TGF-β1 application increases the expression of moesin manifold at the sire of corneal stromal injury
- Moesin reduces the expression of α-SMA induced by TGF-β1. This is brought about by the reduced Smad 2 and 3.

CLINICAL SIGNIFICANCE:

- Mouse model is a suitable animal model to study the regulation mechanisms of corneal fibrosis
- Moesin is a novel approach to reduce the occurrence of fibrosis post-corneal stromal injury without any significant side-effects
- The results can be extrapolated to other parts of body to reduce fibrosis.
Diabetic macular edema (DME) is a major cause of visual loss in adults of the working age group. Vascular endothelial growth factor (VEGF) plays a major role in the pathogenesis of diabetic retinopathy (DR) when it mediates active intraocular neovascularization and blood retinal barrier breakdown. The key form of VEGF in DR is VEGF$_{165}$ and elevated levels are found in experimental diabetes and the vitreous of eyes with proliferative DR. The aims of current DME treatment are to reduce retinal vascular hyperpermeability and leakage.

One of the most important aspects in the management of DME is the systemic optimization of blood pressure, serum glycaemic and lipid control. Ocular treatment has traditionally centered on focal and grid laser photocoagulation, but recent data has supported the use of pharmacological agents such as intravitreal anti-VEGF agents and steroids. Vitrectomy is reserved for a small group of patients with persistent DME, primarily from persistent vitreous traction.

The ADVANCE study revealed that a good glycaemic control of HbA1c less than 6.5%, combined with a good blood pressure control achieved with perindopril will significantly reduce the occurrence of macula edema and arterio-venous nicking. The ACCORD study showed that a tight Hb$_{A1c}$ control of < 6% significantly delayed the incidence and progression of DR and other microvascular end-points compared to conventional Hb$_{A1c}$ control of 7-7.9%, although it was associated with significantly higher adverse cardiovascular and hypoglycaemic outcomes, prompting an early termination of the trial. The FIELD study showed that the use of fenofibrate significantly reduced the need for a first laser treatment (3.4% vs 4.9%, P=0.0002), as well as the incidence of a 2-step progression of DR (3.1% vs 14.6%, P=0.004). These effects were independent of the lipid lowering effects of fenofibrate.

Laser photocoagulation has been the standard treatment for the past 25 years since the first report by ETDRS in 1985, which showed that laser treatment can stabilize and reduce the risk of moderate visual loss (loss of 3 lines of vision) from 23% to 12% after 3 years. However, visual acuity improvement is uncommon (only present in about 10-15%) and there is a risk of further visual loss due to retinal pigment epithelium damage, scar creep or rarely secondary choroidal neovascularization due to Bruch's membrane rupture. Reports from DRCR.net and RESTORE studies observed an approximately 10% risk of 2-3 lines visual acuity loss after laser treatment.

The RESOLVE study clearly showed that monthly intravitreal ranibizumab treatment increased the mean best corrected visual acuity (BCVA) by 10 letters (2 ETDRS lines) after 12 months. There was a constant slow increase in BCVA throughout the first 12 months. In contrast, there was no change in the mean BCVA throughout the 12 months with sham treatment. A significant reduction in mean central retina thickness (CRT) was also observed for the subjects with ranibizumab treatment compared to sham treatment. The RIDE and RISE studies also observed a mean gain in BCVA by 12.5 letters after 24 months of monthly ranibizumab 0.3mg treatment compared to a gain of 2.6 letters with monthly sham treatment. Interestingly, treatment with a higher dose of ranibizumab at 0.5mg did not achieve a better visual gain compared to 0.3mg treatment.

DRCR.net studies reported a better gain in mean BCVA of 8-10 ETDRS letters after 2 years with ranibizumab treatment combined with prompt or deferred laser, compared to a gain in mean BCVA of about 3 letters for the group with sham injections and laser treatment. Intravitreal triamcinolone with prompt laser treatment achieved an initial BCVA gain of 4 to 6 letters after the first month, but the BCVA became similar or worse than the subjects with sham injections and laser treatment after the first year, even after the exclusion of cases with significant cataracts.

The RESTORE extension study showed that monthly ranibizumab 0.5mg treatment alone (with sham laser) achieved the best mean BCVA gain of 7.9 letters after 2 years, compared to a BCVA gain of 6.7 letters at 2 years after monthly ranibizumab 0.5mg combined with laser treatment. The group with sham injections and laser treatment had a BCVA gain of 2.3 letters at 1 year, but they achieved a gain 5.4 letters at the end of the second year after they were allowed ranibizumab 0.5mg treatment from the 12th month onward.
In view of the current data, intravitreal ranibizumab has been approved in many countries for the treatment of visual impairment due to DME. However, due to the significantly higher cost of ranibizumab, and the fact that diabetic patients with DME typically have many other systemic co-morbidities which also require medical treatment, the off-label use of intravitreal bevacizumab treatment is also considered, although good quality studies on its use for DME is currently lacking. Other issues to consider include the risk of infective endophthalmitis due to compounding issues, as well as a potentially higher risk of adverse thromboembolic cerebrovascular and cardiovascular events due to greater systemic absorption.

A potential treatment algorithm for DME is as shown in Figure 1. If there is clinically significant macular edema (CSME) with no centre involvement, laser treatment can be administered according to ETDRS guidelines. If there is CSME with centre involvement but no vision loss, we can consider laser treatment first without ranibizumab. If there is CSME with centre involvement and vision loss, ranibizumab (or bevacizumab) monotherapy or combined with laser treatment may be considered. Patients should be counseled of the risks of intravitreal anti-VEGF treatment which included a 0.2% risk of endophthalmitis, 2-4% risk of retinal or intraocular injury, and a 1-2% risk of adverse cerebrovascular or cardiovascular thrombo-embolic events. Monthly injections appear to be ideal according to the studies, but the need for injections should be titrated according to the change in visual acuity as well as CRT based on optical coherent tomography scans. A trial of 3 injections to assess treatment response is useful, and dose doubling should be considered if there is poor response in view of the higher VEGF levels in DME compared to ARMD. Monthly treatment for 6 doses should be considered if it is financially feasible for the patients, in view of the potential constant steady gain in mean BCVA based on the studies. For patients who do not respond to treatment, other causes such as vitreo-macular traction should be excluded and treatment using another anti-VEGF agent or steroids can be considered.

So in summary, current data has shown that intravitreal ranibizumab is clearly beneficial in DME with superior visual acuity improvement compared to intravitreal steroids or laser treatment alone. Bevacizumab treatment appears to be similarly effective although further studies are needed. Lastly, the patient should be well counseled on the need for good systemic risk factors control.

Figure 1: Treatment algorithm for DME. (Eye(2012) 26, 485-493)
Evolving Paradigm of Managing Diabetic Retinopathy: A Case of Effective Intervention Model

Presented by Prof Wong Tien Yin on 6 June 2012 | Written by Dr Lim Hou Boon

In recent times, there is increased recognition that diabetic macular oedema (DME), and not proliferative diabetic retinopathy, is the major cause of vision loss in diabetic patients. As such, the goals of treatment of DME have changed, and the role of laser as a gold standard treatment is now questioned. With the advent of Anti-VEGF treatment and its superior results compared to laser, its use as a first line therapy is an area of interest. There is thus a need for better classification of DME, understanding of its sub-types, and their responses to treatment.

For 50 years, focal or grid laser has been considered the gold standard for the management of DME. However, it is lacking in 3 areas. First, while it is useful in stabilising vision, visual improvement is uncommon. Second, many patients still lose vision despite laser therapy. Third, laser therapy may not be possible or effective in many eyes with DME.

To date, a number of large scale randomised controlled trials has demonstrated the effectiveness of Anti-VEGF therapies for the treatment of DME. Between 2009 and 2012, results of 5 major randomised controlled trials on ranibizumab were published (The RESOLVE, RISE, RIDE, DRCRNet and RESTORE studies) while 1 was published on bevacizumab (BOLT Study).

Notably, these trials show that anti-VEGF therapy addresses 2 areas that laser therapy is lacking. Not only is the continued loss of vision halted, anti-VEGF therapy is effective in improving vision in patients with DME. However, some questions remain in the clinical implementation of the anti-VEGF therapy. For example:

- Is Ranibizumab or Bevacizumab better for treating DME? While there is tentative evidence supporting the use of bevacizumab, the quality of this evidence is on average lower and follow-up is shorter in those studies than those on ranibizumab. There are also currently no head-to-head randomised controlled trials between these 2 agents.

- What would be the role of laser if anti-VEGF becomes the first line of treatment? So far, no additional benefit has been shown with adding laser in studies on ranibizumab. In fact, 2 trials demonstrated that poorer outcomes when patients underwent laser therapy in addition to anti-VEGF injections. Similarly, the role of intra-vitreal steroids would also be called into question as it has been shown to be less effective than laser therapy in most DME patients.

- What kind of regime should be adopted in treating patients using anti-VEGF agents? Patient selection, initiation and frequency of injections, as well as the duration and continuity of treatment are parameters that have yet been established. Also, should visual acuity alone, or a combination of visual acuity and OCT findings, be used to guide therapy, is currently an unanswered question.

In summary, anti-VEGF therapy is a major advancement in the treatment of DME. There is currently a high level of evidence of ranibizumab’s effectiveness and safety, while less exists for bevacizumab. To implement the use of these agents clinically, there is a need to establish updated guidelines to assess and manage DME.

Macular Oedema: Underlying Mechanisms and Emerging Concepts of Management (Prof Albert Augustin)

Macular oedema is defined as the accumulation of fluid in outer plexiform layer and inner nuclear layer, as well as swelling of the muller cells, leading to retinal thickening. It is a non-specific sign that complicates the course of many ocular diseases and can be considered chronic when it persists for more than 6 months.

Many disease processes can cause macular oedema, including diabetes mellitus, retinal vein occlusion, inflammatory eye diseases, intraocular tumours, vitreo-retinal tractional disorder, as well as hereditary vitreo-retinal diseases.
Pathophysiology

The macular area in particular has a predisposition to the development of oedema due to its unique anatomy. It has a high concentration of cells, high metabolic activity, and the outer plexiform layer (Henle’s fiber layer) courses laterally away from the central fovea, creating a potential reservoir for the accumulation of extravascular fluid due to its thickness and laxity. Also, the central avascular zone creates a watershed arrangement between the choroidal and retinal circulations, thus decreasing resorption of extracellular fluid.

Nonetheless, different factors, interacting with one another, prevent the accumulation of extracellular intraretinal fluid. By keeping the rate of capillary filtration equivalent to the rate of fluid removal from the extracellular retinal tissue space, a balance across the blood retinal barrier (BRB) is maintained. However, this physiological status is only possible when tight junctions forming the BRB, both on the endothelium of retinal capillaries, as well as those on the retinal pigment epithelium, are functioning. A breakdown of these can lead to the development of oedema.

“Pathobiochemistry”

Numerous Inflammatory mediators have been found to be involved in the development of macula oedema. These include angiotensin II, vascular endothelial growth factor, prostaglandins, other cytokines and chemokines, matrix metalloproteinases, interleukines, etc. Amongst these, the three major players, and thus therapeutic targets, are:

- Angiotensin II. It increases vascular permeability, promotes leukocyte infiltration and causes tissue remodelling. These lead to inflammation and endothelial dysfunction, resulting in tissue oedema.

- Vascular Endothelial Growth Factor (VEGF). VEGF causes inflammation in the retina, leading to macular oedema. Inflammation of the retina can cause more release of VEGF, resulting in a vicious cycle.

- Prostaglandins E1. This causes breakdown of blood retina barrier via opening of the tight junctions, leading to development of macula oedema.

What can be done to counter the processes that lead to macular oedema? While laser photocoagulation and vitrectomy are currently used to reduce or reverse the pathological movement of fluid, addressing the “pathobiochemistry” is emerging as the new approach to therapy. Specifically, intra-vitreal steroids or anti-VEGF agents, or a combination of these, may be the ideal therapeutic strategy. However, while the literature has demonstrated the effectiveness of these agents, it has also been shown that their effects are not persistent. There is thus an impetus to look into slow release intravitreal devices like the Ozurdex.
Corneal Endothelial Diseases and CHED

Endothelial diseases have a Mendelian inheritance pattern, albeit some with a complex genetic basis such as Fuchs Endothelial Corneal Dystrophy (FECD). Examples include: Congenital Hereditary Endothelial Dystrophy (CHED) – Type 1 (autosomal dominant, AD) or Type 2 (autosomal recessive, AR); Posterior Polymorphous Corneal Dystrophy (PPCD) and X-linked Endothelial Dystrophy.

Identification of the CHED2 Gene, SLC4A11

Both CHED1 and CHED2 map to chromosome 20 at two distinct loci. The locus for CHED2 lies on the short arm of chromosome 20 (20p13) flanked by the markers D20S113 and D20S882, which corresponds to a gene dense ~3.5Mb of genomic sequence. SLC4A11 was found to be down regulated in the cornea of FECD patients.

Role of SLC4A11 in the Cornea

SLC4A11 gene encodes BTR1 (Bicarbonate transporter related protein-1), which is a 891 amino acid novel member of the SLC4 bicarbonate transporter family. SLC4A11 belongs to the SLC4 family of bicarbonate transporters. All 10 SLC4 members are integral membrane proteins. BTR1 mutants are retained in cytoplasmic locations including the endoplasmic reticulum, while WT BTR1 targets mostly to the plasma membrane. Corneal disease is caused due to the functional loss of SLC4A11/BTR1. Loss of endothelial cells may arise from cell death resulting from the stress induced by endoplasmic reticulum-retention of SLC4A11 mutant proteins. Fluid accumulation in the human cornea, resulting from loss of SLC4a11 water movement function, may itself trigger endothelial cell death since mechanical stress is reported to trigger apoptosis in cells.

SLC4A11 and Fuch’s Dystrophy

FECD is caused through insufficient SLC4A11 protein levels at the cell surface. Gradual accumulation of the aberrant mis-folded protein may also play a role in FECD pathology. Reduced levels of SLC4A11 influence the long-term viability of corneal endothelial cells. Two studies demonstrated: approximately 5% (4.7%, 95% CI=0.98% to 13.1%) of common late onset FECD in the Chinese can be attributed to SLC4A11 mutations; while another study in Caucasian FECD subjects also found heterozygous loss-of-function mutations in SLC4A11 to be modest contributors (2-4%) to the pathogenesis of adult FECD.

Development and Characterization of a Mouse Model

The SLC4A11 null mice recapitulate the human phenotype to a large extent. The SLC4A11 null mice did not exhibit the loss of endothelial cells seen in human CHED. The rodent corneal endothelium has the capacity to regenerate itself upon injury, unlike the human counterpart. Thus, cell loss due to lack of SLC4A11 may be compensated by new proliferating cells may explain the milder corneal phenotype. The mouse model will be used to confirm water transport function of SLC4A11 and useful in studying the role of gene replacement therapy.

Conclusion and Future

FECD and CHED are allelic variants of the same disease continuum. Identification of additional genes for any endothelial corneal dystrophy, such as the SLC4A11, has the potential to inform the genetic architecture of other allied clinical phenotypes. The overlapping genetic continuums suggest potential for sharing of therapies, which may be beneficial across the disorder spectrum.
Corneal dystrophies are inherited disorders characterized by progressive accumulation of deposits in the cornea causing visual impairment. Transforming Growth Factor induced protein (TGFBIp) is a 68 kD (683 amino acid residues) ubiquitously expressed extracellular protein. It is induced in most cell types in response to transforming growth factor (TGFb) stimulation. Mutation in a single gene results in several different phenotypes, which may be inherited in an autosomal dominant manner.

TGFBIp is present in actively growing zones in organs such as skin, bone, kidney and cornea. They binds with ECM proteins-collagens, fibronectin and proteoglycans to mediate cell adhesion and/or migration through integrins family. Other inflammatory diseases such as rheumatoid arthritis shows upregulation of TGFBIp. In TGFBIp corneal dystrophies, cornea deposits of amyloid are found which are insoluble fibrous protein aggregates.

Current treatment strategies for TGFBIp corneal dystrophies include corneal transplantation, surface ablation, electrolysis, photodynamic laser therapy, anti-TGFBIp therapy and even gene therapy. Newer developments include TGFBIp proteomics therapy.
ANSWERS TO PHOTOQUIZ 21

Q1: What signs are seen?
A: • Peripheral anterior synechiae, iris atrophy, corectopia

Q2: What are possible diagnoses?
A: • Anterior segment dysgenesis
• Iridocorneal endothelial syndrome

Q3: This condition occurred unilaterally in a middle-aged gentleman. What is the most likely diagnosis?
A: • Iridocorneal endothelial syndrome

Q4: What is the underlying pathology? What are the clinical variations seen?
A: • It is a spectrum of disorders characterized by an abnormal corneal endothelium, where a membrane grows progressively from the corneal endothelium across the angle onto the iris surface, causing formation of PAS and other iris abnormalities.

• The three clinical variations described include Iris nevus (Cogan-Reese) syndrome, Chandler’s syndrome, and Essential iris atrophy.

Q5: What problems may arise from this condition?
A: • Secondary glaucoma
• Corneal decompensation
PHOTOQUIZ 22

Q1: What is the likely diagnosis?
Q2: How would you manage the patient?
Q3: How would you reconstruct the defect, assuming that the defect measures 40% of the lower eyelid after excision?
Q4: What are some of the predisposing risk factor for this condition?
Q5: What are the typical pathological findings?

Please send your entries to: cmenewsletter@snec.com.sg or fax to: (65) 6226 3395 Attention: CME Newsletter Secretariat. Winners will each receive a 4GB thumbdrive and will be notified by post. The answers will be published in the next issue.