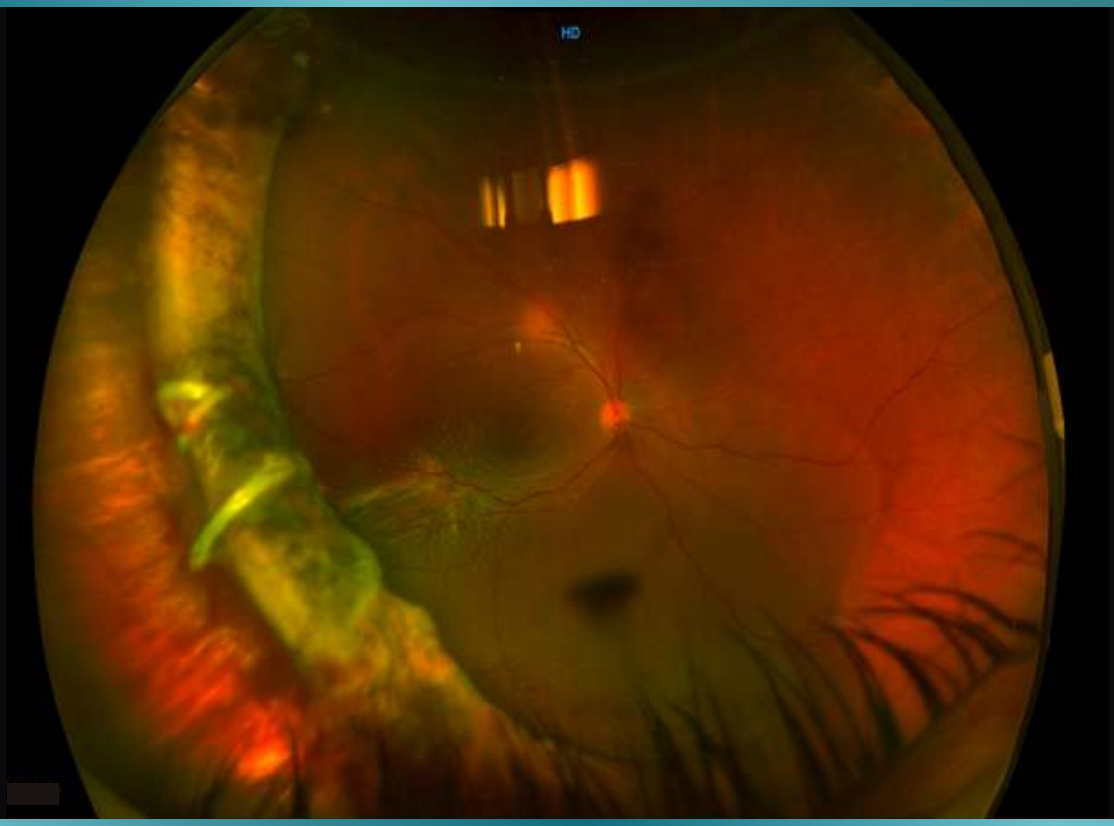
JUNE 2020

The Official Newsletter of the

VITREO RETINAL SOCIETY-INDIA



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1. CHRISTIAN PRÜNTE, NICOLE ETER Retina Today - March 2018

Contents

From the President's Desk

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Medical Director and Chief - Vitreo Retinal Services
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Dear Friends and Colleagues,

Trust I find you all in good health and robust spirits despite the challenges and change in work and lifestyles we face in COVID times. On the optimistic side I see these two months have given us each novel opportunity to pause from our demanding work schedules and rethink how to move ahead with our lives and careers. It has given us a chance to connect via webinars organised by VRSI. One on ocular imaging and one on Retina Practice in the COVID era.

Looking at experience from other countries which have had their brunt of Covid 19 and have moved forward to safer times, fortunately the same should be in store for our country with safer times ahead. Dr Anand Rajendran and Dr. Manisha Agarwal have in this newsletter presented a response based spotlight article on Retina practice in COVID times, with contributions from a panel . Hope you find it useful in your practice.

Wish you all a safe and heathy time ahead

Regards and best wishes
Dr. Shobhit Chawla
President
Vitreo-Retinal Society of India

From the Honorary Secretary's Desk

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Dear Friends

Warm greetings from VRSI. An excellent issue of VRSI Newsletter of June 2020 has been compiled by Dr. Anand Rajendran and his team. A special focus on modifications in retina practice during COVID has been compiled by him along with Dr. Manisha Agarwal. A copy of this panel discussion as well as VRSI guidelines published in IJO can be accessed at www.vrsi.in. I am sure that you will find the articles extremely valuable for your daily practice, and to provide the best care to your patients. I take this opportunity to request you all to submit your interesting cases, articles and innovations to the VRSI newsletter, which will help improve the scientific knowledge base of our members.

Abstract submissions for VRSI 2020 Annual Meeting at Nagpur, from Dec 3 to Dec 6, is open. I request you all to participate enthusiastically in the activities of VRSI. Stay safe from COVID, and follow all precautions with discipline. Together, we can win this war.

Regards
Dr. Raja Narayanan
Hon. Secretary
Vitreo-Retinal Society of India

From the Convenor, Scientific Committee's Desk

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Dear Friends and Colleagues

As we live through these uncertain and troubled times in this COVID era, I sincerely hope all of you are in good health and cheer. It has, nevertheless, been a pleasure bringing out the June edition of the VRSI Newsletter and I would like to thank all the contributors for making the extra effort, in this difficult phase, and providing us these fine articles.

In the current issue, we have Dr. Srinivas Sadda, a world renowned retina specialist from Doheny Eye Institute, Los Angeles, giving us an erudite account of "Advances in Widefield Retinal Imaging" in the'StalwartSpeak'section. The Spotlight article of the issue, anchored by Dr. Manisha Agarwal, is focused on the current rage – Retina Practice in these COVID times with an eminent panel of national experts holding forth on a slew of challenging situations. Dr. Rajani Battu, the worthy recipient of the prestigious JM Pahwa Best Paper Award 2019 has highlighted her award-winning work on de-novo generation of RPE cells from human induced pluripotent stem cells. The winner of the Best Poster of the Year 2019, Dr. Vivek Dave, summarises his work on a similar area - the safety of ex-vivo stem cell RPE cell cultures. In the Innovator's Isle section, Dr. Srikanth YN, describes his innovative smartphone based AI algorithm for DR screening. Finally, we have an interesting case report to round off the issue.

We look forward to contributions from all members to future issues. The Abstract Submitter for the VRSI 2020 Annual Conference, scheduled to be held at Nagpur from Dec 3-6 2020, is open. We hope to see the same enthusiastic response as we have last year and welcome your whole-hearted participation and involvement.

Dr. Anand Rajendran Convenor
Scientific Committee
Vitreo-Retina Society India

Guidelines - Manuscript Submission for VRSI Newsletter

Original articles:

These include randomized controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 words (excluding Abstract, references and Tables) should be divided into sections with the headings Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Case reports / Challenging case /Innovations / Instruments /Techniques :

New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported. They should be unique and providing learning point for the readers. Manuscripts with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and references) and should have the following headings: Abstract (unstructured), Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order.

The manuscript could be of up to 1000 words (excluding references and abstract) and could be supported with up to 10 references. Case Reports could be authored by up to four authors.

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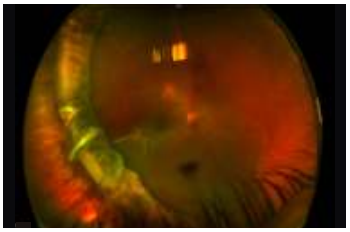

The Cover page Image - **" Subretinal Suture Migration "**
was contributed by
Dr. Raja Narayanan, LVPEI, Hyderabad

STALWART SPEAK

Advances in Widefield Retinal Imaging

Dr. Srinivas Sadda
President and CSO, Doheny Eye Institute
Stephen J. Ryan – Arnold and Mabel Beckman Endowed Chair
Professor of Ophthalmology
University of California – Los Angeles

Decades of landmark clinical trials have used retinal imaging to assess the progression of disease and to determine the impact of novel therapeutics. Most of these historic studies were limited to an assessment of posterior pole findings or a region corresponding to the field of view (roughly 70 degrees) of the reference 7 standard fields defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS). Many retinal diseases, however, have clinically important findings that extend well-beyond these fields. While they may be studied by ophthalmoscopy, the ability to efficiently image these peripheral findings would be expected to enhance our ability to evaluate these abnormalities accurately.

Technological advances over the last several decades have allowed a wider region of the retina to be studied with a single acquisition. Early devices and techniques such as the Staurenghi contact lens, PanoRet, and RetCam, were contact-based and of limited resolution, but highlighted the potential value of widefield imaging. The development of the non-contact Optomap (Optos) systems represented a significant breakthrough as they facilitated rapid acquisition of high-resolution images suitable for a busy clinical practice environment. Initial non-contact systems allowed only pseudocolor imaging but over time new iterations have progressively added new modalities (fluorescein and indocyanine angiography, autofluorescence, etc), including most recently, the ability to perform peripheral swept source optical coherence tomography (OCT). As the importance of widefield imaging in clinical practice became well-established, a number of additional devices with various capabilities (“true color”, “multicolor”, “retromode”, etc) have become available from other manufacturers. As the field of view of many ophthalmic imaging devices and technologies has expanded, the terms “widefield” and “ultrawidefield” have been variably used. To address this confusion and establish consistency in the literature, the International Widefield Imaging Study Group, proposed a nomenclaturebased on easy to identify anatomic landmarks such as the major vascular arcades and the vortex vein ampullae.[1]The term ultrawidefield (UWF) was to be reserved for only those images which demonstrated retinal anatomic features anterior to the vortex vein ampullae in all 4 quadrants, whereas images extending only beyond the arcades but ending posterior to the ampullae were termed widefield.

Regardless of terminology, it has become apparent, that widefield imaging has become an integral component of retinal clinical practice and clinical research, and has led to a number of new insights into the pathophysiology of retinal disease. One significant discovery is the recognition of new phenotypes of diabetic retinopathy (DR). Using UWF fluorescein angiography (FA), Wessel and colleagues[2] demonstrated that while some patients with DR manifest extensive posterior polar disease with relative sparing of the peripheral retina, others showed significant peripheral non-perfusion and neovascularization (NV) with relatively mild posterior disease. Silva, Aiello, and colleagues, observed that in many eyes, consideration of peripheral lesions (beyond the 7 standard ETDRS fields) led to a more severe assessment of the retinopathy level.[3]Importantly, diabetic eyes which had predominantly peripheral lesions (PPL) seemed to be at a substantially higher risk for progression to proliferative disease,[4] an observation that is currently being evaluated in DRCRnet Protocol AA. This is a potentially critical finding as our current DR staging systems are based exclusively on disease evident in the 7 standard fields. Notably, in an evaluation of over 700 Indian subjects with DR, the Indian Retinal Research Associates demonstrated that one third of

individuals had PPL.[5] Based on these stuides, UWF imaging is evolving to become the gold standard for DR diagnosis and classification.

Another concept of interest and potential controversy, is the use of UWF FA to identify regions of peripheral non-perfusion which can be selectively targeted with scatter laser photocoagulation. While such a targeted and less-destructive approach appears to be potentially effective for the treatment of proliferative DR (PDR),[6] it does not appear to be of value for diabetic macular edema (DME).[7] How to best use laser in the era of anti-VEGF therapy and UWF imaging remains a topic of interest, and we can expect that future studies will provide additional guidance on this subject.

Major clinical applications of widefield retinal imaging extend well-beyond diabetic retinopathy to a wide range of retinal diseases including other retinal vascular diseases (e.g. retinal vein occlusions), inflammatory and infectious disorders, inherited retinal degenerations, and neoplastic diseases to name only a few. Describing the application of UWF imaging for evaluation of the peripheral retina in all of these conditions is beyond the scope of this article, but we have described these in detail in a recent review.[8]

Perhaps one surprising potential application of UWF is the assessment of age-related macular degeneration (AMD). Although, the name AMD would appear to suggest that only the macula is involved, it has become increasingly clear that AMD may actually be a panretinal disease. A number of studies including the OPERA substudyof AREDS2,[9] have highlighted the frequency of peripheral drusen and retinal pigment epithelial alterations in AMD patients. Atrophic lesions may also be observed in the periphery in these individuals. Studies are in progress to determine if the presence of peripheral abnormalities may portend a worse prognosis.

In terms of how I use widefield imaging in my own clinical practice, my utilization goes beyond specific disease applications. Much as OCT has become an adjunct to slit-lampbiomicroscopy, UWF imaging has become an adjunct to ophthalmoscopy. Virtually all new patients to my clinic receive a UWF pseudocolor and autofluorescence image upon their initial visit. Not only is this an excellent tool to document the clinical findings (in accordance with the adage “a picture is worth a thousand words”), subtle abnormalities (particularly on autofluorescence imaging) are often revealed, which may be difficult to discern in a rapid clinical exam, especially in a poorly cooperative patient or in the setting of significant media opacity or poor dilation UWF devices such as the Optos devices are able to obtain useful images in these settings. We have also found the documentation capability of UWF imaging to be an asset in the context of electronic medical records, where tools to perform a detailed retinal drawing may be cumbersome and inefficient. Documentation of the extent of a retinal detachment and the position of retinal tears may also be facilitated by widefield imaging.

These capabilities of UWF imaging may be particularly important in the current era of COVID-19. Ophthalmologists are at particular risk for infection with the novel coronavirus as ophthalmic examination may require relative close proximity between the examiner's and the patient's faces. Limiting the examination time is an important component of improving safety for both the patient and the physician. By providing a comprehensive survey of the retina, UWF imaging may be used as a tool to streamline the exam to focus on those areas that are not adequately visualized by the UWF image.

In summary, widefield retinal imaging, particularly UWF imaging, has become an indispensable tool in ophthalmic clinical practice. With the inclusion of UWF imaging in many ongoing clinical trials of various retinal diseases, one can anticipate that the applications of retinal imaging will continue to expand.

References

1. Choudhry N, Duker JS, Freund KB, Kiss S, Querques G, Rosen R, Sarraf D, Souied EH, Stanga PE, Staurenghi G, Sadda SR.Classification and Guidelines for Widefield Imaging: Recommendations from the International Widefield Imaging Study Group.Ophthalmol Retina. 2019 Oct;3(10):843-849.

2. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina. 2012 Apr;32(4):785-91

3. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology. 2013 Dec;120(12):2587-2595.

4. Silva PS, Cavallerano JD, Haddad NM, Kwak H, Dyer KH, Omar AF, Shikari H, Aiello LM, Sun JK, Aiello LP. Peripheral Lesions Identified on Ultrawide Field Imaging Predict Increased Risk of Diabetic Retinopathy Progression over 4 Years. Ophthalmology. 2015 May;122(5):949-56.

5. Verma A, Alagorie AR, Ramasamy K, van Hemert J, Yadav NK, Pappuru RR, Tufail A, Nittala MG, Sadda SR, Raman R; Indian Retina Research Associates (IRRA). Distribution of peripheral lesions identified by mydriatic ultra-wide field fundus imaging in diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2020 Apr;258(4):725-733.

6. Muqit MM, Young LB, McKenzie R, John B, Marcellino GR, Henson DB, Turner GS, Stanga PE.Pilot randomised clinical trial of Pascal TargETEd Retinal versus variable fluence PANretinal 20 ms laser in diabetic retinopathy: PETER PAN study. Br J Ophthalmol. 2013 Feb;97(2):220-7.

7. Brown DM, Ou WC, Wong TP, Kim RY, Croft DE, Wykoff CC; DAVE Study Group. Targeted Retinal Photocoagulation for Diabetic Macular Edema with Peripheral Retinal Nonperfusion: Three-Year Randomized DAVE Trial. Ophthalmology. 2018 May;125(5):683-690.

8. Quinn N, Csincsik L, Flynn E, Curcio CA, Kiss S, Sadda SR, Hogg R, Peto T, Lengyel I. The clinical relevance of visualising the peripheral retina.Prog Retin Eye Res. 2019 Jan;68:83-109.

9. Writing Committee for the OPTOS PEripheralRetinA (OPERA) study (Ancillary Study of Age-Related Eye Disease Study 2), Domalpally A, Clemons TE, Danis RP, Sadda SR, Cukras CA, Toth CA, Friberg TR, Chew EY. Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2: Age-Related Eye Disease Study 2 Report Number 12 by the Age-Related Eye Disease Study 2 OptosPEripheralRetinA (OPERA) Study Research Group. Ophthalmology. 2017 Apr;124(4):479-487.

SPOTLIGHT

Retina Practice in COVID times

Dr. Manisha Agarwal [1] (MA)
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In this hour of a global public health crisis due to COVID-19 all over the world, all of us retina specialists are forced to modify our practice patterns to make it safer for our patients and for ourselves without compromising on the quality of care .Additionally, we need to make the system accessible and available to those who are the most in need of it..

We have put forth some common problems and case scenarios which many of us may face in our day to day practice to a panel of senior vitreoretinal specialists comprising of Dr. Pramod Bhende (PB), Dr. MaheshP Shanmugam (MPS), Dr. Manish Nagpal (MN), Dr.Hemanth Murthy (HM), Dr Raja Narayanan (RN), Dr. Hemant Singh Trehan (HST). We asked them to share how they would resolve such problems or manage such case scenarios in the current COVID times.

Q1. If there is a diabetic patient who has a history of travel and COVID test done 1 week back which was negative, now requiring a vitreoretinal surgery would you be getting the test done again and wait for the result or take up the surgery with universal precautions?

PB : There are no clear guidelines and they are evolving from time to time depending on the situation. Usually if the first test is negative in an asymptomatic patient, repeat test is not recommended unless patient has symptoms suggestive of suspected COVID. Definite quarantine is advised at least for 14 days as there is positive travel history. (Each state has its own protocol.) The surgery can be delayed at least for 2 weeks from the date of travel, unless it is an emergency. State recommended universal precautions should be followed for surgery.

MPS : We do not do pre-op COVID test as of now as it is not recommended by ICMR as part of pre-op protocol. There is no 100% sensitive test to detect COVID at present and a negative

test does not imply that the patient does not have COVID. As per literature, there is a possibility of false negative even with the second test (RT-PCR). The sensitivity of the test can vary based on the manufacturer as well. If the eye condition can wait, I would wait for another week before taking up the patient for surgery. If the eye condition cannot wait, we would take universal precautions as we usually do to perform the surgery.

MN : Would go ahead and operate with universal precautions.

HM : I would enquire about symptoms and after investigations including CRP and chest x-ray discuss with the patient. If the patient is ready for a second test then it would confirm whether he/she has the infection or not. If the patient refuses a second test then we have to proceed with universal precautions and PPE.

RN : No, but will take all precautions. The negative predictive value of COVID test is poor. Universal precautions are meant to be used at all times, irrespective of whether we know a patient is positive or negative.

HST : I assume this is an urgent situation. I would not wait, instead I would take up for surgery assuming the patient is COVID positive and use universal precautions. At the most I would retest the patient for administrative purposes to decide his postoperative point of care. If the patient subsequently turns positive, then he/she would need to be shifted to a COVID facility. If the situation is not so urgent, then there are many nuances. If in the intervening period since the test, there is a history of travel or possible exposure to a COVID environment, then I would retest and wait. If no such history is forthcoming, I would even consider operating based upon the previous test.

MA : The RTPCR maybe false negative in a patient and therefore we are not sure of his status in terms of having COVID infection. Therefore if the patient is asymptomatic one may operate with universal precautions.

Q2. If there is a 70 year old diabetic and hypertensive patient with a history of CAD having chronic retinal detachment and the other eye normal- will you be planning the surgery as per the availability of your slot or counsel the patient against the surgery keeping in mind that he is a high risk patient especially during COVID era?

PB : Prefer to postpone the surgery during COVID lockdown period. Thereafter the surgery can be scheduled as per the institutional SOP.

MPS : Considering that the patient does not have an ocular emergency, the surgery can be postponed to a relatively safer future, rather than counseling against surgery. The decision to operate would depend on the keenness of the patient to have the surgery, and one's own practice pattern in the pre-COVID era. If you would have offered surgery to this patient in the pre-COVID era, it is best to offer the same now after taking the requisite precautions. COVID will linger on and it is essential that we get back to our preferred practice patterns, within the confines of the new-normal.

MN : Would have delayed it if I had seen in the last two months but at this point I would go ahead and post the patient with universal precautions.

HM : The patient has all the risk factors so I would counsel the patient against surgery as the risk far outweighs the benefit.

RN : I will go ahead with surgery with universal precautions if I am in a green zone, which I am currently in. It can certainly be delayed for a few weeks if you are working in a red zone.

HST : I would advise against surgery assuming it was a chronic rhegmatogenous retinal detachment. If it is a chronic TRD with chance of providing useful vision, I would consider surgery. The virus is here to stay. By waiting, the number of cases are only going to increase and we don't know the end point. I would book at an available slot. The only condition I would defer surgery in would be if there is a significant concentration of COVID Positive patients in the facility in that period. This would prompt a referral to another less affected hospital or a deferral till the spike of cases decreases. As surgeons, we can control the immediate environment of the patient in the OT but a patient visiting the hospital can have a number of unsupervised interactions and we have practically observed this. Due to the presence of asymptomatic spreaders, these interactions cannot be prevented and hospitals that have a spike of cases within the premises may have asymptomatic spreaders that are unknown. Therefore, I would defer surgery in this particular situation only.

MA : Keeping in mind the high-risk status of the patient one may discuss with the patient the risk benefit and decide against the surgery if the patient is not keen for it however if he decides in favor of the surgery, then to perform with universal precautions. The decision need not change in current times.

Q3. A patient with idiopathic polypoidal choroidal vasculopathy (IPCV) would you opt for anti- VEGF injections monotherapy or a combination therapy of PDT + anti-VEGF as first line? Will you like to avoid frequent visits to the operation theatre or avoid a contact lens and intravenous line in OPD?

PB : Will not change my management protocol. Anti-VEGF monotherapy would be my first choice.

MPS : Photodynamic therapy is currently ruled out as we use the laser-on-demand; the current travel restrictions would not allow access to the laser machine. I may consider a combination treatment of anti-VEGF with steroid in select patients in an attempt to prolong retreatment interval.

MN : I normally treat these patients only with monotherapy and hence would go ahead with the same decision.

HM : Either of the procedures would require the patient to come for anti VEGF injections monthly for at least the first 3 months. I would prefer anti VEGF monotherapy as doing a combination treatment would involve in addition a contact lens procedure with higher risk of transmission of the virus.

RN : COVID has not changed my practice pattern in PDT. I start with monotherapy and discuss with the patient about possible PDT. Baseline PDT would still require frequent anti-VEGF injections in the first 3 months. I am not avoiding contact lens procedures as instillation of betadine eye drops are very effective against coronavirus.

HST : I would prefer Anti VEGF and PDT combination to decrease hospital visits. Contact lenses can be disinfected and Starting an IV line is the same as any contact with the patient.

MA : The treatment decision need not change in current times and one may consider PDT if decided upon and available with due precautions of sterilization of contact lens, instillation of betadine drops after lens application and wearing of face masks and gloves during the procedure.

Q4. A young patient with a history of COPD and requires an elective surgery for a macular hole with the other eye normal - will you advise surgery or defer it as the patient is a high-risk patient during COVID times?

PB : Prefer to postpone the surgery during lockdown as per ICMR and state government guidelines. Subsequently will plan surgery as per institutional SOPs using universal precautions.

MPS : Same as the answer for question 2. We need to follow precautions and try to get back to our pre-COVID routine as much as possible, rather than trying to be defensive and defer surgeries.

MN : Would go ahead at this point as he would lose vision due to a delay.

HM : Macular hole in the young could probably be due to trauma and we can wait for 1-2 months before we decide on surgery as there is a possibility of spontaneous hole closure. Further the patient is a high-risk patient so waiting for a few months would not adversely affect the outcome.

RN : I will proceed with the surgery using universal precautions in a green zone. Patients in hot spots then should defer macular hole surgery and re-assess after a few weeks.

HST : This is a tricky situation. There is a treatable condition with potential for a significant visual improvement. The patient is young and may have a predilection for a similar event in the other eye in the future. If we leave him untreated, then recovering vision in the currently affected eye at a later date will be difficult. On the other hand, he has a real risk to life if infected. I would not be able to take a decision without the patients inputs and the decision matrix is something like this: Patients fall into one of three categories generally, one set is the commando mentality who often say, I want this fixed and I accept the risks whatever they are, I don't want to be visual handicapped at any cost and quality of life is paramount in such patients I would operate. Another category of patients is the definite no risk category, who first want guarantees of no harm in such a patient I would not operate. The majority fall into the middle group where the patient would get my inputs on risk and benefit and then decide in conjunction with me these are the most time consuming and difficult decisions because they will depend on my guidance. For these patients I would advise that they wait for 2-3 months till we know more about the real risks of surgery in our country and situation and then reassess the risk benefit of surgery. I would dare to suggest that a standalone ophthalmic facility may be a lower risk environment for such a patient rather than a multispeciality hospital.

MA : The decision to operate need not differ from the usual practice and If the patient is fit to undergo surgery and the surgeon decides to operate then one may consider it with universal precautions.

Q5. Any special investigations or precautions while operating a patient with a history of being COVID positive in the past?

PB : If the patient was COVID positive in past but had subsequent RTPCR negative, he does not need any other specific test. Routine institutional protocol should be followed.

MPS : If patient was COVID positive in the recent past (~less than a month), a repeat test may be preferable. I would also refer the patient to an infectious disease specialist with COVID experience to seek his / her opinion prior to surgery. If negative and found fit to undergo surgery, we will go ahead subsequently with the surgery with full precautions. If positive and the eye condition

needs emergency care, I would refer the patient to a COVID center equipped to perform surgery on COVID patients.

MN : Shall definitely ensure a COVID negative test prior to surgery and then operate with universal precautions
HM : If the patient was positive for COVID then I would request a repeat RT- PCR to see if we get a negative report. Even after this I would proceed with universal precautions.

RN : If a patient has fully recovered and has tested negative, I would operate using universal precautions.

HST : I have no experience of this, but I guess no special steps are needed.

MA : Preferable to do a repeat RTPCR test prior to surgery and take an opinion from an infectious disease expert prior to operating the patient with universal precautions.

Q6. A diabetic patient on dialysis requiring a vitreoretinal surgery in the COVID era- any special precautions to be taken other than the universal precautions?

PB : If surgery is an emergency, I would request for COVID test (RTPCR) prior to surgery. Elective surgery can be postponed.

MPS : Patients with co-morbidities have an increased risk of acquiring COVID infection. Hence, where possible, we can delay the surgery until the curve flattens so that they are not exposed to asymptomatic carriers at the hospital. If it cannot be delayed, minimizing exposure by decreased hospital visits, enhanced isolation procedures and minimizing the time spent by the patient at the hospital can be steps to be followed in the event of the surgery being inevitable.

MN : None other than the universal precautions

HM : These are high risk patients and it would be preferable to get a pre surgery COVID test done along with a clearance from the Nephrologist. We will have to follow universal precautions.

RN : A lot of emphasis has been given to universal precautions by doctors and medical personnel. Patients should also follow precautions such as wear masks in the hospital, maintain distancing, and carry hand sanitizer and use it whenever they touch any document, surface, or stationery in the hospital.

HST : I would like to take all steps to make sure this patient does not have significant postoperative inflammation because putting this patient on oral steroids would be a double whammy. If in doubt I would even give a PST or intravitreal steroid at the end of surgery. Otherwise, no special precautions.

MA : If the surgery cannot be postponed then we need to reduce the exposure of such high risk patients during their hospital visit by reducing their throughput time and taking all precautions such as proper sanitization, gloves and face masks. Plan the surgery with universal precautions if the patient is fit by the Nephrologist.

Q7. A case of a fresh, phakic retinal detachment with an inferior break would you prefer vitrectomy or scleral buckling during COVID times?

PB : My preference would be scleral buckling in this case. Choice of procedure should be dictated primarily by the clinical setting in a given case. At present there is no substantial evidence of COVID transmission through blood or body fluids however technique with minimal tissue handling and shorter surgical time is preferred when choices are even.

MPS : The issue here is risk of exposure to the surgeon and the OT staff from an asymptomatic patient. Scleral buckling is my preference it is as quick / faster than vitrectomy. Fluid gas exchange during vitrectomy runs the risk of aerosol formation while there may be a bit more exposure to blood of the patient with scleral buckling. While there is paucity of viral RNA in the blood and plasma, the infectivity from blood and it's constituents is currently unclear. Ultimately the choice of surgery is based on surgeon's familiarity with either technique, the risk to surgeon and the team, possibly being equal.

MN : If it's a young patient I would definitely do buckling

HM : This is a difficult situation, as scleral buckle is best done for this situation but vitrectomy surgery is more controlled and safer to do during this pandemic. As also mentioned in the recently issued AIOS guidelines.

RN : My practice would not change in COVID times. I always prefer valved cannulas for vitrectomy, and that would help if I choose to do vitrectomy.

HST : I would still prefer a buckle because I'm an old conventional fuddy-duddy. I would try and avoid cautery though and nothing else would change.
MA : We do not need to change our surgical decision and if scleral buckling is the choice of the surgeon then it may be performed with universal precautions in place.

Q8. How do you use PPEs or COVID protective gear in the OT for the surgeon /OT assistant? Do you follow specific donning-doffing protocols?

PB : Continue to follow the standard institutional protocol for

HIV cases with few modifications. Use N95 mask with/without surgical mask and protective glasses. Face shield is difficult to use while operating through microscope. Wearing plastic waterproof gown under the sterile surgical gown and shoe covers.

MPS : The COVID protective gear comprises of a half-sleeve waterproof gown which is worn immediately over the OT dress and face shield for the assistant and glasses for the surgeon, the sterile gown, shoe-cover and double gloves. Donning-doffing is done with the help of a buddy and in the pre-specified manner.

MN : None other than routine surgical mask for myself and assistants. In case it's a GA case then PPE is donned by my anesthetist and other staff. I do not use any shield or eye cover. Surgeon enters only after patient is draped. We are making sure patient has a mask and we cover patients mouth with opposite to reduce any chance of air contamination in case of inadvertent coughing etc.

HM : We use the recommended PPE- disposable gowns, cap, N95 mask, goggles, gloves and shoe covers for the surgeon and assistant. We have a simple protocol of discarding the gown and gloves and rescrub for the next surgery.

RN : As VR surgeon, I use N95 mask, water proof gown and leggings, and goggles. Assistants wear N95 masks, gown, leggings and visor.

HST : The surgeon and assistant are both in sterile PPE. We have always assumed that the patient is COVID positive since beginning March 2020 and have experimented with various PPE combinations. Our current favored combination is a gown, mask, goggles and hood and shoe covers. We have also worn coveralls with gowns over them and used integrated PPE hoods. Some may find this excessive but we have experience of previously COVID negative patients turning positive in the admission period. Therefore, we prefer to go beyond recommendations rather than under protect ourselves, especially since these surgeries take long and duration is prolonged even further due to the visualization issues with goggles, fogging, IPD, field of view etc. Yes, we follow very specific donning and doffing protocols. We have an earmarked donning room where we don PPE under each others supervision. We take care to wear our masks, shoe covers and goggles prior to hand wash. We also adjust the masks and goggles to ensure minimum or no fogging as this can rapidly worsen during surgery and make surgery very difficult especially if you have a long nose like mine which doesn't lend itself to a good mask fit. There is a specific doffing room adjoining the OT and we doff under each other's supervision and emerge in scrubs. We have learnt new things with each surgery.

MA : There may be a slight variation in the protocols however it is universally recommended that the surgeon wearsN95 mask, gloves, goggles, shoe covers and a water proof gown. Donning and doffing protocols need to be in place and followed strictly.

Q9. Have you made any modifications in the Air-conditioning systems in the OPD and OT?

PB : In the OPD- wherever possible windows and doors are kept open for ventilation and air conditioning is kept off. Exhaust fans in all the toilets are kept on all the time. Places where there are no windows then the air conditioners are kept on with increased rate of air exchanges per hour with increased ratio of fresh air mixing.

In OT- we do not switch off air conditioners. We have increased the rate of air exchanges per hour at AHU. Also 20-30 minutes of interval between two cases helps to reduce the particle load, if any, in the OT.

MPS : In the OPD we are not using air-conditioning, leaving the windows and doors open this is aided by the fact that our hospital is not centrally air-conditioned, allowing us this luxury. No specific modification has been made for the air-conditioning system in the OT except for a simple modification to vent the Boyle's apparatus exhaust safely.

MN : None whatsoever. In between cases we just open the door of our individual theatre to not let positive air pressure build up. Otherwise regular HEPA filtered air conditioning is used. In OPD the airconditioning is working normally except that doors and windows are frequently opened to allow exchange of air.

HM : No, we have the AHU with HEPA filters for the OT. We have adequate number of air exchanges.

RN : There is no major modification. In the OT, we have turn of positive pressure during intubation and extubation. Air conditioning is being used in OPD and offices.

HST : Yes, we have recently converted to a Negative pressure OT. It took a few hours. Earlier we operated in a positive pressure OT.

MA : Air conditioning is preferably not used in the OPD and have maximum air circulation by opening windows and doors. In the OT may not be possible to operate with the air conditioning off however we need to ensure a gap of 20-30 min in between the cases to allow air exchange

Q. 10 Are you now more inclined to follow a treat and extend protocol for all patients requiring anti-VEGF therapy?

PB : No. we are continuing the treatment as per our institutional preferred practice pattern.

MPS : Either way I was not using monthly injections except for the loading dose. Hence would lean more towards treat and extend or PRN protocol. However, considering that we need to learn to live with COVID-19 ultimately, we may go back to our prior practice patterns but with advised precautions.

MN : No change in protocols of injection, these are conditions leading to severe visual loss if untreated and one must make sure that we follow them up and inject as per our routine patterns. I may add that we could reduce the need for frequent OCT examinations and rely more on a quick clinical check wherever possible

HM : We find that treat and extend protocol to be a better way to reduce patient visits and at the same time have a better efficacy than PRN regimen.

RN : Yes.

HST : Yes, that was also the case in the BC era (before COVID)

MA : In order to reduce patient visits to the hospital one may consider using treat and extend regimen more frequently at such times, however individualization of treatment maybe done as in the past.

References

1. Gupta V,Rajendran R,Narayanan R, et al. Evolving consensus on managing vitreo-retina and uvea practice in post COVID -19 pandemic era. Indian J Ophthalmol2020;68:p 962-973.

2. Sengupta S, Honavar SG, Sachdev MS, Sharma N,Kumar A. All India Ophthalmological Society Indian Journal of Ophthalmology consensus statement on preferred practices during the COVID-19 pandemic. Indian J Ophthalmol. Vol. 68(5).2020.711-724.

3. VRSI Webinar on Retina Practice guidelines in the COVID-19 Era.Availablefrom :https//www.vrsi.in/webinar-retina-practice-guidelines-in-the-covid-19-era/.

4. Mario R. Romano, AlessioMontericcio, Clara Montalbano, Raffaele Raimondi, DavideAllegrini, Gabriella Ricciardelli, Martina Angi, Luca Pagano & Vito Romano (2020) Facing COVID-19 in Ophthalmology Department, Current Eye Research.

5. Eggers M. Infectious Disease Management and Control with Povidone Iodine Infect Dis Ther 2018,June 7 (2),249-259.

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JM PAHWA AWARD 2019

Denovo generation and characterization of RPE from human induced pluripotent stem cells (hiPSC) and its subretinal transplantation in RCS rats

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Abstract:

*Title:**Denovo*** **generation and characterization of RPE from human induced pluripotent stem cells (hiPSC) and its subretinal transplantation in RCS rats**

Purpose: Retinal degenerations like AMD and RP cause retinal cell death and progressive vision loss. Subretinal transplantation of retinal pigment epithelial(RPE) cells is a promising method in cell therapy. Here, we tested *denovo* generation of hiPSC from peripheral blood, its differentiation into RPE, characterization, and transplantation into RCS rat model to rescue photoreceptors and visual function.

Results: All the experimental animals showed bleb formation and successful delivery of cells. Optomotor tracking thresholds were rescued in each cell treated dose group. Histological analysis revealed significant photoreceptor protection above that of controls at both time lines in both cell dose groups. Quantification of cone counting revealed a significantly higher number of cones in cell treated groups compared with control eyes, most evident at P90. Mild inflammation was noted in 2 animals.

Conclusion: When transplanted into the subretinal space of RCS rats, our RPE cells delayed the loss of visual acuity in the RCS rat over that of controls at all ages tested. Rod and cone photoreceptors were rescued in the area of the grafts for up to 70 days post-transplantation. RPE transplantation is a promising treatment for degenerative retinal diseases.

Introduction:

Replacing defective retinal pigment epithelial (RPE) cells with those derived from humaninduced pluripotent stem cells (hiPSCs) is a potential strategy for treating retinal degenerative diseases. (1)

RPE cells form a specialized epithelial cell layer in the retina that is critical for photoreceptor cell homeostasis and survival. Several diseases lead to loss of RPE cells with major consequences for vision. Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of inherited retinal dystrophies. Multiple gene mutations have been shown to cause retinitis pigmentosa and each mutation induces a specific phenotype affecting either the RPE cells or photoreceptor cells or both. (2) Age-related macular degeneration (AMD) is a pathological condition leading to the degeneration of RPE cells with a complex etiology comprising both genetic and environmental factors. (3) AMD is one of the leading causes of blindness and an increasing global burden with 196 million patients projected to suffer from this disease worldwide by 2020. (4)

Treatment of RP and dry AMD, the major form of AMD around the world has met with limited success. Several therapeutic trials involving gene therapy and cell replacement therapy are underway.(5) Cell replacement therapy has been proposed as a strategy to replace dead or damaged retinal cells with cells derived from different sources including mesenchymal stem cells, peripheral or fetal RPE cells, or human embryonic stem cells (hESC) or human induced pluripotent stem cells (hiPSC). (6)

Here, we have tested transplantation of RPE cells generated from hiPSC into RCS rat model to rescue photoreceptors and visual function.

Materials and Methods:

***Denovo*generation of retinal cell types from iPSC**:

Induced Pluripotent Stem cells (iPSC) have the ability to generate any cell type of the body with unique set of their genomic information. Disease modelling with iPSCs can serve as a promising tool to learn the pathophysiological changes in the disease progression at cellular level. *In vivo* organogenesis can be recapitulated *in vitro* via thorough understanding of highly regulated molecular and cellular signalling within and between the cells. We have patented tightly orchestrated differentiation protocol to generate RPE from iPSC. (7,8)

The signs of successful RPE induction includes(i) tightly packed cuboidal cells (ii) blackish pigmentation (iii) apical/ basal polarity along with absence of undifferentiated pluripotent cells. The functional characteristics of RPE include (i) the ability of cells to secrete cytokines such as VEGF and PEDF in a polarized fashion (ii) ability of cells to phagocytose the photoreceptors outer segments.

The RPE thus generated was termed **Eyecyte-RPE**

Subretinal transplantation in the RCS rats:

Method:

We tested the efficacy of transplantation of (Eyecyte-RPE) RPE cells to rescue photoreceptors and visual function in the Royal College of Surgeons (RCS) rat model of retinal degeneration. A total of 16 RCS rats received a single injection of vehicle or Eyecyte-RPE on P21. One animal died shortly after injection of the cells as a result of anesthesia. Half the animals were sacrificed for histological study at P60 (n=7), and the remaining animals at P90 (n=8).*(Table 1)*

Surgery:

A small tunnel incision was made through the conjunctiva and sclera in the dorso-temporal region of the eye using a 30-gauge needle. A small glass pipette connected through microtubing to a 10µL Hamilton syringe was then inserted into the subretinal space and 2.0 uL of cell suspension was injected. The needle was held in place for a count of 10 before removal to limit efflux of cells. Successful injection was confirmed by manual visualization of the fundus and lack of abnormal or negative outcomes.

Optokinetic Tracking:

Optokinetic tracking (OKT0 thresholds were assessed using a virtual optomotor system (VOS; Cerebral Mechanics) comprising four computer monitors arranged in a square, displays facing inwards. On the monitors, a virtual cylinder was generated that displayed sine-wave gratings that can be rotated either clockwise or counter clockwise permitting evaluation of both the left and right eyes independently. On any given trial, the cylinder was centered on the animal's head effectively clamping the spatial frequency from the animal's viewing point. Beginning with a low spatial frequency, the cylinder was rotated and if the grating was resolved, the animal then responded with a reflexive head and neck movement tracking the grating. The spatial frequency of the grating was then incrementally increased until the animals no longer tracked the stimulus, resulting in a maximal spatial frequency threshold. Thresholds were evaluated in all live animals on P60 and P90.

Histology:

Both eyes from each animal were harvested, fixed, cryoprotected, embedded, and frozen individually in Optimum Cutting Temperature (OCT) compound blocks, and were cryosectioned at 12 µm. Approximately 40 slides containing 4 sections per slide were obtained from each eye. Sections werecollected in a 5-slide series to provide a representative section every 60 µm on each slide throughoutthe eye-cup. The first slide in each series was stained with cresyl violet or hematoxylin and eosin. Stained sections were examined for 1) retinal damage/toxicity and 2) evidence of photoreceptor rescue. For each slide, the average outer nuclear layer thickness in temporal and nasal retina was recorded for quantification of photoreceptor rescue.

Results:

Animals and surgery:

All animals had successful delivery of Eyecyte-RPE into the subretinal space of RCS rats on P21. One animal did not recover from anesthesia at the time of injection and thus was removed from the study. Typically, eyes with evidence of any exclusion criteria including retinal tears/puncture, excessive reflux of cells, severe cataracts, excessive bleeding, excessive swelling and/or inflammation, anophthalmia, or micro-ophthalmia were removed/not assigned to the study, and replacement eyes/animals were allocated.

OKT:

Optokinetic tracking (OKT) thresholds were measured through both eyes of each animal on post-nataldays 60 and 90. **(Figure 1)** There was no significant difference between the high and low dose cell treated eyes at either age (p = 0.467). However, there was significant rescue of OKT thresholds in both high and low dose cell treated eyes compared to vehicle injected controls (p <0.001). OKT values declined in vehicle injected control eyes from P60 to P90 as would be expected, however, both high and low dose cell treated eyes remained unchanged. This rescue in spite of degenerating controls emphasizes the strength of the rescue effect achieved.

Histology:

All eyes from surviving animals in the study (n=15) were processed successfully for histological study. After cryosectioning and staining, outer nuclear layer thickness (ONL) was measured as the primary indicator of photoreceptor rescue. **(Figure 2)** At P60, cell treated eyes (temporal region) had significantly thicker ONL measurements than untreated areas of the same eye. However, by P90 the transient effect of the BSS+ had waned and the only eyes that showed any rescue effect were those that received implantation of Eyecyte-RPE. At P90, cell treated retinas had significantly thicker ONL than untreated regions of the same eye.

Quantification of cone counting revealed a significantly higher number of cones in cell treated groups compared with control eyes, most evident at P90.Approximately 10% of the transplanted RPE cell markers expressed Ki67, a cell proliferation marker. Mild inflammation was noted in 2 animals.

Conclusion:

When transplanted into the subretinal space of RCS rats, our RPE cells delayed the loss of visual acuity in the RCS rat over that of controls at all ages tested. Rod and cone photoreceptors were rescued in the area of the grafts for up to 70 days post-transplantation. Eyecyte-RPE provided significant beneficial / efficacious effects on the degenerating retina in RCS rats without any significant safety concerns suggesting this cell type may have substantial therapeutic value in human retinal degenerative disease.

Summary:

Cell transplantation is a tempting therapeutic approach to replace lost neurons in the central nervous system and the retina. The retina is accessible to surgery and convenient for cell delivery. Studies like this help us understand the functional efficacy of RPE cells in vivo. These data along with safety studies in cGMP laboratory would help us move towards Phase I clinical trials for the treatment of retinal degenerative diseases like age-

Table 1- Study Design

Group	Total Animals per group	Treatment	Dose volume (µL)	Dose Level (cells per eye)	P60	P90
1	8 RCS P+ (4 M, 4 F)	Left eye: RPE cells Right eye: 8 vehicle	2.0 µl	50 x 10^3	OKT, histology/IHC (n=4)	OKT, histology/IHC (n=4)
2	8 RCS-P+ (4 M, 4 F)	Left eye: RPE cells Right eye: 8 vehicle	2.0 µl	100 x 10^3	OKT, histology/IHC (n=4)	OKT, histology/IHC (n=4)

Figure 1

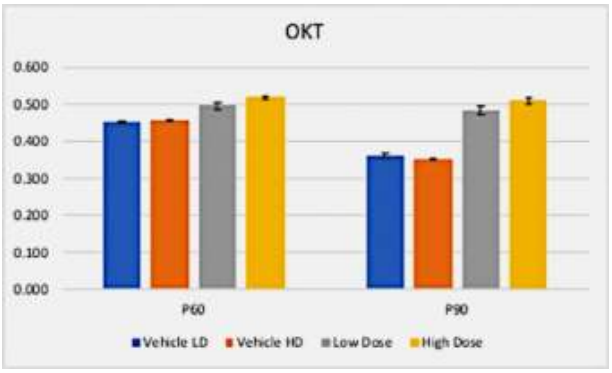

Figure 1: Optokinetic tracking thresholds measured from all animals at P60 and P90. Both the low and high dose cell treated groups were different from controls (p <0.001 for both), but were not different from each other (p = 0.467).

Figure 2

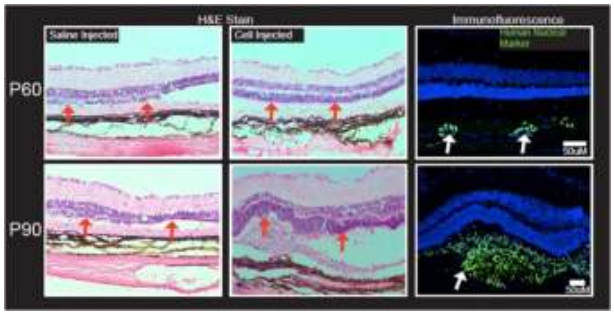

Figure 2: Summary of histological data at P60 of each eye for each animal. H & E on the left panel shows the rescue of the outer nuclear layer in the cells-injected eyes. Note the significant destruction of the outer nuclear layer in the saline-injected eyes. Immunofluorescence images show presence of transplanted cells if detected using human nuclear marker and PMEL17.

related macular degeneration and some cases of inherited retinal diseases.

References:

1. Schwartz SD, HubschmanJP,Heilwell G, et al. Embryonic stem cell trials for macular degeneration: A preliminary report. Lancet 379, 713720 (2012).

2. Hartong DT,Berson EL, Dryja TP. Retinitis pigmentosa. Lancet 368, 17951809 (2006)

3. Swaroop A, Chew EY, Rickman CB, Abecasis GR. Unraveling a multifactorial
late-onset disease: From genetic susceptibility to disease mechanisms for age-related macular degeneration. Annu. Rev. Genomics Hum. Genet. 10, 1943 (2009)

4. Wong WL, Su X , Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020and 2040: A systematic review and meta-analysis. Lancet Glob. Health 2, e106e116 (2014)

5. Thompson DA, Ali RR, Banin E, et al. Monaciano Consortium, Advancing therapeutic strategies for inherited retinal degeneration: Recommendations from the Monaciano Symposium. Invest. Ophthalmol. Vis. Sci. 56, 918931 (2015)

6. Nazari H, Zhang L, Zhu D, et al. Stem cell based therapies for age-related macular degeneration: The promises and the challenges. Prog. Retin. Eye Res. 48, 139 (2015).

7. Rathod R, Surendran H, Battu R et al. Induced pluripotent stem cells (iPSC)-derived retinal cells in disease modeling and regenerative disease. J Chem Neuroanatomy. 95, 81-88 (2019)

8. Surendran H, Rathod R, Pal R. Generation of Transplantable Retinal Pigmented Epithelial (RPE) Cells for Treatment of Age-Related Macular Degeneration (AMD). Methods in MolBiology. 283-298 (2019)

VRSI BEST POSTER AWARD 2019

Safety of induced pluripotent stem cell derived enriched RPE cultures : A prospective ex-vivo animal study

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Introduction

Retinal dystrophies are a group of progressive genetic disorders, resulting in gradual degeneration of retinal pigmented epithelium and photoreceptor cells of the retina, leading to night blindness, gradual loss of vision, which later progresses to complete visual impairment and blindness.

An adult retina does not harbor any stem cells to regenerate the lost cells. This has initiated a search for suitable stem cell sources that can differentiate into retinal cell types and most adult sources explored have proved to be inadequate so far. Over the past two decades, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have become valuable sources for generating retinal types for regenerative applications.

- Our lab had derived RPE cells sheets from healthy control iPSC line (hIPSC-F2-3F).
- iPSC derived enriched RPE cells in culture may contain a small population of undifferentiated stem cells/early neuro-retinal progenitors that may proliferate and form tumors post transplantation.
- Hence it is important to check if the fully differentiated RPE cells are devoid of any contaminating undifferentiated cells and are safe for transplantation purposes.

Materials and Methods

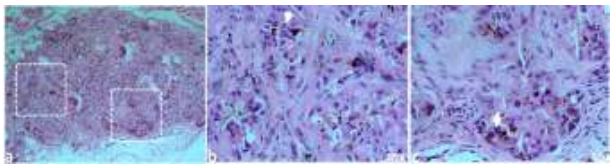
- This is an ex vivo preclinical animal study performed at LVPEI and at NCLAS, NIN, Hyderabad. This study was approved by the LVPEI institutional review board (IRB), Institutional Committee for Stem Cell Research (IC-SCR) and the NIN Animal Ethics Committee (AEC). All animal handling were done in adherence to the ARVO statement.
- A normal iPSC line (hiPSC-F2-3F) was derived by reprogramming human dermal fibroblasts established from skin biopsy cultures of an healthy control. Extensive characterization of this line for stemness, pluripotency and genomic integrity was reported earlier (Susaimanickam PJ et al., 2017).
- An in-house developed and optimized protocol to obtain enriched neuro-retinal cells and RPE cells from hESCs was reported earlier (Mariappan I et al., 2015).

Results

Subcutaneous injection of enriched human iPSC-RPE cells in nude mice:

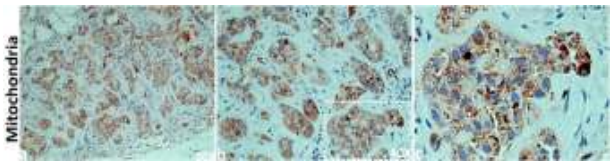
In order to check for the safety and purity of hiPSC-derived RPE cells, 2 months old enriched and mature RPE cells were suspended in 20% Matrigel solution. 50 µL of the above suspension containing 2 million cells were injected subcutaneously into 7 to 8 week old nude mice ($Foxn1^{nu}/Foxn1^{nu}$), using an insulin syringe with a 26G needle and the animals were monitored for up to 8 weeks. The study animals were then sacrificed and the pigmented tissue that developed subcutaneously at the site of injection was excised, fixed in 10% formalin for 24 hours and paraffin embedded. Tissue sections of 4 micron thickness were analyzed by haemotoxylin and eosin (H&E) staining and by immunohistochemistry.

No abnormal growth or migration of pigmented cells to ectopic sites were noted. Histological examination showed monolayered pigmented epithelial cells, organized into circular clusters within the pigmented cell patch.



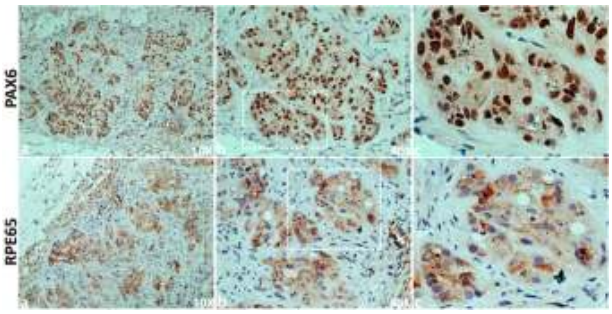
H&E stained sections of human iPSC-derived RPE cell patch

The pigmented cell clusters at the transplant site expressed the human mitochondrial antigen and we could not detect any human cells beyond the pigmented patch. This confirmed that the human iPSC-derived RPE cells survived and remained confined to the injection site.



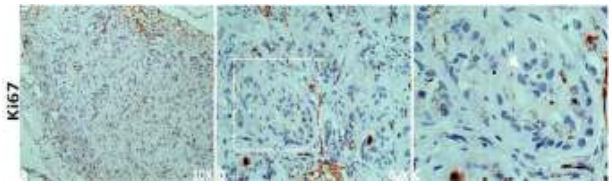
IHC for human mitochondrial antigen expression in hiPSC-derived RPE cell patch

The cells within the pigmented patch were positive for RPE-specific markers such as, PAX6 and RPE65, thus confirming that the human RPE cells maintained their cellular identity in nude mice.



IHC for RPE-specific marker expression in hiPSC-derived RPE patch

The RPE cells within the pigmented clusters did not express the cell proliferation marker, Ki67; thus confirming their non-proliferative status in vivo.



IHC for Ki67 expression in hiPSC-derived RPE patch

Conclusion

Pure cultures of iPSC derived human RPE cells neither proliferated abnormally nor induced any teratomas in nude mice. This demonstrated the efficiency of our cell enrichment protocol and the purity and safety of RPE cells for future in vivo applications in cell therapy for retinal dystrophies.

INNOVATOR'S ISLE

MEDIOS : A Smartphone based Artificial Intelligence Algorithm in Screening for Diabetic Retinopathy

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Introduction

Diabetic retinopathy (DR) is a common cause of preventable blindness. India has close to 73million individuals with diabetes and 14 million diabetic retinopathy cases.[1,2] Screening and early diagnosis of DR results in early referral to a retina specialist for treatment, and also helps the physician to initiate measures to improve glycemic control and which in turn can reduce long term progression of DR.[3,4]

The challenges to screening at the physician level include practices which are not comprehensive, lack of awareness, barriers with infrastructure, economic challenges, and patient acceptance for referral.[1] In several remote places, access to ophthalmologists may also be a barrier to screening. Although teleophthalmology has made screening more accessible, it also has its caveats. The need for pupil dilatation, size and cost of fundus cameras, camera portability, internet access, intergrader variability and access to ophthalmologists or trained readers are the current gaps in teleophthalmology that we need to overcome.

Artificial intelligence (AI) is a potential novel technology for DR screening that can solve several current gaps in the screening process described above. It can reduce the manual burden on ophthalmologists and in addition be scaled to reach a greater number of individuals living with diabetes. These AI algorithms run onconvolutional neural networks are trained analyze large amounts of data, recognize patterns of disease and generate reports. Most AI algorithms developed for DR screening work on cloud-based platforms.[58] The captured images taken from a traditional desktop fundus camera are uploaded online and the algorithm generates a report after due analysis of the image. In the developing world, lack of electricity, lack of reliable continuous high speed internet, and the start-up cost associated with equipping one's practice with a traditional expensive, desktop fundus camera are the challenges to use AI.

The AI algorithm by Medios Technologies, Singapore is to our knowledge the first offline software for DR screening. It is integrated with the Remidio non-mydriaticfundus-on- phone (FOP).[10] We present here the results of a study which aimed to evaluate the performance of the Medios AI.

AIMs

Primary aim

To evaluate the performance of the AI algorithm in detecting any grade of DR using non-mydriatic retinal images captured from patients with diabetes mellitus.

Secondary aims

To evaluate the performance of the AI algorithm in detecting referable diabetic retinopathy (RDR). RDR is defined as presence of disease greater than moderate non-proliferative DR or the

presence of diabetic macular edema (DME). To evaluate the ability of the algorithm to correctly identify all cases identified as STDR (severe NPDR or more severe disease or the presence of DME).

Materials and methods

This study prospectively enrolled patients attending the outpatient department of Diacon Hospital, a university recognized, tertiary center for diabetes care and research, Bangalore, India in 2018. Subjects, above the age of 18 years, with diabetes mellitus were enrolled for the study. Eyes with significant media opacity (corneal opacity or cataract that precluded retinal imaging) were excluded, and those with known retinal vascular (artery or vein) occlusion were excluded. Enrolment continued until gradable retinal images were obtained from 900 patients. All consenting individuals meeting the inclusion criteria were screened for DR as part of routine care.

Retinal image acquisition

Undilated retinal images were captured using the smart-phone based 'Remidio FOP camera' (Remidio Innovative Solutions, Bangalore, India) by a trained technician. Two images (ie, disc centered (nasal field) and macula centered (posterior pole)) were captured from each eye of each patient.

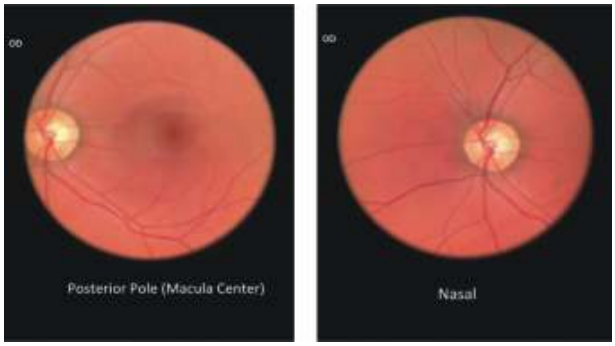

Fig 1: A macula centered and disc centered image captured with the RemidioFundus on phone camera

Image grading by retina specialist

The de-identified images were uploaded online from the FOP and accessed by five retina specialists. The specialists individually graded the retinal photographs from every patient using the International Clinical Diabetic Retinopathy Classification Severity Score. The patient-wise diagnosis obtained from the retina specialists were considered as gold standard for comparison. Each retina specialist was blinded to the diagnosis of the others and to the diagnosis of the AI. The majority diagnosis was considered as the ground truth.

Description of the AI software

The AI diagnosis system developed by Medios Technologies is based on Convolutional Neural Networks. It consists of a first neural network for image quality assessment and two other distinct neural networks that detect DR lesions. A final per-patient DR diagnosis is computed from the outputs of both DR neural networks and applied on all images of that patient.

The neural networks have been trained to separate healthy images from images with referable DR (moderate NPDR and above). The final output is a binary recommendation of referral or no referral to an ophthalmologist. No mild NPDR images have been used during training of the AI. The system has thus been engineered to maximize the sensitivity for referable DR and the specificity for any DR. A patient is deemed as a referable case if the prediction for one or more images is positive.

Neural networks traditionally run on computationally powerful servers to which the end user connects and sends images. In this case, the neural network is deployed directly on the phone, leveraging smartphone technologies to make full usage of the inbuilt hardware. The whole AI diagnosis pipeline runs offline on the iPhone (iPhone 6 or higher) of the Remidio NM FOP. There is no degradation in performance of the algorithm as a result of deploying it offline versus online. This is because, the offline mode is primarily a method of deployment that uses the smartphone to run the same algorithm as it would have on a cloud server. With newer updates, continuously trained models can be deployed through the app store, which will enable the model to get the best inferencing convenience, re-training and continuous deployment using the iPhone as a platform. The interface and the report also provide a visual representation of the areas of the retinal images that are responsible for a positive diagnosis. This is based on a deep learning technique called class activation mapping.

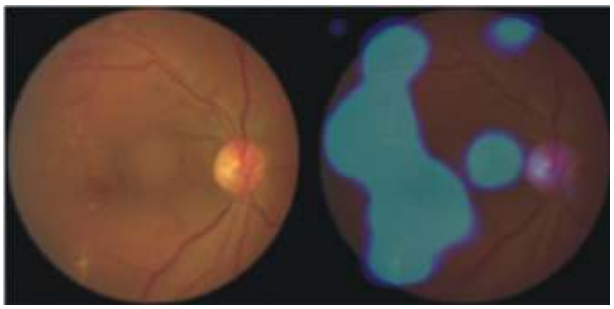

Figure 2: Visual representation of areas of the retina with signs of diabetes retinopathy

Outcome measures

The primary aim was to determine the sensitivity and specificity of the AI algorithm in detecting all DR compared with the gold standard diagnosis by retina specialists. The secondary aims were to determine the sensitivity and specificity of the algorithm in the diagnosis of RDR and STDR.

Results

The study enrolled 922 patients and the analysis included images from 900 patients. Based on the image diagnosis, there was no evidence of DR in 648 participants (72%). Mild NPDR was seen in 51 (5.67%), moderate NPDR in 163 (18.11%), severe NPDR in 3 (0.33%) and PDR in 35 (3.89%). Mild DME was present in 12 (4.76%), moderate DME in 32 (12.69%) and severe DME in 3 (1.19%) individuals with DR with different grades of DR.

The AI classified 239 (26.5%) of images as DR and 661 (73.4) % as no DR. The performance of the AI in detecting all DR and RDR is summarized in table 1. An example of the output from the Medios AI algorithm with an image diagnosis of RDR is shown in figure 3.

Table 1: Performance of the Medios AI

	Sensitivity	Specificity	AUC
All DR	83.3% (80.9% - 85.7%)	95.5% (94.1% - 96.8%)	0.9
RDR	93% (91.3% - 94.7%)	92.5% (90.8% - 94.2%)	0.88

Sensitivity for STDR was 95.2% (95% CI 88.2% to 98.6%). The three PDRs missed by the AI were postlaser images with no active changes visible. When these three images were excluded, the AI correctly identified 76/77 cases of STDR as having signs of retinopathy. The sensitivity for STDR was found to be 98.7% (95% CI 92.9% to 99.7%).

Discussion

This is the first study to evaluate the performance of an AI algorithm for DR screening using NM images captured from a portable smartphone-based fundus camera. The analysis from this large study showed that the Medios AI has a high sensitivity in the detection of RDR and STDR.

The Medios AI is distinct from other AI solutions, in being the first offline end-to-end solution integrated on the smart phone camera. The Remidio FOP is an FDA510k cleared medical device

Result: Diabetic Retinopathy Detected. Referrel to an ophthalmologist recommended
Confidence: 99%

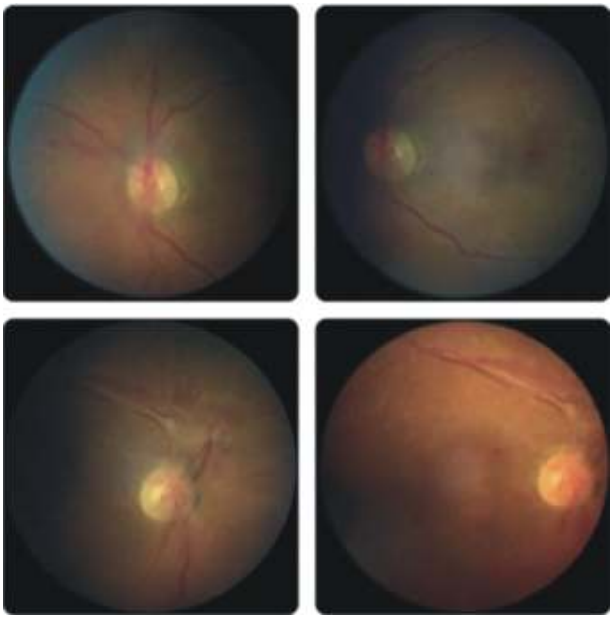

Figure 3: A report generated by the Medios AI in an individual with diabetic retinopathy.

validated in head-to-head studies against Topcon TRC 50DX and Zeiss FF450. It is the only smartphone- based device shown to have a high sensitivity and specificity in detection of all grades of DR, in non-mydriatic imaging.[11] The results seen with the Medios AI using images captured from the Remidio FOP meet the FDA superiority cut-offs and are comparable to results observed with other AI algorithms, such as Google AI, EyeArt or IDx-DR for the detection of RDR.[7,9]

A recent study by Natarajan et al evaluated the performance of the Medios AI using dilated retinal images captured using the Remidio FOP from 231 individuals with diabetes. The images were captured by a healthcare worker in a primary healthcare community screening camp. The authors reported that the sensitivity and specificity of the AI in the diagnosis of RDR as 100% and 88.4%, and for any DR as 85.2% and 92%.[14]

Developing countries like ours with geographic and infrastructure challenges need affordable and portable technology to make mass screening for diabetic retinopathy reach the outreach camps in remote corners. It is all the more important to justify whether a poor patient needs to travel hundreds of kilometers to a tertiary care centre for further assessment or treatment. Mass screening can be scaled only with the use of technology.

Anyone who can click a photo on a smartphone can operate such a device - a community healthcare worker, camera technician, receptionist, ASHA worker or volunteer. The results observed with both mydriatic and NM images support the use of smart phone fundus imaging and AI-based reporting for DR screening.

Cloud-based AI algorithms require internet access for real time reporting. In countries like India, where mass screening is the need of the hour, access to continuous electricity and internet is a constraint. The FOP with inbuilt offline AI can address these operational challenges in rural and urban areas in countries with limited resources. The offline mode of AI can ensure that DR screening can move forward without interruptions.

Screening in elderly or in those with a small pupil (<3 mm) can be a challenge. Dilatation with a drop of 1% tropicamide solution may be necessary in these cases.

Our study is the first in validating the use of Medios AI in a large clinical setting using NM images. Our results show that the AI has a high sensitivity and specificity in the detection of RDR. This is the only AI system that works offline and produces real time reports on a smart phone.

The Medios AI has the potential to be the scalable solution to make DR screening accessible at the primary care level.

References

1. Graham-Rowe E, Lorencatto F, Lawrenson JG, *et al*. Barriers to and enablers of diabetic retinopathy screening attendance: a systematic review of published and grey literature. *Diabet Med* 2018;35:130819.

2. Gadkari SS. Diabetic retinopathy screening: telemedicine, the way to go! Indian. *J Ophthalmol*2018;66:1878.

3. Solomon SD, Chew E, Duh EJ, *et al*. Diabetic retinopathy: a position statement by the American diabetes association. *Diabetes Care* 2017;40:4128.

4. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. *Int J Diabetes Dev Ctries*2018;38:1115.

5. Abràmoff MD, Lavin PT, Birch M, *et al*. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care of ces. *NPJ Digit Med* 2018;1:39.

6. Abràmoff MD, Lou Y, Erginay A, *et al*. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. *Invest Ophthalmol Vis Sci*2016;57:52006.

7. Bhaskaranand M, Ramachandra C, Bhat S, *et al*. The value of automated diabetic retinopathy screening with the EyeArt system: a study of more than 100,000 consecutive encounters from people with diabetes. *Diabetes Technol Ther*2019; 21:63543.

8. Gulshan V, Peng L, Coram M, *et al*. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus Photographs. *JAMA* 2016;316:240210.

9. Rajalakshmi R, Arulmalar S, Usha M, *et al*. Validation of smartphone based retinal photography for diabetic retinopathy screening. *PLoS One* 2015;10:e0138285.

10. Rajalakshmi R, Subashini R, Anjana RM, *et al*. Automated diabetic retinopathy detection in smartphone-based fundus photography using articial intelligence. *Eye* 2018;32:113844.

11. Ting DSW, Cheung CY-L, Lim G, *et al*. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA* 2017;318:221123.

12. Sengupta S, Sindal MD, Baskaran P, *et al*. Sensitivity and speci city of smartphone-based retinal imaging for diabetic retinopathy. *Ophthalmology Retina* 2019;3:14653.

13. Natarajan S, Jain A, Krishnan R, *et al*. Diagnostic accuracy of community-based diabetic retinopathy screening with an Of inearticial intelligence system on a smartphone. *JAMA Ophthalmol*2019;137:1182.

14. Sosale B, Sosale AR, Murthy H, Sengupta S, Naveenam M. Medios An of ine, smartphone-based artifcial intelligence algorithm for the diagnosis of diabetic retinopathy. Indian J Ophthalmol 2020;68:391-5.

CASE REPORT

Spontaneous separation of secondary epiretinal membrane following cryotherapy for primary retinal vasoproliferative tumor

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Abstract:

A 32-year-old male presented with right eye decreased vision for 10 days. The best-corrected visual acuity (BCVA) was 20/40, N10. Right eye fundus showed a reddish-white vasoproliferative tumor (VPT) in the temporal periphery along with epiretinal membrane (ERM) at the macula with retinoschisis and hard exudates. VPT was treated with trans-conjunctival double-freeze thaw cryotherapy and intravitreal triamcinolone. Spontaneous separation of ERM was noted one month after the complete regression of the VPT. At final follow up, BCVA improved to 20/20, N6, complete separation of ERM from macula was noted along with the resolution of hard exudates and schisis.

Keywords:

Retinal vasoproliferative tumor, Epiretinal membrane, Cryotherapy, Anti-VEGF, Intravitreal steroids

Introduction:

Vasoproliferative tumor (VPT) of the retina is a reactive proliferation of blood vessels secondary to retinal ischemia or inflammation. It can be primary or secondary.[1, 2] In the west, about three-fourths of VPT are primary whereas in Indian population, majority are secondary VPT (60%) with a bimodal onset in the first and second decade of life, and beyond the sixth decade.[3] Primary VPTs are idiopathic while secondary VPTs result from various diseases including retinitis pigmentosa, Coats' disease, retinal vasculitis etc.[2] Vision loss in VPT could be due to vitreous hemorrhage, macular exudation, macular edema, epiretinal formation and exudative retinal detachment. Management options of VPT include laser photocoagulation, trans pupillary thermotherapy, cryotherapy and plaque brachytherapy.[2]

Case presentation:

A 32-year-old male presented with right eye diminution of vision for the past 10 days. He had defective vision in the left eye for the past 13 years. He gave history of previous laser photocoagulation and vitrectomy being performed for the left eye in 2006, however, past reports were not available to identify the etiology. The best corrected visual acuity (BCVA) in right eye was 20/40, N10 and no perception of light in left eye. The left eye was phthisical. Anterior segment in the right eye was unremarkable and fundus examination showed a reddish-white

lesion measuring 5 x 4 x 3mm in the temporal periphery anterior to the equator along with presence of epiretinal membrane (ERM) at the macula causing internal limiting membrane (ILM) folds, macular thickening with intraretinal hard exudation (figure 1). A diagnosis of right eye primary vasoproliferative tumor (VPT) of the retina with secondary ERM (stage 3B) was made. Optical coherence tomography (OCT) of the right eye showed epiretinal membrane with schisis temporal to macula with hyperreflective dots in outer nuclear layer correlating with hard exudates (figure 1).

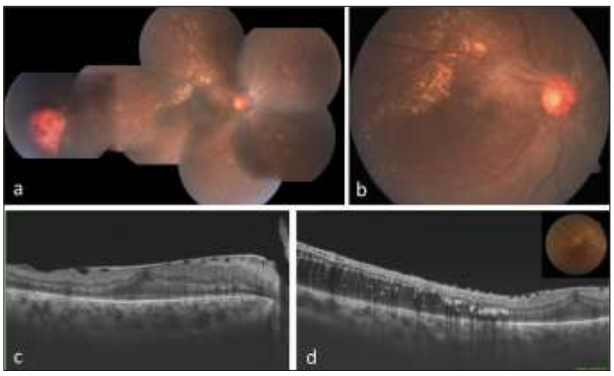

Figure 1: (a) Right eye fundus showed a reddish-white VPT measuring 5 x 4 x 3mm in the temporal periphery anterior to the equator. (b) Macular ERM was visible along with hard exudates in the superotemporal quadrant. (c) Opticalcoherence tomography (OCT) confirmed ERM (d) OCT line scan showed retinal schisis along with hyperreflective dots in outer nuclear layer correlating with hard exudates.

Intravitreal triamcinolone (2mg/0.05ml) and trans-conjunctival double freeze-thaw cryotherapy of the tumor was performed. Two months post treatment, a small reddish tumor along with chorioretinal atrophy surrounding it was seen. An increase in the intra-retinal hard exudation was noted. OCT showed ERM with distortion of inner retinal architecture, resolution of the schisis with hyperreflective dots in inner nuclear-outer plexiform (IN-OP) layer (figure 2). As some part of the tumor was still active, trans-conjunctival double freeze-thaw cryotherapy was repeated to the active part at the end of 3 months. On subsequent follow up at 4 months, one month after the repeat cryotherapy procedure, BCVA improved to 20/20, N6. The VPT had completely regressed, the hard exudates had reduced and the ERM had spontaneously started to separate from the macular region. A focal attachment of ERM was noted superotemporally with ILM folds radiating towards it. The OCT showed intraretinal fluid with inner retinal folds and complete resolution of the schisis. A few hyperreflective dots were seen in the IN-OP layer (figure 2).

On the final follow at 10 months, his BCVA had improved to 20/20, N6; complete separation of ERM from the macula was noted along with reduction in hard exudates and resolution of retinal schisis (figure 2).

Discussion:

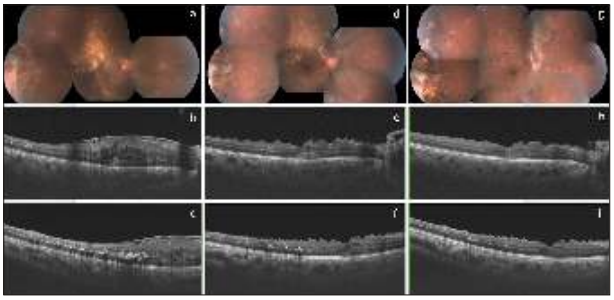

Figure 2: (a) Partially regressed VPT 2 months post cryotherapy with increase in hard exudates (b) ERM with distorted inner retinal architecture (c) Resolved schisis with hyperreflective dots in inner nuclear-outer plexiform layer (d) Four months later, VPT had completely regressed (e) OCT confirmed separation of ERM (f) Reduction of the intraretinal dots with inner retinal folds and complete resolution of the schisis (g) Ten months later, ERM had completely separated from the macula (h) Complete resolution of the macular edema noted (i) Reduction in hard exudates and resolution of retinal schisis noted.

Epiretinal membrane could be either idiopathic or secondary. Secondary ERM may lead to vision loss in 20% of cases with vasoproliferative tumor.[2] This ERM can be macular or extramacular. Honavar has classified VPT with ERM as stage 3 in his proposal for classification; stage 3A when the ERM is not involving the fovea and stage 3B when the ERM is involving the fovea.[3] In a study by Manjandavida, ERM in VPT involved the macular region in 12 cases and extramacular region in 4 cases.[4]
It is hypothesised that VPT is not a true tumor but represents reactive proliferation of blood vessels in response to some form of retinal ischemia, injury, or inflammation.[1, 5-8] This unchecked localized proliferation of blood vessels in a loose glial matrix organizes itself into a vascular mass. Over time in a long-standing mass, or following treatment, reactive gliosis predominates over the vascular component, and in the end-stage, the colour of the mass changes to yellow or white.[1, 5-]

On histopathology, VPT shows glial cells interlaced with a fine capillary network and dilated, hyalinised partially occluded blood vessels, with exudates, macrophages, and foreign body giant cells.[7-8] Histopathologically, ERM is composed of retinal pigment epithelial cells, fibroblasts, vascular endothelial cells, retinal glial cells, and monocytes.[9-12] The retinal pigment epithelial cells that reach the retinal surface can transdifferentiate into mesenchymal cells, capable of collagen production and modulate the matrix and cellular activities.[9, 10, 12]

One hypothesis for the spontaneous separation of ERM following cryotherapy could be that once the inciting pathology is dealt with, this process of inflammation is halted and the stimulus for the formation of ERM is stopped. As the retina enters the reparative phase, as indicated by reduction in hard exudates and resolution of schisis as in this case, the ERM may start to spontaneously separate. This spontaneous separation of ERM started in our case only once the complete tumor had regressed, supporting our hypothesis.

Conclusion:

In summary, we like to put forth our consideration that, epiretinal membrane associated with vasoproliferative tumor may be observed till the VPT regresses, as spontaneous separation of ERM may occur.

References:

1 Shields CL, Shields JA, Barrett J, De Potter P. Vasoproliferative tumors of the ocular fundus. Classification and clinical manifestations in 103 patients. Arch Ophthalmol. 1995 May;113(5):615-23.

2. Shields CL, Kaliki S, Al-Dahmash S, Rojanaporn D, Shukla SY, Reilly B et al. Retinal vasoproliferative tumors: comparative clinical features of primary vs secondary tumors in 334 cases. JAMA Ophthalmol. 2013 Mar;131(3):328-34.

3. Honavar SG. Retinal vasoproliferative tumor - A proposal for classification. Indian J Ophthalmol. 2018 Feb;66(2):185-186.

4. Manjandavida FP, Shields CL, Kaliki S, Shields JA. Cryotherapy-induced release of epiretinal membrane associated with retinal vasoproliferative tumor: analysis of 16 cases. Retina. 2014 Aug;34(8):1644-50

5. Jain K, Berger AR, Yucil YH, McGowan HD. Vasoproliferative tumours of the retina. Eye (Lond). 2003 Apr;17(3):364-8.

6. Heimann H, Bornfeld N, Vij O, Coupland SE, Bechrakis NE, Kellner U et al. Vasoproliferative tumours of the retina. Br J Ophthalmol. 2000 Oct;84(10):1162-9.

7. Smeets MH, Mooy CM, Baarsma GS, Mertens DE, Van Meurs JC. Histopathology of a vasoproliferative tumor of the ocular fundus. Retina. 1998;18(5):470-2.

8. Irvine F, O'Donnell N, Kemp E, Lee WR. Retinal vasoproliferative tumors: surgical management and histological findings. Arch Ophthalmol. 2000 Apr;118(4):563-9.

9. Oberstein SY, Byun J, Herrera D, Chapin EA, Fisher SK, Lewis GP. Cell proliferation in human epiretinal membranes: characterization of cell types and correlation with disease condition and duration. Mol Vis. 2011;17:1794-805.

10. Snead DR, James S, Snead MP. Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation. Eye (Lond). 2008 Oct;22(10):1310-7.

11. Hogg PA, Grierson I, Hiscott P. Direct comparison of the migration of three cell types involved in epiretinal membrane formation. Invest Ophthalmol Vis Sci. 2002 Aug;43(8):2749-57.

12. Shankar P, Bradshaw SE, Ang A, Rennie IG, Snead DR, Snead MP. Vascularised epiretinal membrane associated with vasoproliferative tumour. Eye (Lond). 2007 Jul;21(7):1003-4.

Notes

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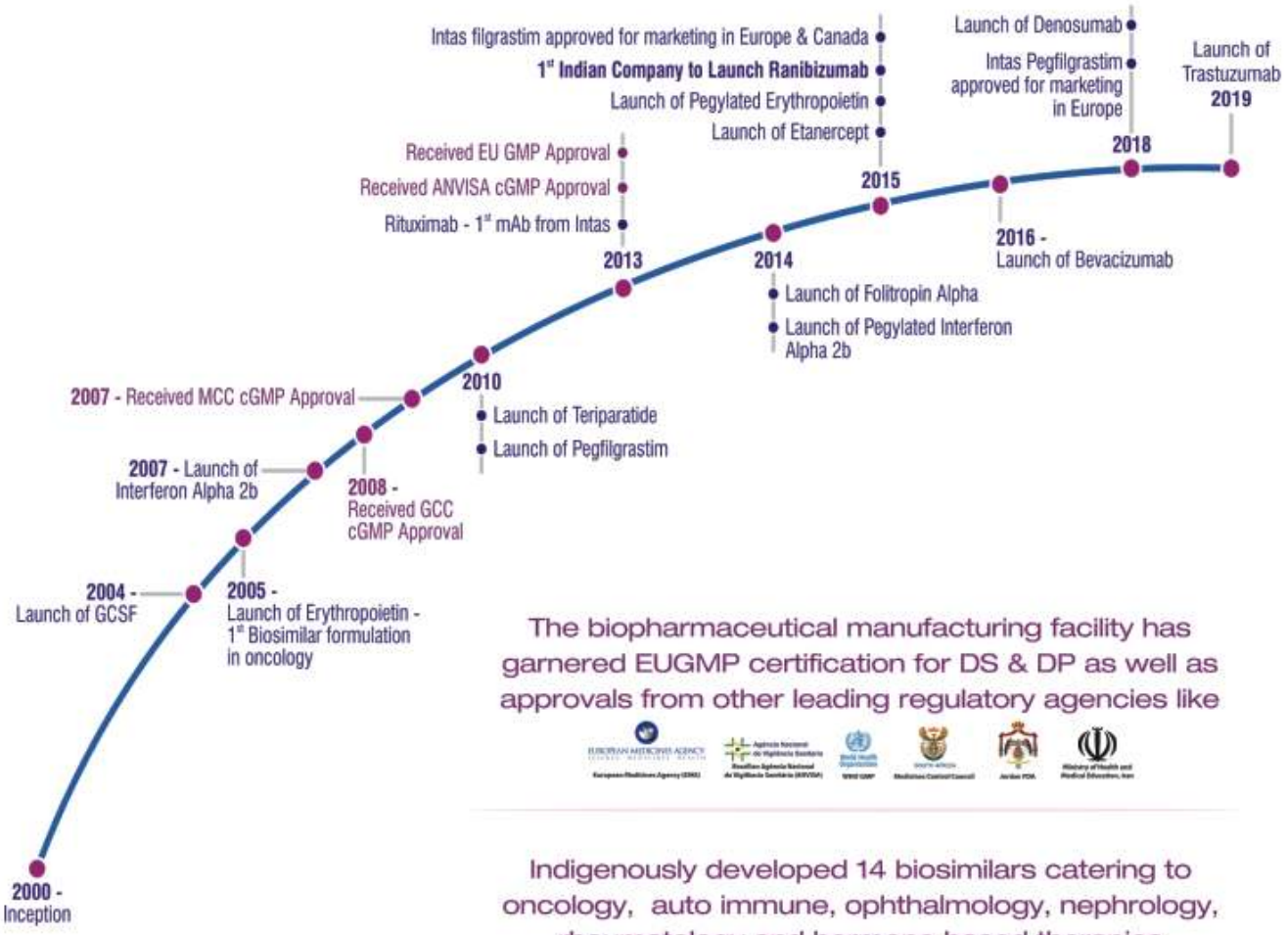

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