

# APVRS SHOW DAILY

The Official Conference News of APVRS 2019

by **pie** magazine  
posterior segment • innovation • enlightenment

## Highlights

- 6** Experts shared **pearls of wisdom** on how to **prevent** and manage 'mystery cases' of **macular surgery**.
- 9** World-renowned speakers weighed in on **advances in gene therapy** for retinal diseases.
- 12** Experts continue to find the balance between the latest in **diagnosis** and **treatment** of **retinal diseases** for the best patient outcomes.



## Scientific Advances to Bring Dramatic Change

by John Butcher

**A**dvances in medical science will have a major impact on ophthalmology in the coming years, doctors at Shanghai's APVRS conference said yesterday.

Research into genetics, artificial intelligence and other areas will lead to greater efficiency, personalized medicine and better diagnoses, Lijia Chen, winner of the Constable Award and Suber Huang, winner of the International Award, told delegates.

Assoc. Prof. Chen, from the Chinese University of Hong Kong, talked about age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV), which are leading causes of irreversible blindness among the elderly in developed countries.

Both AMD and PCV are complex diseases involving multiple genetic and environmental risk factors, he told delegates, for which a number of susceptible genes have been identified.

Many of those genes are shared between the two conditions, according to Assoc. Prof. Chen, but some, such as the HTRA1 gene, show

a significant difference between them. Other genes demonstrate strong ethnic diversities, he added, including the CFH gene variants.

Assoc. Prof. Chen's work has focused on the neovascular AMD and PCV genetics of Chinese people. That has included adopting different genetic strategies to discover new genes and variants for neovascular AMD and PCV, including a genome-wide association study, an exome-wide association study and pathway-based candidate gene association analyses.

It has also encompassed biological studies of the genes identified, such as HTRA1 and PGF, to investigate their functional roles.

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## Photo of the Day



APVRS President Prof. Dennis S C Lam (center) transfers the presidency to incoming APVRS President Prof. Chi-Chun Lai (right), as Prof. Lam's son looks on.



Published by:

MEDIA  
**MICE**

**Matt Young**

CEO & Publisher

**Robert Anderson**

Media Director

**Hannah Nguyen**

Production & Circulation Manager

**Gloria D. Gamat**

Chief Editor

**Brooke Herron**

Associate Editor

**Ruchi Mahajan Ranga**

Project Manager

**Travis Plage**

Director of Finance

**Alex Young**

Publications & Digital Manager

Graphic Designers

**Winson Chua**

**Edison Tan**

Writers

**Hazlin Hassan**

**Joanna Lee**

**John Butcher**

**Khor Hui Min**

**Tan Sher Lynn**

**Media MICE Pte. Ltd.**

6001 Beach Road, #19-06

Golden Mile Tower,

Singapore 199589

Tel: +65 8186 7677

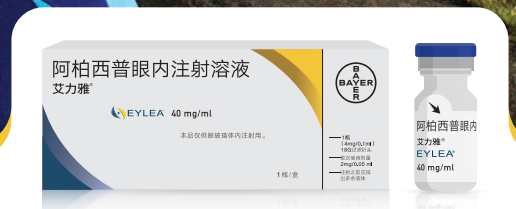
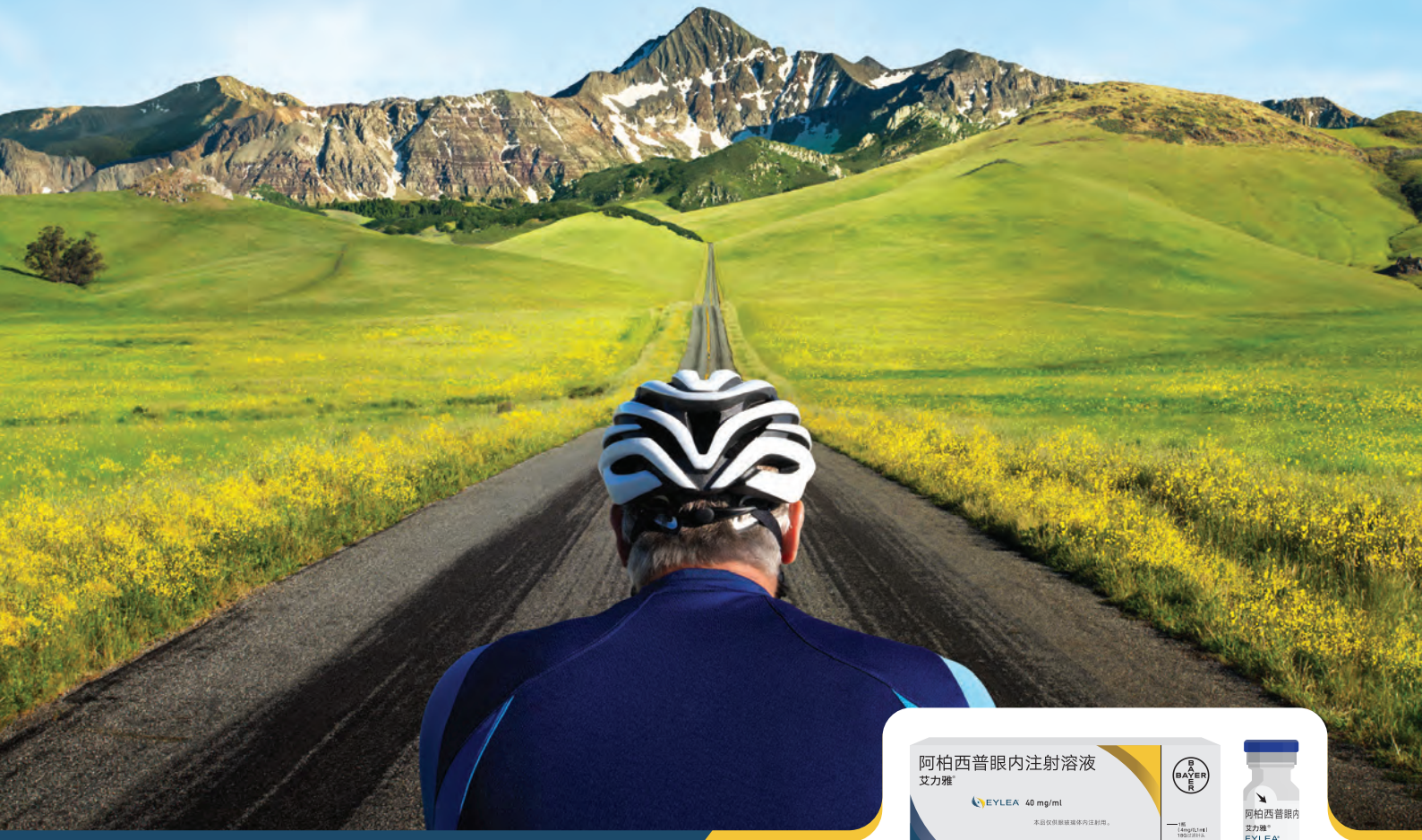
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## Briefing Instructions

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A/ Prof. Lijia Chen

Over the past few years, Assoc. Prof. Chen and his collaborators in the studies have identified a number of novel genes for AMD and PCV, including HTRA1, FGD6, PGF, ANGPT2, TIE2 and ABCG1.

They plan to continue their efforts to identify new genes for AMD and PCV, using new technology such as whole-genome sequencing, said Assoc. Prof. Chen. Transnational studies will also be conducted to investigate the role of the genes in modifying clinical manifestations and therapeutic responses.

Genetic and genomic investigations will lay an important foundation for personalized and precision medicine in the management of AMD and PCV in the future, he told the audience.

“Our journey will continue,” he added, with genome sequencing identifying new genes that could be used in research and studies of gene-gene interaction providing a better understanding of the role genes play in disease.

“Our eventual aim is to achieve personalized precision medicine,” said Assoc. Prof. Chen.

Suber Huang, CEO of the Retina Center of Ohio, began by expressing his emotions at receiving his award in the city where his father was born, before moving on to talk about new challenges facing the treatment of ocular diseases.

He outlined five “critical trends” in the industry’s direction, including genetic determinants to ocular health, how to use the body’s own immune system, regenerative medicine, artificial intelligence and collaboration between experts in their field.

Great advances are being made in identifying genetic determinants to health and developing gene therapy, he said.

He played a video of a young girl who had undergone gene therapy to demonstrate its possibilities. In the first part, before therapy, she was shown having trouble finding her way around a small maze laid out on the floor of a laboratory. In the second part, post

therapy, she easily navigated the maze in what showed an ‘absolutely stunning result’ of the treatment, said Dr. Huang.

Gene therapy is progressing rapidly for a range of eye disease, he told delegates, with the hope to be able to move away from managing conditions to permanently curing them.

“The concept of boosting the body’s own immune system to fight disease is also growing,” he said, adding that scientists are also looking at the potential role of auto-antibodies being used to sensitize target cells for immune repair.

Regenerative medicine is another area of potential breakthroughs, and one the human body already understands having done it at birth. “The question that could perhaps hold it back though is, whether we are ‘ready to play God,’” he added.

He also addressed the burgeoning use of artificial intelligence (AI) by the ophthalmology industry, which has progressed from pure AI, to machine learning, to today’s deep learning technology, which can learn independently of human beings.

Resisting its arrival is futile, he told the audience, before suggesting this could be seen as a ‘golden age’ for ophthalmology.

“This could be the savior of health care,” he said, bringing with it incredible levels of cost savings and efficiency.

Finally, he spoke about the need for collaboration, which he said was already widespread within ophthalmology.

He referred to the Retina Image Bank project, where clinicians upload images of eyes, plus information on them, to a globally-accessible database.

The site receives 31,000 page views per month from 181 countries across the world and is the “largest open access comprehensive website of its kind”.

“We need to share our findings so that we can all benefit,” he said, before quoting an ancient Chinese saying: “If you want to go fast, go alone, if you want to go far, go together.” ☺



Dr. Suber Huang



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# Experts Discuss Individualized, Patient-Centric Treatment Regimens for AMD

by John Butcher



Clinicians focused on the treatment of age related macular degeneration (AMD), one of the leading causes of vision loss for people over 50, during the Bayer Lunch Symposium at the 13th Asia-Pacific Vitreo-retina Society Congress (APVRS 2019) in Shanghai, China, yesterday.

During the symposium, the presenters reviewed treatment options, in particular the use of proactive treat and extend (T&E) dosing regimens with EYLEA (Aflibercept, Leverkusen, Germany) in patients with AMD.

Under a T&E regimen, following a set number of initial doses, clinicians adjust the treatment schedule to the individual needs of each patient. This involves gradually extending or shortening the injection dosing interval by 2 or 4 weeks, based on the patient's disease activity.

The symposium began with Dr. Lee-Jen Chen, of MacKay Memorial Hospital in Taiwan, who spoke about the evolution of treatment for neovascular AMD.

Dr. Chen talked the audience through how he decides whether or not, and by how much, to adjust the treatment schedule and length. A variety of treatment regimens are used in clinical practice, he said, including fixed dosing, pro re nata (PRN) and T&E.

Fixed dosing involves providing regular injections at planned intervals that are not dependent on visual acuity

(VA) or anatomic outcomes. Under a PRN regimen the clinician monitors the patient and treats according to VA and anatomic criteria. T&E involves injecting at scheduled visits and adjusting the treatment intervals according to VA and anatomic response.

The first choice of treatment for patients suffering from wet-AMD with active choroidal neovascularization (CNV) varies widely between countries, he told delegates. In the United States, the majority (66.2%) of patients are given T&E, compared to just 30.4% in Europe, where PRN is more popular (40.6%) and 36.5% in the Asia-Pacific region.

T&E is a 'concept', said Dr. Chen, with each patient subject to very individual and active treatment.

The treatment approach has been shown to be effective in a number of studies, including the ALTAIR study, which was used as the basis for its approval as a dosing regimen for aflibercept across Europe.

The ARIES study meanwhile saw a proactive T&E regimen with aflibercept leading to strong visual acuity gains with the distribution of injection intervals comparable to that seen in previous studies.

Prof. Tien Yin Wong, chair and medical director at the Singapore National Eye Centre (SNEC), focused on



Dr. Xun Xu



Dr. Lee Jen Chen

the treatment of polypoidal choroidal vasculopathy (PCV).

Understanding of PCV has increased significantly over the years, he told delegates, as it was initially thought to affect mainly African Americans, but it is now known to also be prevalent among Asian populations.

"It is also now understood to be a variant of AMD, which has been an important development in terms of how it is treated," he said. "As a sub-type of AMD, T&E has proved an effective method for tackling the disease," he added.

The latest treatment algorithm for PCV involves first diagnosing it using multi-modality imaging with indocyanine green angiography (ICGA), according to Prof. Wong.

That should be followed by initial loading with three-monthly anti-VEGF injections, he added, and then assessment for VA and optical coherence tomography (OCT) for fluid and polyp activity.

The final stage of recommended treatment is to use anti-VEGF monotherapy followed by T&E, if there is loss, no change or insufficient VA gains or active polyps, to add rescue photodynamic therapy (PDT). ☺

# APVRS

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### The 14th Asia-Pacific Vitreo-retina Society Congress



# When a BBG injection turned into a BB gun and other macular mysteries

by Hazlin Hassan

While vitreoretinal surgeons can probably perform most macula surgeries with their eyes closed, but on the rare occasion something goes wrong in the operating theater.

And sometimes, a mysterious case walks into the clinic and stumps the doctor, while certain questions are mired in perennial controversy.

Yesterday's session on *Mystery Cases of Macular Surgery* at the 13th Asia-Pacific Vitreo-retina Society Congress (APVRS 2019) discussed a few cases which initially stumped the experts, and shared pearls of wisdom on how to prevent and manage them.

Professor Taiji Sakamoto, MD, Kagoshima University, Japan, shared an interesting case of when an internal limiting membrane (ILM) stain injection inadvertently became a BB Gun.

In describing the incident, Professor Sakamoto said that after a vitrectomy was performed, the non-toxic Brilliant Blue G (BBG) stain was injected to the macula.

Although the surgeon felt some resistance, he pushed the inner syringe strongly. Suddenly, a crystal-like material was released and hit the retina very close to the macula.

"It was like a bullet being fired. After that, the surgeon was called 'BB Gun Man' by his colleagues," said Prof. Sakamoto.

The patient's vision deteriorated but returned to 20/20 one year after surgery. "We have to be very careful. If you inject something, don't do it to the macula. You have to inject not to the macula," he explained.

Associate Professor Andrew Chang, director, Sydney Retina Clinic, Head of Retinal Unit, Sydney Eye Hospital, talked about *Optic Disc Pit Maculopathy: Tips and Pitfalls*.

Optic disc pit is a rare congenital defect which appears as a circumscribed greyish depression in the lamina cribrosa.

A/Prof. Chang presented the case of a 35-year-old woman, who is a spy for the Australian Army, with a 2-month history of painless vision loss.

She was referred for a macula hole, and optical coherence tomography (OCT) showed she had an optic disc pit. Management options include observation, laser to the edge of the pit, laser and gas and vitrectomy and ILM peeling.



A/Prof. Andrew Chang

A three-port vitrectomy and ILM peeling were performed. Her vision started improving two weeks post-surgery but six weeks after surgery, she developed a full-thickness macular hole. A second surgery was performed. Six-days after surgery, her macula hole started to close, and six months following surgery, she has a "remarkably normal anatomy", described A/Prof. Chang.

Although there is a wide variety of treatments available with varying degrees of success, there is yet no clear consensus on the optimal management of optic disc pit-associated maculopathy.

"These conditions can be quite difficult to treat. Laser barricade alone is not effective," said A/Prof. Chang.

Treatment approaches for symptomatic maculopathy include combinations of laser barricade, vitrectomy, ILM peeling and gas tamponade.

In summary, he said that optic disc pit is often asymptomatic, and that surgeons should look for optic disc pit in cases of macular schisis in young patients.

Surgery is indicated for symptomatic and progressive maculopathy, while vitrectomy and ILM peeling should be done with care.

Surgeons should consider ILM sparing techniques to reduce the risk of developing macular holes, and preserve the foveal cones.

Kazuaki Kadonosono, MD, Department of Ophthalmology and Microtechnology, Yokohama City University Medical School, Japan, discussed the case of *Sudden Visual*

*Impairment in Young Female Patient with Normal Appearance of Macula.*

A 34-year old woman with visual impairment, but no abnormalities, turned out to have vitreous floaters.

Treatment options include observation, surgery including core vitrectomy with and without PVD, and YAG vitreolysis.

The benefits of vitrectomy include increased visual acuity, resolution of contrast sensitivity, but there is a risk of retinal detachment and endophthalmitis.

The patient underwent vitrectomy, and one week later, her visual acuity improved to 20/20 with a full resolution of her symptoms.

He said he suspected some possibility of other disease, but there was no evidence of this.

To conclude, Dr. Kadonosono said that vitreous floaters may be a cause of visual impairment, floaterectomy is effective in certain patients, and surgical treatment should be done only after careful consideration.

Dr. Manish Nagpal, vitreoretinal consultant from the Retina Foundation, India, spoke about a case of *Toxoplasma with Epiretinal Membrane*.

Toxoplasmosis, a disease caused by the protozoan *Toxoplasma gondii*, commonly involves the retina.

The disease has a higher impact in immunocompromised individuals and in congenital infection because of the severity of central nervous system involvement.

The 28-year-old male patient had presented with decreased vision for six months due to epiretinal membrane formation. Best corrected visual acuity (BCVA) for the left eye was 6/36.

He was treated with a standard anti-toxoplasmosis regime, which included clindamycin and steroids.

After vitrectomy with epiretinal membrane removal, the patient improved clinically but then developed some inflammation and cells after one month, when he complained of floaters.

"An anti-toxoplasmosis regime and steroids was started, and eventually he recovered," shared Dr. Nagpal. 🌐



# *Uveitis Pearls* for Diagnosis

by Tan Sher Lynn

Uveitis is a heterogeneous group of ocular inflammatory conditions presents in all age groups. The condition is often seen in patients with no family history or who are otherwise healthy, and can be challenging to treat for comprehensive ophthalmologists, as well as retina and uveitis specialists.

A/Prof. Lyndell Lim in her presentation entitled *Investigations in Uveitis* at the 13<sup>th</sup> Asia-Pacific Vitreo-retina Society Congress (APVRS 2019) in Shanghai, China, emphasizes that investigation helps in making a diagnosis and determining the best treatment, while increasing the understanding of disease pathogenesis.

She shared that a 18-year-old male patient came to see her with a 12-month history of bilateral acute anterior uveitis (AAU). He had always responded well to Prednisolone Forte and was having the sudden onset blurred vision OU after tapering of drops. It was associated with worsening anterior uveitis (2+) AC cell and his previous doctor told him that "it was probably cystoid macular edema (CME) secondary to his anterior uveitis and will get better once you are prescribed some steroid tablets".

"After investigating further, it turns out that was not that case. He actually had occlusive retinal vasculitis for the past 12 months. He was put on high doses of prednisolone, Avastin, Scatter laser, steroid sparing agent, he was switched to Adalimumab after prednisolone was

successfully tapered and ceased. It is important to remember that it is not anterior uveitis until posterior uveitis has been completely ruled out, with a fully dilated posterior segment and indirect ophthalmoscopic examination. If his initial ophthalmologist had dilated the eye, he would have found the actual condition earlier.

"So, remember that the most important investigation in the workup of uveitis is a thorough history and examination. Look at the pattern of uveitis, and look at the patient – there is more to the patient than just their eyes!" A/Prof. Lim stressed.

Meanwhile, Dr. Thanapong Somkijrungrroj shared tips for diagnosis in suspected viral/infections uveitis. According to him, uveitis is not a single disease, but a group of diseases that share the common characteristic of intraocular inflammation. Hence, clinical evaluation and differential diagnosis are important to determine the severity and urgency of disease. Local infection tends to be unilateral (e.g. viral associated anterior uveitis and toxoplasmosis) while systemic infection can be bilateral (e.g. cytomegalovirus retinitis [CMVR] and acute retinal necrosis).

"Iris atrophy/nodule can also be revealing. And we need to check on intraocular pressure (IOP). Acute uveitis usually presents with low IOP due to ciliary inflammation. Other important things is to do are a dilated eye exam and looking at the vitreous haze. Imaging and laboratory workup are essential. It is important that infections are ruled out before systemic steroids. And if you have any doubts, always treat it as infection," he said.

Dr. Quan Dong Nguyen, in *Management of Posterior Uveitis: What Can Imaging Tell Us?* highlighted that optical coherence tomography (OCT) helps to

monitor changes of lesions precisely, while OCT angiography (OCTA) in PIC is extremely useful in detecting idiopathic choroidal neovascularization (i-CNV). The healing of the lesions is accompanied by a reduction in the choriocapillaris flow deficit area. OCTA shows flow deficits in acute posterior multifocal placoid pigment epitheliopathy (APMPPE) – predominantly in choriocapillaries.

He noted that the role of fluorescein angiography (FA), UCG and OCT remain critical in selected cases. And lesions in wide-field imaging (FA and FP) are not visible on ophthalmoscopy, as lesions less than 0.1mm<sup>2</sup> tend to resolve with minimal flow voids. "OCTA allows better understanding of CNV lesions in posterior uveitis and evaluation of the morphology and natural course of these lesions," he concluded.

Dr. Diana Do, in her presentation entitled *Diagnostic Vitrectomy and Retinal Biopsy*, said that surgery plays an important role in the management of uveitis. Surgery may be indicated in selected cases of uveitis as it is helpful in diagnostic dilemmas. Surgery and vitrectomy may be required when there is media opacity, structural complications such as retinal detachment, endophthalmitis or sustained intravitreal drug delivery.

"Diagnostic vitrectomy or retinal biopsy will be needed when there are diagnostic dilemmas, such as uveitis of unknown etiology, inadequate response of empiric therapy and inflammatory response localized to the retina – doing so allows for the retrieval of affected tissue for proper diagnosis and treatment," she said. Nevertheless, she noted that the procedure has its cons, as it is invasive and carries a risk of adverse events such as cataract progression, hemorrhage and retinal detachment. 🌐



# What's New in Medical Retina?

by Joanna Lee

The field of medical retina is witnessing rapid changes – discoveries in terms of conditions, diagnoses and modes of drugs and treatments along with the emerging presence of AI in the mix of development.

For an update on nAMD (neovascular age-related macular degeneration) masqueraders, Dr. Timothy Lai from Chinese University of Hong Kong, showed that there the various causes of CNV which could also masquerade as nAMD. Other than choroidal neovascularization (CNV) caused by nAMD, many other ophthalmic conditions can also cause CNV: pathologic myopia, central serous chorioretinopathy, angioid streaks, pachychoroid eye diseases, uveitis, or it could even be idiopathic.

Myopic CNV is the most common cause of CNV in patients under the age of 50 years. These are mainly type 2 CNV, i.e. above the RPE layer.

He also brought up various studies that demonstrated that intravitreal injection anti-VEGF agents, including ranibizumab, aflibercept and conbercept, are effective for treating myopic CNV (phase 3 randomized controlled clinical trials including RADIANCE, BRILLIANCE, MYRROR and SHINY).

In the update on diabetic retinopathy (DR), Prof. Tien-Yin Wong from Singapore National Eye Centre (SNEC) discussed the seriousness of the global epidemic, which may affect up to 415 million people by 2030. He asserted a better focus and strategy for DR would be to shift from tertiary prevention (ocular treatment) towards primary prevention to control the disease systemically. This is because DR is a microvascular condition, so doctors should work with general physicians and endocrinologists (for instance).



Prof. Tien-Yin Wong



Prof. Wong also touched on secondary prevention via DR screening and new models of care. For DR screening, he showed how there was a 47% reduction in reports of diabetes-related blindness in Sweden after 5 years of implementing a screening program for all diabetic patients. There is a need for more national screening programs. Another mode of screening could be using artificial intelligence (AI) like Google, IDx, SELENA, Zhongshan, EyeART algorithms. He noted the need to develop guidelines and best practices in DR management, particularly in Asia.


Dr. Motohiro Kamei from Aichi Medical University (Japan) gave a fresh look at retinal vein occlusions (RVO). Getting into the heart of the collateral vessels, he discussed at length the pathophysiology of central RVO (CRVO), pointing that the conversion to ischemic in CRVO does not occur suddenly, but gradually in some cases. He also explained how dilated capillaries in BRVO represented vessel remodeling and that CV's might be called remodeled vessels in the future. "Trend analysis in OCTA might be useful to detect the conversion to ischemic type," he said as he demonstrated his analysis.

In the update on nAMD, Assoc. Prof. Adrian Koh expounded on the new therapeutic innovations for nAMD with results from the latest studies indicating their pharmacokinetics, efficacy and safety. In addition to faricimab (STAIRWAY study), abicipar pegol (CEDAR and SEQUOIA) and the ranibizumab port delivery system (RPDS, in the LADDER study), the latest anti-VEGF to be

approved is the brolucizumab, which could be used as q12 dosing in over 50% of treatment-naïve patients with superior efficacy over aflibercept in terms of fluid retention and disease activity control. "Exciting times are ahead for potential novel treatments for wet AMD," he said.

Renowned for his work in PCV, Prof. Won Ki Lee brought up features of the latest discovery of pachydrusen, a distinctive form of drusen that has been described in eyes with a thicker choroid. In particular, he pointed out its characteristics in focal atrophy.

Prof. Tomohiro Iida next shared about the pathophysiology and treatment of central serous chorioretinopathy (CSC), and discussed highlights from a published paper, "Central Serous Chorioretinopathy: Towards an evidence-based treatment guideline". For treatment, he said there has been good evidence for the efficacy of eplerenone for BCVA improvement, citing the VICI and SPECTRA trials. However, its side effects of cardiac arrhythmia and hyperkalemia should warrant closer monitoring of renal function and potassium levels in patients on this treatment. Overall, the potential for treatment would be seen more clearly with the results of the VICI and SPECTRA trials.

The last speaker, Dr. Shih-Jen Chen from National Yang Ming University, Taipei, Taiwan, shared that so far, there hasn't been any success for dry AMD therapies. He explained how functional tests for dry AMD should include rod sensitivity test besides looking at BCVA. Bringing in AI, he also showed how it could help in morphology based function prediction for nAMD. 



# Advances in Gene Therapy of Retinal Diseases

by Konstantin Yakimchuk and Brooke Herron

Ocular gene therapy has been successfully implemented for the treatment of retinal diseases, however, delivery of gene modifying reagents to the retinal cells still requires optimization. Intravitreal and subretinal routes are the most common methods of gene delivery into the retina.<sup>1</sup> Adeno-associated viruses (AAV) remain the most efficient vehicles for gene delivery into the retina due to high safety and stability of transgene expression.

## Clinical trials using AAV vectors

Several clinical trials have been launched to test AAV vectors in retinal pathologies. One clinical trial has been initiated by Spark Therapeutics and demonstrated efficacy of subretinal injections of AAV2-RPE65 viral vector in patients with Leber congenital amaurosis.<sup>2</sup> Other clinical trials using AAV-based gene delivery have been launched for achromatopsia<sup>3</sup>, RP40 characterized by PDE6B mutations and X-linked RP3 characterized by RPGR mutations.

With regard to choroideremia, which is caused by a mutation in the gene encoding Rab escort protein-1 (REP1), clinical trials have been implemented to apply an AAV vector. The results have shown an increase of visual acuity (VA) in several patients involved in the trials and improvement of dark-adapted microperimetry.<sup>4</sup>

In her presentation, Dr. Kanmin Xue discussed the subretinal delivery of an AAV vector for choroideremia, which she says is one of the more common retinal dystrophies: "It is one of the easier ones to diagnose, because of the particular appearance of the retina."

Dr. Xue explained that they used a two-step approach: 1) creating a foveal detachment by subretinal BSS injection; and 2) injecting AAV vector into the same bleb.

"The amount of vector you can inject is quite small," she explained. "Beyond that you can get excessive stretching of the retina which could be quite damaging."



Overall, she says gene therapy could maintain or improve VA in choroideremia, with gains sustained up to five years. "It has a good safety profile, but we need to monitor for rebound retinal inflammation around one month," she said.

Another recent clinical trial has investigated the efficacy of voretigene neparvovec-rzyl (VN) AAV vector for the treatment of RPE65 mutation-associated inherited retinal dystrophy.<sup>5</sup> Following the course of treatment with VN, the patients have demonstrated positive dynamics in light sensitivity and navigational ability. However, the production of AAV vectors is still very expensive, while the yield remains rather low.

## Non-viral gene delivery and future directions

Non-viral delivery methods have also been suggested for gene therapy of retinal diseases. In addition to AAV vectors, siRNAs and antisense oligonucleotides (AONs) demonstrate promising results in clinical trials. For instance, AONs have been applied to target mutant allele CEP290 IVS26, which induces Leber's congenital amaurosis.<sup>6</sup>

In his presentation, Dr. Elliot Sohn from the University of Iowa (USA) discussed AON therapy for CEP290-associated Leber's congenital amaurosis. He detailed results from a recent open-label, unmasked trial of 6 adults and 5 children who received 4 intravitreal injections over one year of seposfarsen (QR-110). Patients were monitored at least monthly.

"In terms of VA, there was clinically meaningful improvement, defined at 0.3

logMAR," he explained. "If you compare the mean VA to the contralateral eyes, there was significant improvement."

Looking toward the future, Dr. C. F. J. Boon from the Netherlands said: "The possibility and choice of (future) therapeutic intervention depends heavily on the phenotype, genotype, severity and stage of the disease."

"The value of novel therapies depends on their impact on outcomes that matter to patients in their daily life," he concluded. ☺



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# Innovation and Controversies in *Retina Surgery*

By Khor Hui Min



In the symposium on 'Innovation and Controversies in Retina Surgery', a variety of topics were presented by distinguished speakers from many countries. The session was chaired by Dr. Suber Huang, CEO of the Retina Center of Ohio; Dr. Hai Lu, Department of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing; and Dr. Doric Wong, head of the Vitreo-Retinal Department at Singapore National Eye Centre.

Dr. Daniela Bacherini from the University of Florence, Italy, presented on optical coherence tomography angiography (OCTA) and integrated microperimetry (MP) in macular surgery. According to Dr. Bacherini, predicting postoperative visual outcomes is difficult because of the large number of associated factors, such as the minimum diameter of the macular hole (MH), basal hole diameter, hole height, and ellipsoid zone defect length, which all have a negative correlation with postoperative visual acuity (VA). On the other hand, there are the hole form factor (HFF), MH index and tractional hole index, which have a positive correlation with postoperative VA.

"When we conduct an integrated evaluation with OCTA and MP, precise registration between OCTA and MP exams can be achieved, as both pieces of software can be managed by the same filing software. Absolute scotomas were observed corresponding to the MH. In addition, rings of relative scotomas extending in the perilesional areas were detected," said Dr. Bacherini.

According to a study by Dr. Manish Nagpal et. al., combining the findings of OCTA and MP using 'overlay' features can give us precise information of structure-function correlation at presentation and also in response to treatment. Moreover, it also helps to improve patient's compliance, confidence in treatment, and their understanding of the disease process as well.

For his part, Dr. Nagpal spoke about the usefulness of the retinal massager, a tool for massaging the edges of MHs and for ironing folds in proliferative vitreoretinopathy (PVR) cases.

In gene therapy, Dr. Suber Huang discussed using the RGX-314 for the treatment of neovascular age-related macular degeneration (nAMD).

"In the RGX-314 Phase I/IIa nAMD clinical trials, 42 patients with severe nAMD requiring frequent anti-VEGF injections were enrolled in five dose cohorts. The subretinal RGX-314 was well tolerated. Cohort 3 subjects continued to demonstrate good vision and anatomic outcomes over 1.5 years. In Cohort 4, there was a reduction in injection burden with stability to improve anatomic and visual outcomes. In Cohort 5, the highest clinical response was observed, with 75% of patients injection-free, with stability to improve anatomic and visual outcomes," elaborated Dr. Huang.

Next, Dr. Magno Ferreira from Brazil presented on reoperation for macular hole using amniotic membrane (hAM). "hAM seems to be well-tolerated without evidence of inflammation. In all cases observed, anatomical success

was obtained in all cases. Moreover, all patients improved their vision by at least four logMAR lines," said Dr. Ferreira.

The following speaker, Dr. Raymond Wong from the Centre for Eye Research Australia, Melbourne, presented on autologous retinal transplantation for persistent macular hole. He discussed a retrospective international multicenter study involving 41 patients in four centers located in the USA, Italy and Japan. Complete MH closure was achieved for 36 of the patients, with significant change in visual acuity – improvement in 15 eyes (36.6%), stable in 17 eyes (41.5%), but worsened in 9 eyes (21.9%).

Then Dr. Hai Lu from the Beijing Tongren Eye Center spoke on intraoperative optical coherence tomography (iOCT) for pediatric retina surgery. According to Dr. Lu, iOCT may be a valuable technique for pediatric retina. He emphasized that further innovations of compact and portable OCT for pediatric retina are needed.



Dr. Hua Yan from Tianjin Medical University General Hospital, China, presented on treatment of severe cases in open-eye injury with no light perception.

"It is important to complete panretinal photocoagulation (PRP) as soon as possible, to save money and time. Anti-VEGF and anti-inflammatory drugs could be injected at the same time. The chamber angle should remain open, to make it easy to control the IOP. It is also critical to maintain timely follow-up after operation," said Dr. Yan.

Lastly, Dr. Kenneth Fong from Sunway Medical Center, Malaysia, presented on 3D vitreoretinal surgery. According to Dr. Fong, it is good to be able to view and record high-definition 3D surgery, and it is particularly useful for teaching hospitals. However, it's expensive and not all surgeons can adapt to the 3D view.

All in all, it was a great session where researchers presented their latest findings and clinical trials, while delegates were quite interactive in asking questions. 🍷

# Managing PCV and DME Effectively with Aflibercept

by Hazlin Hassan



Dr. Neil Bressler



Dr. Youxin Chen

The use of proactive treat and extend (T&E) dosing regimens with aflibercept is an effective strategy for patients with polypoidal choroidal vasculopathy (PCV), as well as those with diabetic macular edema (DME), but who possess good visual acuity (VA), renowned experts told delegates at Bayer's Lunch Symposium yesterday at the 13th Asia-Pacific Vitreoretinal Society Congress (APVRS 2019) in Shanghai, China.

Polypoidal choroidal vasculopathy (PCV) is a common subtype of exudative age-related macular degeneration (AMD), and is a leading cause of blindness globally.

DME is responsible for most of the visual impairment that affects people with diabetes, and can occur at any stage of diabetic retinopathy (DR).

Professor Tien Yin Wong, medical director of the Singapore National Eye Centre (SNEC), said that his recommendations for treating PCV includes multimodal imaging with ICGA, 3 monthly loading doses of anti-VEGF injections, and an assessment of VA and OCT for fluid and polyp activity.

"If there is improvement, there is no fluid, you are doing well, continue monotherapy, with a T&E pattern like AMD," he shared.

"For those that don't do so well, consider rescue photodynamic therapy (PDT). But if we do not have PDT readily available, I think anti-VEGF monotherapy is really useful," he added.

He explained to the audience that the current understanding of PCV in

2019 is that it is a sub-type of AMD (type 1 CNV), it should be diagnosed using multimodal imaging and not ICGA alone, and it can be managed like AMD using anti-VEGF monotherapy.

The PLANET study, which evaluated intravitreal aflibercept injection (IAI) in participants with PCV and compared IAI monotherapy with IAI plus rescue photodynamic therapy (PDT), shows aflibercept monotherapy leads to favorable vision gains (10 ETDRS letters) similar to classic AMD trials and clinical experience over 2 years.

Dr. Neil Bressler, the James P. Gills Professor of Ophthalmology, Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine and Hospital, United States, spoke on Diabetic Macular Edema Management Guided by Baseline Visual Acuity.

Previously, anti-VEGF agents have not been evaluated in eyes with center-involved DME with good visual acuity of 20/25 or better.

He shared the results of a study where researchers compared three strategies for managing eyes with center-involved DME: aflibercept, laser photocoagulation and observation.

At 2 years, the percentage of eyes with at least a 5-letter VA decrease was similar in the aflibercept (16%), laser photocoagulation (17%) and observation groups (19%).

At 2 years, the percentage of eyes with at least a 10-letter VA decrease was also similar in the aflibercept (9%), laser (7%) and observation groups (7%).



This study demonstrates that patients with center-involved DME and good vision ( $VA \geq 20/25$ ) can be closely monitored without treatment until their vision declines, without compromising their long-term visual acuity outcomes.

For those 20/50 or worse VA, consider aflibercept. "If aflibercept is superior to ranibizumab at one year, but not at two years, why still consider aflibercept instead of ranibizumab? Because aflibercept group outcomes are superior to ranibizumab over a period of 2 years when baseline VA is 20/50 or worse," said Dr. Bressler.

He added that the objective of DRCR. net anti-VEGF treatment regimen for DME is to try to maximize VA improvement while minimizing the number of injections, as well as the number of visits.

The three principles of the DRCR. net anti-VEGF regimen are: Six monthly injections unless visual acuity is 20/20 and OCT is 'normal'.

Thereafter, anti-VEGF is to be continued only if the OCT of the central subfield thickness (CST) or VA improves or worsens compared with the last two injections. No injections are needed if the OCT of the CST is stable, and VA, whether flat or thickened. 🌐

# Diagnostic and Treatment Conundrums in Retinal Diseases

by Konstantin Yakimchuk and Brooke Herron



Unlocking mysterious retinal cases at APVRS 2019

There are two sides to every coin. And in retinal diseases, there are two aspects that matter most: **diagnosis and treatment**. Equipped with the latest advances in diagnosis and treatment of retinal diseases, experts continue to find the equilibrium between these two for the best patient outcomes.

## Diagnosis

Today, retinal optical imaging techniques include optical coherence tomography (OCT), scanning laser ophthalmoscopy (SLO), OCT angiography (OCTA), photoacoustic microscopy (PAM), adaptive optics (AO), fundus autofluorescence (FAF), and molecular imaging (MI).

Among these methods, OCT remains the most valuable non-invasive imaging technique to diagnose retinal diseases. Using spectral-domain OCT (SD-OCT), the development of deep learning methods allowed distinguishing the following subtypes of retinal diseases: age-related macular degeneration (AMD), choroidal neovascularization (CNV), diabetic macular edema (DME) and drusen.<sup>1</sup> Functional imaging of the retina with high contrast is usually performed by SLO.<sup>2</sup>

On the other hand, OCTA is highly applicable for the analysis of flow within the retinal microvasculature.<sup>3</sup> This method is commonly used to detect the features of diabetic retinopathy (DR), such as microaneurysms, neovascularization and other microvascular anomalies. In addition, OCTA has been effective in evaluating the therapeutic outcomes in intraocular tumors.<sup>4</sup>

The advanced imaging methods provide valuable input to the understanding of the pathophysiology of retinal disorders and become crucial for the early diagnosis of these pathologies.

## Treatment

Several effective therapeutic approaches with low side effects have recently been developed for treating posterior segment conditions. For example, patients with neovascular AMD (nAMD) are usually treated with anti-VEGF, which inhibits neovascularization, decreases edema, averts subretinal fibrosis and prevents vision deterioration. Anti-VEGF drugs, such as aflibercept, bevacizumab and ranibizumab, have been effectively used to treat AMD, DME and retinal vein occlusion (RVO). However, in contrast to prospective clinical studies, it is not always possible to pursue the flexible anti-VEGF treatment regimens in real situations.<sup>5</sup> Besides, optimizing the methods of anti-VEGF delivery to the macula remains an important challenge.<sup>6</sup>

Also, intravitreal administration of corticosteroids is often used to treat retinal vein occlusion. Dexamethasone implants significantly improved visual function and decreased central macular thickness.<sup>7</sup>

Alternatively, laser and photodynamic therapies (PDT) have shown high efficacy against neovascularization. Surgical methods with vitrectomy demonstrate promising results for the treatment of macular edema associated with RVO or DR.<sup>8</sup> Pars plana vitrectomy (PPV) might be the preferable surgical method for ME associated with vein occlusion. The progress in the development of successful treatment strategies requires the active collaboration between fundamental researchers and ophthalmologists and the development of the relevant models to evaluate the efficacy of novel therapeutic approaches.

## A balancing act

Given what's available today to retinal specialists in terms of diagnostic tools and treatment regimens, there is no one-size-fits-all combo in the real world. In their clinical practice, retinal specialists remain puzzled by challenging and rare cases encountered.

Here at the APVRS 2019 Congress, one session titled *Diagnostic and Treatment Conundrums in Retinal Diseases*, was dedicated to presentation of such cases, where experts discussed and exchanged clinical pearls to provide patients the best treatment management possible.

One such mystery case was presented by Dr. K. Bailey Freund, from Vitreous Retinal Macular Consultants of New York and a clinical professor of ophthalmology at the NYU School of Medicine. In this instance, the patient was a 70-year-old woman who was referred in 2010 for suspected nAMD in the left eye, with a history of autoimmune retinopathy, hypertension and hypercholesterolemia.

"I treated her with anti-VEGF, she did well with a T&E regimen in 2010. Then in 2012, there was a small subretinal hemorrhage in her right eye," said Dr. Freund. "I think in the left eye it [vision loss] could have been explained by chronic exudation, but we hadn't come up with the reason for the loss of vision in her right eye."

From here, he said the case got more complicated as there were aneurysms and polyps. Not wanting to treat continuously with anti-VEGF, Dr. Freund did one session of PDT in 2012. He continued that the patient said she had autoimmune retinopathy . . . but that's not what it looked like. "If you just saw the retina, it would suggest macular dystrophy," he noted.

It wasn't until they used whole exome sequencing that they realized the patient had a gene mutation. "For all her life, this patient has had a different retinal problem," said Dr. Freund. Eventually, the patient was diagnosed with cuticular drusen/nvAMD OU, aneurysmal type 1 NV (PCV) OU (secondary to the first diagnosis) . . . and finally autosomal dominant cone dystrophy (heterozygous missense variant in the GUCA1A gene).

Commenting on this mystery case, Prof. Paisan Ruamviboonsuk, from Rajavithi Hospital in Bangkok, Thailand, added: "Whenever you see PCV with a thin choroid, you've got to think of something else."

Furthermore, Dr. Kelvin Yi Chong Teo described a case of a 67-year-old male with a history of progressive vision loss in the right eye and type 2 diabetes mellitus who was referred to him after non-response to four anti-VEGF injections.

Dr. Teo ended up doing a panel blood test, which was sent to a hematologist – this resulted in a diagnosis of Waldenström Macroglobulinemia.

Another case, presented by Dr. Seung-young Yu from Korea, detailed the case of a 42-year-old Asian cook with blurred vision in his left eye for one week; the patient was referred to Dr. Yu with the suspicion of central serous chorioretinopathy (CSC). Ocular examination on FAF showed a VA of 20/50 in his left eye with a large hyperfluorescent area, as well as changes in the outer segments. Eventually, the patient was diagnosed with ocular syphilis. Dr. Yu said that a “high degree of suspicion is crucial to diagnosis and that serologic testing should be sought even for cases of isolated anterior inflammation”. In this case, it was a rare ocular manifestation of acute syphilitic posterior placoid chorioretinopathy (ASPPC); in its clinical manifestation it appears as a presence of placoid,

yellowish, focal and deep retinal lesions.

She added that it’s important to note that its pathophysiology is both autoimmune and infectious.

The case presented by Dr. Usha Chakravarthy concerned a 21-year-old male healthy male who complained of blurred vision in his left eye for one week. The patient had no other illnesses or systemic comorbidities.

Under examination, an unexplained foveal cyst was found; the patient had no history of trauma and was not highly myopic. The patient received an intravitreal dexamethasone implant, and 40 days later the cyst resolved and the patient’s BCVA was 20/20.

“He was initially treated with Ozurdex implant . . . the patient was extremely uptight and his parents wanted something done immediately,” she explained. “But in a matter of two weeks, things began to improve. Whether giving the Ozurdex made the difference, I don’t know for sure.”

At 90 days, the patient’s BCVA was marginally reduced to 20/30. Dr. Chakravarthy then performed a post YAG vitreolysis and the BCVA returned to 20/20.

These interesting cases illustrate the necessity of the various imaging platforms for disease detection, as well as the different treatment options currently available. And with continued advancement in the field, in the future, these cases could be less mysterious . . . and more straightforward. 🌟

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**Presidential Dinner & Congress Party**



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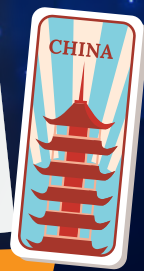
PROF. TIEN-YIN WONG PRESENTS BEST VIDEO AWARDS TO DRS. YI-TING HSIEH, SABIA HANDA, AND BHAVIK PANCHAL AT THE PRESIDENTIAL DINNER AND CONGRESS PARTY.



[FROM L-R] CONGRESS PRESIDENTS PROF. XUN XU, PROF. XIAOXIN LI, CONGRESS PRESIDENT OF THE 14TH APVRS 2020 HONG KONG PROF. DENNIS LAM, AND ORGANIZING COMMITTEE CHAIR A/PROF. MARTEN BRELEN



A/PROF. ANDREW CHANG PRESENTS BEST POSTER AWARDS TO DRS. SHYAN LI, LONGHAO KUANG AND ROGIE DAWKING AT THE PRESIDENTIAL DINNER AND CONGRESS PARTY.





Unfolding the Mystery Cases of by Tan Sher Lynn

# Non-Macular Retinal Surgery

The retina is the layer of nerve cells lining the back wall inside the eye, which sense light and sending signals to the brain. It is the place where vision is formed. Made up of intricate structures including the peripheral retina, fovea, photoreceptors, rods and cones, sometimes, it can be a place of mystery as well. In these instances ophthalmologists may need to act as detectives to solve these unique cases. Below, our 'ophthal-detectives' reveal their mystaries...

In his presentation entitled *Where was the IOFB*, Dr. Lawrence Lee shared about a 64-year-old male whose rifle exploded on him, causing traumatic hyphema (3mm). Shrapnel had entered his eyes as a lenticular intraocular foreign body (IOFB). The metallic subretinal IOFB was detected near the sclera via CT Scan. However, as Dr. Lee was performing the surgery, the IOFB did not appear as easily as he thought when he cut down on the sclera.

"Even though we can see the foreign body internally, we are still looking for it from the outside. It is actually much smaller than what we saw on the X-ray," he said. He uses two magnets as well as forceps, but they couldn't pick up the foreign body. During the procedure, the eye perforated and Dr. Lee thought that he had lost the foreign body and had to report this to the patient. He even thought that the foreign body might have fallen on the floor. Moments later, he spotted the tiny shrapnel which was still in the surgical field. After removing it, he sutured the wound and the patient's vision subsequently returned to normal.

"In cases like this, we can learn that IOFB are often magnified in CT scans,

so before removal, you should perform vitrectomy to prevent vitreous explosion and beware of exploding rifles!" he remarked.

Endophthalmitis is a purulent inflammation of the intraocular fluids (vitreous and aqueous) which usually occur due to infection. In *A Case of Endophthalmitis After Primary Repair of Globe Rupture*, Dr. Yoon Jeon Kim discussed the case of a 22-year-old male with ocular pain and visual loss.

The patient sustained ocular injury to the right eye while hammering a piece of brick at a construction site. The case was diagnosed as ruptured globe and referred for primary repair. At the time of the incident, he was not wearing safety glasses. On the other hand, he was wearing soft contact lenses (SCL) and the right SCL was missing after the incident. The patient was diagnosed to have full thickness corneal laceration at 3 o/c limbus (3 mm length) and iris defect (2 mm), with shallow anterior chamber and traumatic cataract.

One day after primary repair, his visual acuity (VA) is 'counting fingers' (CF) and 3 days later his VA is 'hand motion' (HM). It was found that the SCL entered into the vitreous cavity and remained there for 3 days. He also complained of halo and pupilloplasty was performed. Four months after vitrectomy, his best corrected visual acuity (BCVA) was 0.2 logMAR and intraocular pressure (IOP) OD was 14 mmHg. He had sympathetic ophthalmia (SO) removal and second intraocular lens (IOL) implantation.

Dr. Kim stressed that ophthalmologist should be aware that in eyes wearing SCL, the object causing

the open globe injury can cause the folding up and posting of the SCL into the vitreous through the wound. Hence, thorough evaluations should be performed before and after primary surgical repair. "Particularly in cases where contact lens foreign bodies are suspected, ultrasonography might be helpful," she said.

In her presentation *Surgery for PVR in a Boy with Familial Exudative Vitreoretinopathy*, Dr. Hiroko Terasaki mentioned that familial exudative vitreoretinopathy (FEVR) is a group of inherited diseases with abnormal retinal angiogenesis leading to incomplete vascularization of the peripheral retina, including exudation, retinal folds, retinal detachment, foveal displacement and retinal dysplasia.

She shared a case where a 12-year-old patient visited her hospital at age 1 with retinal folds. When the patient was referred to her hospital again at 12, the pupil was closed. Lens sparing 25G vitrectomy via Pars Plana (2mm) with membrane peeling was performed. After peeling away the membrane slowly, she finally found the retinal hole and covered it with perfluorocarbon before lasering. "The surgery was successful, although anatomical reconstruction is not easy; functional recovery is more difficult," she said.

From the cases above, we can conclude that having thorough investigations and a keen eye to see beyond the norm of a retinal procedure are necessary to obtain the best possible outcome. ☺

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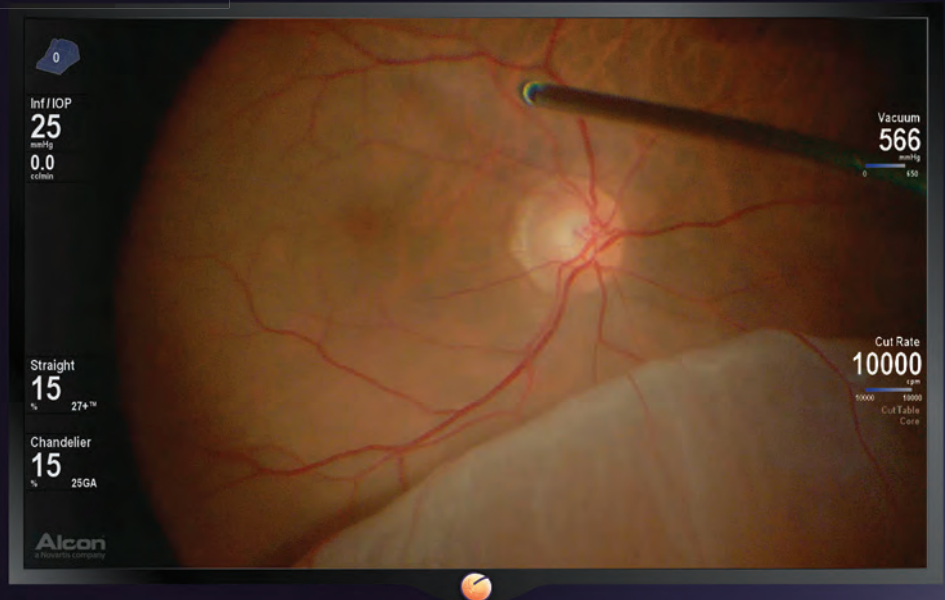
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