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Highlights

- COVID and Eye- What is Known Till Now ?
- Corona – The Testing Conundrum
- Review on Covid-19-A Novel Virus-Ocular Implications
- Revisiting Ocular Effects of Hydroxychloroquine

The Scientific Journal of U.P. Ophthalmological Society

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UP JOURNAL OF OPHTHALMOLOGY

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PRESIDENT'S MESSAGE

Dear Friends,

"Trust Yourself; create the kind of self that you will be happy to live with all your life. Make the most of yourself by fanning the tiny inner sparks of possibility into fumes of achievement".

Above words of wisdom are bending to the situation of uncertainty in view of CORONA PANDEMIC all over the world. The developed countries like Italy. France, Germany, UK & USA are worst affected. The number of cases is mounting day by day; there is no flattening of disease curve.

It is herculean task of improving scientific material by the editor Dr. Shalini Mohan, Kudos to her sincere efforts. I congratulate her for upcoming issue of UPJO.

There is no friend as loyal as a book. Literacy is a bridge from misery to hope. No one will forget this dark period, but adversay might also help us by its leading us to discover new appraoches.

Wishing you all great scientific treatise and great reading experience. Be Positive.

Dr. Shrikant, MS
President, UPSOS
Former Professor & Head, Regional Institute of Ophthalmology
Institute of Medical Science BHU, Varanasi
Presently Prof. & Head Department of Ophthalmology
Heritage Institute of Medical Sciences, Varanasi

Burning Issue : The Pandemic

Dear Friends,

"The State of Lockdown"

'***Our Mother Earth closed for renovation***' the thought floated by unknown..... but filled me with so much of positivity amidst this unprecedented crisis where unforeseen events were cropping up as each day passed by. The sky getting clearer and thoughts getting clouded, rivers flowing to full and flow of thoughts getting stationary...such was the state when the lockdown was announced as the only solution for this Pandemic – 'COVID'

When the cobwebs of COVID covered the clarity of mind, when uncertainty unwinded and stole away the peace of heart and all theories of science were thrashed by a virus, still the optimism filled the atmosphere with this wonderful quote - '***Hope is above all Fear***'. And we can see people around full of confidence showcasing their amazing qualities despite the fact that their routine work is Locked!!!!! People helping the needy with a smile despite the fact that even they are not sure till when???? People proudly sharing their knowledge and skills online despite the fact that they are unable to use it on their patients as of now.

Amidst fumes and storms, I firmly believe...."***We shall overcome...***" and singing the same song... I remember those gongs...the sweetness of mother and the serene weather...the chirping of birds and the flutter of those herds... will all return... and we shall overcome.....

That eternal belief, that unsurpassed confidence in science makes me generate a positivity within, to move ahead and make out more avenues for science and humanity in this period too. I bow down in front of Almighty and wish all the humanity the strength and confidence that the we shall win this war. And when we conglomerate next, we shall share good experiences of lockdown and learn to spread smiles seeking some lessons from this bleak phase of our life.

I wish everyone the best of health and spirits

Warm Regards

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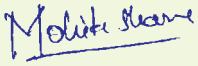
Dear Members,

COVID-19 has shaken up the whole world. It has resulted in not only a health impact but a huge psychological and economic impact on all. Most of the ophthalmologists are in a dilemma as to how to continue to work circumventing the risk of catching infection. However there are some ophthalmologists within our own state of Uttar pradesh who are fighting corona and are the true COVId warriors. our salute to these COVID warriors. we are really proud of them. I appeal to all ophthalmologists to remember the hippocratic oath and take it as a moral responsibility to serve people by providing emergency services as catering to the surgery follow up patients.

Simultaneously I want you all to take this period as an opportunity to learn new skills and take care of your own health and fitness. This period is also a great opportunity to go heavily into academics. With a number of webinars happening all over including those by your own society UP State ophthalmological society, you have a huge variety of academics to choose from. UPSOS has already held 2 webinars including one international webinar which had a large number of views from all over the world. So we are proud to tell you that now your State society is internationally known and appreciated.This is the time to read good journals as well as contribute as an author in UP Journal of ophthalmology as well as other journals.

Congratulations to Dr. Shalini Mohan for continuing her efforts in bringing out yet another issue of the journal. Do contribute generously and take this journal to very high academic standards. Last and the most important, corona is having a huge impact on psychological health. So remain positive, find ways to remain happy and spread positivity and happiness to all others around you. I would like to thank our President Professor Srikant and our Chairman Scientific committee Dr. Deepak Mishra who are continuously helping and giving suggestions for the academics to continue in the lockdown perios also.

Stay safe, stay healthy, stay happy and stay connected.



Dr. Mohita Sharma,
General Secretary, UPSOS

Current Perspectives in Keratoconus

Dr. Chitra Ramamurthy, Chairperson, ARC – AIOS, 2020 - 2023
Medical Director, The Eye Foundation group of hospitals

Keratoconus is a bilateral, progressive, non inflammatory thinning of the cornea stroma. It has a reported prevalence rate of 20 in 10,000[1,2] to 1 in 500,000.[3]

The disease is multifactorial and is influenced by genetic, environmental and biochemical factors. Again although both genders are affected, men seem to be more commonly involved.

Various grading systems have evolved. The Amsler - Krumeich classification system, Ectasia Risk Scoring Systems, Maeda and Klyce Keratoconus Prediction Index, KISA % of Rabinowitz and Rasheed are naming a few of the standard practicing norms.

The biomechanical weakening of the cornea pervades all the layers with its characteristic disruption of bowman's layer, collagen fragmentation, fibrillation and fibroblastic activity.[4]

Clinically, the early onset of the disease with presentation in teens with progressive visual blur and distortion secondary to myopia and high astigmatism is a disabling event.

The breakthrough to the disease entity and its ambiguities came with the evolution of CXL and the biomechanical strengthening it seemed to offer to halt the disease progression. The standard accepted Dresden protocol of CXL which relied on the interaction of UVA at a wavelength of 370 nm and the topical riboflavin releasing singlet oxygen and enhancing the covalent bonding among the collagen fibrils gained footage. Wollensak et al observed a 328.9% increased corneal rigidity and complimented by various studies, CXL came to be the accepted modality of treatment of KC if there was evidence of progression with a minimum CCT criteria of 400µ.

Hypoosmolar riboflavin was considered for CCT less than 400 u abetted by novel approaches of contact lens assisted CXL and the smile lenticule assisted CXL[5] which augmented the thickness of these thinner corneas. The trans epithelial Crosslinking had a small window for treating thinner corneas, Paediatric KCs with severe allergic manifestations and epithelial breakdowns.

The positive change came with the accelerated protocols of CXL which lent reasoning to the alternate method of high fluence energy with commensurately reduced UV irradiation times. Various protocols emerged and the 3 MW and the 9 MW protocols gained wider acceptance abetted with the electron microscopy and confocal studies which elaborated on the more effective crosslinking in these ranges.

As we continued to understand that the oxygen free radicals were critical for crosslinking and the rapid depletion was not in tandem with the reformation, pulsed irradiation came into vogue with pulsed on off times to better replenish free oxygen radicals during the rest periods for a more effective crosslinkage.

There has been an ongoing study of Customised CXL which further looked at the concept that Keratoconus was a focal disease and driving high fluence over the focal cone with lesser energy to the surrounds capitalized interest for evaluation as one more approach to customised CXL. Having discussed the various modes of crosslinking in vogue, we are still not clear as to which modality of crosslinking is the best way forward. We do have the ORA and Corvis but we are not able to acquire any standardized valuation of corneal hysteresis or its biomechanics. In other words, although we accept that there is a presumed increase in corneal rigidity and progression of KC has stalled, we do not have any authentic measure of which crosslinking works best. We realize that in accelerated crosslinking, 3MW and 9 MW work best by assessing the electron microscopic and confocal studies and the evidence of demarcation lines at the right depth and it getting patchy at higher fluence levels. These throw light on the validity of these lower fluence levels working better than the higher 30 MW and 45 MW levels. but we are also now talking about adaptive fluence for different thickness of corneas as one more novel more approach to consider. We are talking of customised crosslinking on the surmise that the disease has a focal propensity and hence could do better with higher focal energy delivery. This is augured by Brillion microscopy studies of higher viscosity in the surrounding area of the affected cone as compared to the area of cone which corroborates you the understanding of a focal disease process[6].

But again no measure is fool proof and we are left with conjectures. We believe that progression of Keratoconus is far more rapid in Paediatric age group and that should expediate us to treat these eyes on primary diagnosis of KC but again the protocols are not defined. We also are realistic that crosslinking in the young with a more plastic cornea may not be too effective

and further progression of KC is a possibility with the need of repeat crosslinking7. So here again that's a quandary. While so much was happening, in this era of crosslinking, what also came to light was the need to regularize the corneal distortion and the need to improve BCVA and not a mere stiffening and strengthening of the corneal lamellae was sufficient. This set the stage for the inception of Topoguided PRK with CXL with proponents like Kanellopoulous and Binder and many more fixing the criteria for treating early to moderate Keratoconus[8].

The essential dictums for combining cxl with Topoguided regularization was a CCT of at least 450u and a clear cornea, largely centered cones with a maximum ablation of 50u to reshape the corneal curvature and enhance the quality of vision. This was a bimodal approach with a combination of central myopic ablation to flatten the cone and a mid-peripheral hyperopic ablation to steepen the flatter areas and thus provide a larger flatter cone which could better withstand the biomechanical stress combined with crosslinking. But again was 50 u of tissue ablation the clear margin for safety or do we transgress a bit more? Are we completely and irrevocably sure that removal of this 50 u of tissue was not going to be hazardous in this already weakened corneas?? These elemental doubts did remain but there were many articles that came forth substantiating the intent of Topoguided PRK combined with CXL and its safety and efficacy. However, there were some questions that loomed in the background. Do we perform both in the same sitting or do we fall back on sequential treatment. The pros for simultaneous treatment came up with the discussion that it made no sense to crosslink a tissue and then ablate it later to regularize it? The purpose of cxl was defeated. Again there were no nomograms fixed for laser ablation on a cross linked tissue. And further more, doing Topoguided treatment first and then crosslinking in the same sitting made sense as the bowman's layer was disrupted and this allowed better perfusion of riboflavin. Again do we perform Topoguided treatments only for centered cones or did it perform well for mildly decentered cones?

Post Lasik ectasia was another enigma. In fact, crosslinking itself was not claimed to be as efficient as the pathophysiology of these eyes were questioned and also the diffusion rate of riboflavin and of course the challenge of these corneas being thinner.

But while we could discuss unending on Cxl, we also need to remember the ingress of cxl with LVC and the arguments for and against it. We claimed to better augmentation of corneal rigidity by combining low fluence cxl with LVC with no compromise of refractive result but had no absolute fool proof evidence that it was the only way to go in borderline topographies.

Then again, there had to be a solution for the decentred cones in KC and a solution of sorts to better capitulate an acceptable BCVA.

Therein clamoured a solution for eccentric cones and the intracorneal ring segments combined with cxl drew large acceptance.

Four types of ICRS are available for Keratoconus management .1- Intacs 2- Intacs SK 3- Ferrara Rings 4- Kerarings.

Table of intracorneal ring segments ...

The characteristics of the most popular intracorneal ring segment implants.

Characteristics	INTACS	Ferrara Ring	Keraring
Arc, length/degree	150	160	90,120,160,210,240
Cross section	Hexagonal	Triangular	Triangular
Thickness/mm	0.25–0.45 (0.05 increments)	0.20–0.35 (0.05 increments)	0.15–0.30 (0.05 increments)
Internal diameter/mm	6.77	4.40	5.0
External diameter/mm	8.10	5.60	6.0

The popular choices were the intacs which came as the standard 150 arc length PMMA segments, hexagonal in cross section and various sizes ranging from 0.210-0.450mm which were chosen based on the amount and type of refractive errors. Nomograms were evolved to choose between symmetric and asymmetric ring segments for centered and decentered cones. New smaller arc segments of 90 degrees came in when a more focal astigmatism needed to be corrected. Largely these segments were placed in channels created manually or by femtosecond lasers at 70% depth of the thinnest pachymetry.

As if challenging the scene which was already caught in the fray of controversies, Cxl pushed its way to enhancing the results of intacs by the favoured argument of simultaneous cxl with intacs placement. Herein the keratoconic cornea was displaced to a more physiological position by the intacs placement and further strengthened with cxl. This seemed to improve the BCVA and an augmented strengthening of the cornea.

There were always parallels and controversial statements floated whether a simultaneous or a sequential treatment could be done and each had its study comparisons with its arguments. Out of this discussion what came to light was the simultaneous intacs placement combined with cxl was more effective possibly potentiated by exaggerated effect of flattening by the pooling of riboflavin along the intacs segments

While a solution was being derived for strengthening corneas and reshaping, with ICRS and cxl, there were a subset of eyes with significant residual myopia and astigmatism which demanded a corrective measure.

Phakic Iols which were largely meant for treating larger refractive errors with its own stringent criteria came into the scenario but was questioned for treating the irregular KC corneas and their dubious outcomes. Early KCs,

topographically regularised corneas or centered cones came under the purview of Phakic Iols. A wait of 6 months to stabilize the topography and refraction following cxl seemed the ideal requisite to venture to debulk the residual refractive errors following Keratoconus progression with Phakic Iols and a larger stage was set for better KC management.

While contact lenses with their varied options remained as the preliminary options for KC management while watching for progression, they underwent reinvention with their hybrid options, piggy back contact lenses, Rose K lenses for smaller residual errors following ICRS and Phakic Iols too. The goal was to give the best to these visually hampered Keratoconus eyes and every nuance was better addressed.

Lots of thoughts, arguments and discussions fragmented the consistency and surieties of KC management when proponents came forth suggesting that rubbing of eyes was a major factor for KC progression and abstaining from rubbing was sufficient in controlling the disease.

There were these allergic eyes of young children wherein it became necessary to include topographic evaluation as a critical protocol to rule out KC and a whole new diversion / aggression in treatment strategy became necessary if KC was diagnosed .Some of these eyes came with limbal stem cell deficiency in advanced stages wherein one wondered whether cxl was possible at all unless we protect the limbus and not to mention the challenges of epithelial surface breakdown which challenged us to reconsider trans epithelial Crosslinking as the only possibility in these select cases.

Then came the last frontier when the visual axis was not clear in a KC patient with corneal scarring, highly distorted thin corneas and hydrops which needed corneal lamellar procedures. DALK in the present settings and its well established protocols came in to visually rehabilitate this lot of patients.

The results have been very encouraging with minimal risk of graft rejection but again the time of suture removal, how to visually rehabilitate these patients were the ongoing challenges.

Having said it all, today with the algorithm that is evolved for KC management, we are definitively on the right crossroad to a more optimal BCVA in these challenging eyes.

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Studies suggest a low risk of COVID-19 transmission from tears

Investigators from Singapore studied viral shedding and infectivity of tears among COVID-19 patients. None of the 17 patients presented with ocular symptoms, but 1 developed conjunctival injection and chemosis during the hospital stay. Of 64 tear samples collected between day 3 and 20 from initial symptoms, neither viral culture nor RT-PCR detected SARS-CoV-2. This contrasts with findings from a prior 30-patient study in which 1 patient had conjunctivitis. Only that patient had virus particles in their ocular secretions. Collectively, these studies suggest conjunctivitis is an uncommon complication of COVID-19, and that risk of disease transmission through tears is low. Ophthalmology, in press; Journal of Medical Virology, in press

Questionnaire on Astigmatism Management in Cataract Surgery

UPSOS Correspondent : **Mohit Khattri**
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Expert Panel

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Director,
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Trivandrum

Dr. Vinod Arora (VA)
Director,
Navjyoti Eye Hospital,
Dehradun

Dr. Mohan Rajan (MR)
Director,
Rajan Eye Care,
Chennai

Dr. Dharmendra Nath (DN)
Director,
Agre Eye Hospital,
Agra

Management of astigmatism in present day cataract practice is one of the frontline frontiers and toric IOLs are the proven gold standards for its management. In this issue, we have the opportunity to learn from the practice patterns of four eminent cataract surgeons across the country. Here we go...

Q.1: Do you change the location of main incision corresponding to steeper axis in routine phacoemulsification?

AC: No.

MR: Yes. I always make the incision in the steeper axis based on the keratometry.

VA: Any incision on cornea causes fllatenning on the axis of incision. An incision on steep axis can flatten 0.5 – 0.75 D of astigmatism with more than 2.4 mm incision. But with 2.2 mm or less longer incision, the effect may be less than 0.5 D. My incision site is fixed in all cases at 110*. If required I do make some changes but do not do temporal.

DN: In my routine phacoemulsification I always go along steep axis to reduce 0.50 - 1.00 D of astigmatism.

Q.2: Have you calculated your SIA (Surgically induced astigmatism)? If yes, then how?

AC: YES, Warren Hill site.

MR: Yes. I have calculated the SIA using my own data and doctorhill.com website. My SIA is 0.5 D.nowadays since I am using a 2.2 mm incision, it is the CENTROID VALUE (not SIA) which comes into play. Normal CENTROID value is around 0.2

VA: I used SIA calculator. In my case it is 0.25. It is avilable for free at www.doctor-hill.com Try first 50 cases and you will know your exact SIA.

DN: Yes. Its 0.60D

Post-op Ks – Pre-op Ks will give you SIA and adding the SIA to the pre op Ks will give you the Post op Ks on the next case. Toric IOL should always be aligned with the steepest axis of cornea.

Q.3: At what minimum astigmatism would you like to go for a toric IOL?

AC: I use barrett toric calculator for all cases and recommend a toric IOL if the formula suggests a toric lens.

MR: Minimum of 1.25 cylinder for Toric IOLs.

VA: I generally place toric IOL for astigmatism with the rule (WTR) more than 1.25 D, for and for against the rule (ATR) 0.5 D.

In most people WTR will drift to ATR gradually.

DN: 1.5D

Q.4: In your opinion, for a toric IOL, does the design of IOL matter (C loop Vs Plate haptic)?

AC: Yes

MR: In my opinion, the design of IOL does not matter for a Toric IOL.

Both C loop and plate haptic designs are equally good. Among the C loop, ACRYSOF TORIC is the probably the best as far as rotational stability is concerned.

VA: The C loop IOL has tendency for late rotation while plate haptics IOL are more prone for early IOL rotation. The realignment in plate haptic is more difficult.

DN: Plate haptic – during operation a little difficult to dial but post operatively we never encounter any rotation

Q.5: Do you practice LRI in your practice? If yes, then how?

AC: No longer after the advent of toric IOLs

MR: I do not practice LRI in my practice.

I do ASTIGMATIC KERATOTOMY (AK) using my femto CATALYS system for astigmatism less than 1.25 dioptres.

VA: Not as a primary procedure, but for the pseudophakes and refractive surprise following IOL surgery. One requires a micrometer diamond knife and pachymeter to do precise LRIs. It gives better results in hyperopic cylinder because of coupling effect.

The online nomogram can be downloaded at www.lricalculator.com

DN: No

Q.6: How do you place reference markings in your toric IOL patient (Air bubble vs Slitlamp)?

AC: Slit Lamp

MR: I use routinely use the MARKER LESS system,CALLISTO on my zeiss lumera 700 which is connected to the IOL MASTER.

If I have to mark, I use the SLIT LAMP for marking for my TORIC IOLs.

VA: I prefer slit lamp marking. I always take reading in sitting position, head staright and face aligned. The slit lamp is also checked for accuracy by using smartphone axis assistant or BRC Axis Toric Marker from Joja surgicals. I ask the patient to blink 2-3 times before taking reading.

DN: To me slit lamp marking is perfect. Slit passes through visual axis and very much in your control. I make a thin horizontal slit, make it to pass through the centre of cornea, ask the patient to see the light, head is fixed with the help of head band don't ask assistant to hold. Mark at the ends of the slit on clear cornea.

Q.7: What are the two most precious surgical pearls you would like to give readers for toric IOL surgery?

AC: Proper axis marking and Proper IOL alignment

MR: SURGICAL PEARLS

1. Consistent circular centric capsulorhexis (5 mm)
2. Removal of viscoelastic from behind the IOL in Toto

VA: When initially implanting IOL, leave the IOL 20* short of target axis. Then do the fine adjustments.

Be sure to remove all of the viscoelastic from behind the lens or better use hydro implantation.

DN: Proper reference and axis marking, removal of visco from behind the optics, Air in A/C to make close apposition of IOL against Posterior Capsule.

Q.8: What's your experience with toric multifocal implants?

AC: Satisfactory

MR: TORIC MF

Good experience

Implanted more than 500 till date.

Excellent results

Very happy patients (ReStor ,TMF,Acrilisa)

VA: I have done some cases. My number is gradually increasing with advancement in technology. Getting a perfect result and satisfied patient is not easy as the two variables have to be perfected in ideal patient. One should try toric MFIOL after perfecting MFIOL and toric IOL implantation separately.

DN: Considering angle Kappa and angle Alpha patients land on comfortable platform but do not get 100%.satisfaction. Toric EDOF and Zeiss AT LISA are result oriented IOLs.

Q.9: If there is discrepancy between patient's refraction and Keratometry readings, then how do you go about it?

AC: I use barrett toric calculator which factors in the posterior corneal astigmatism

MR: I always go only by keratometry readings and not the refraction.

The refraction may be lens induced.

VA: The most crucial part of procedure is determining the

exact axis as accurately as possible. Measurements should be done before putting anaesthic or dilating drugs. Contact lens should be discontinued two weeks before the checkup. Make sure that two Ks are 90* apart. Always repeat the measurments for verification. Inconsistent keratometry readings are commonly caused by a poor tear film and dry eye syndrome.

The refraction inculdes total astigmatsim that includes lens also. In lenticonus and catarctous lens the K reading and refraction may not coincide. Since we are removing natural lens, the keratomery reading are reliable.

DN: Patients refraction I don't consider it. I consider only keratometry. Lenticular astigmatism is waved off in cataract surgery.

Q.10: Which tool do you trust most for keratometry in toric IOL cases- Autorefractokeratometer(ARK)/ Optical biometer/Pentacam? Why?

AC: Topographer for axis and optical biometer for magnitude of astigmatism

MR: OPTICAL BIOMETER

esp.LENSTAR

LENSTAR is the only machine which gives a 2 zone Keratometry (2.3 mm& 1.65 mm).Also 648 point measurements.

Most accurate keratometry only with LENSTAR.

VA: If there are discrepancies between the readings, I tend to rely on manual or automated keratometry for the magnitude of the astigmatism, and topography for the axis.

DN: We do assay with Autorefkeratometer and also with Optical biometer

Manual Keratometer ------- OK

MK+ARK -------Good

ARK+Opti.Bio(IOLmaster)----Excellent

If you have topographic value it adds to your confidence. Everyone does not have it.

Q.11: With toric IOL what's your preference-Injection of IOL under BSS or under OVD?

AC: OVD

MR: I always implant TORIC IOLs under OVD. I prefer cohesive viscoelastic like HEALON since it expands the CAPSULAR bag and also easy to remove.

VA: I prefer to do hydro implantation for toric IOL. The advantages are – lower risk of TASS, lower risk of IOP spikes following surgery, lower risk of IOL rotation post oprative period, less manipulation inside the chamber.

If one wants to use viscoelastic, it is better to use cohesive visco, which comes out as bolous and chances of retained viscoelasic is less.

DN: Under OVD it facilitates rotation in bag.

Q.12: What's the follow up schedule for your toric IOL patient?

AC: Non ambulatory for 1 hour.. rest routine like any other postop situation.

MR: FOLLOW UP on:

DAY 1

DAY 7

DAY 30

All patients are dilated at day 7 to confirm the axis of location of the IOL.

Also I keep the Toric IOL patients for 1 to 2 hrs after surgery in the supine position. Always check the axis on slit lamp before discharge.

VA: The follow up is very important. At the table I confirm the IOL alignment before sending the patient out. On very next day we record the vision and see if there is any misalignment. The follow up visits are after one week and one month.

DN: They come on 2nd day 10th day and 30th post operative day and keep monitoring on VA and astigmatic fan. After 45 days I allow them for mild outdoor games.

COVID and Eye- What is Known Till Now?

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First case was reported in India from Kerala on January 30, 2020 in a student who had a travel history to Wuhan, China. Subsequently, there has been a sharp spurt, with total number of cases reaching to 5,734 as on the date of writing the article.

WHO has suggested that similar to SARS, COVID-19 also spreads through human to human transmission through droplets, contact and fomites.[1] It is estimated that the number of cases directly produced by one person, in population susceptible to infection for COVID-19 is 2.2% with the epidemic doubling time of 6.4 days.[2,3] It is suggested that transmission occurs during the asymptomatic incubation phase[3]. Person-to-person transmission can occur even in the presence of isolation.[4,5] There is also a risk of environmental contamination[6] hence, strict adherence tohand and environmental hygiene is required[6]. The virus has also been found on the surface of door handles, cell phones and other possessions in residence of confirmed cases.[1] It has also been found in the stools of infected persons.[7] It has been suggested that touching eyes, nose or mouth after contacting the contaminated items can also cause infection.[8] It has not been confirmed yet if vertical transmission of virus can occur and it has not been found in the breast milk of infected mothers either.[8]

Reports suggest conjunctivitis can present as the first symptom of COVID-19.[9,10] In a study published in New England Journal of Medicine, conjunctival congestion was documented in 9 of 1099 patients (0.8%) with laboratory confirmed COVID-19 from 30 hospitals across China[11,12]. Tear samples from these patients were not evaluated.

Reports also suggest that in the absence of eye protection transmission can occur by aerosol contact with conjunctiva.[9,10] On January 22nd, it was reported that Guangfa Wang, a member of the national expert panel on pneumonia, was infected during an inspection in Wuhan. He wore an N95 mask but no eye protection. He had developed conjunctivitis several days before the onset of pneumonia, implying that unprotected exposure of the eyes to the virus in the Wuhan fever clinic may have been the source of his systemic infection.[9]

A retrospective study of patients treated with COVID 19 from February 9 to 15, 2020 at a Centre in Hubei province, China was reviewed for ocular manifestations[13]. It was found that one-third of patients had ocular signs and symptoms, which frequently occurred in patients with more severe COVID 19 infection. Low prevalence of SARS Cov-19 was found in tears, but it was concluded that it was possible to transmit the disease via eyes. A total of 12 of 38 patients had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora and increased secretions. Among these 12 patients, 4 cases were judged as moderate, 2 were severe and 6 were critical patients which was graded according to guidelines of PC-NCP[14]. In these patients, 1 patient experienced epiphora as the first symptom of COVID-19. None had blurred vision. By univariate analysis, it was found that patients with ocular symptoms were more likely to have higher white blood cells and neutrophil counts and higher level of procalcitonin, C- reactive protein and Lactate dehydrogenase than patients without ocular symptoms. Also, 11 out of 12 patients with ocular abnormalities had positive results of SARS-Cov-2 on RT-PCR from both conjunctival and nasopharyngeal swabs. These results suggest that ocular symptoms commonly appear in patients with severe pneumonia. The American Academy of Ophthalmology (AAO) has updated interim guidance for triage of patients under the care of an ophthalmologist and its recommendations on appropriate personal protective equipment (PPE) for ophthalmic use.

In Journal of Medical Virology, a study of 30 patients hospitalized for COVID-19 in China revealed that 1 patient had conjunctivitis. The particular patient also tested positive for RNA in ocular secretions and not the other 29. This suggests that SARS- Cov- 2 might infect the conjunctiva and cause conjunctivitis, and that infectious viral particles might be present in tears of COVID-19 patients with conjunctivitis.[12]

In a study by Zhang et al of 72 confirmed COVID-1 9 patients at Tongji Medical College, 2 patients had conjunctivitis. One of the 2 with conjunctivitis had RNA in tears.[12]

In a paper by Zhou et al. of 63 confirmed COVID-19 patients in Wuhan, 1 had conjunctivitis, but the conjunctival swab was negative for viral RNA. Another patient with no clinical conjunctivitis had conjunctival swab positive for RNA and 2 were "probable".[12]

In a story from CNN, a nursing home in Washington Statereported that red eye was a common early sign in elderly COVID positive patients.[12]

A recent study published by Shaoqing Lei et al[15]. in China focusses on Clinical characteristics and outcomes of patients who underwent various elective surgeries in different hospitals across Wuhan while they were in incubation period of COVID-19. They examined a retrospective cohort of 34 patients who developed symptoms quickly after completion of surgery and eventually tested positive for COVID-19. One of the 34 patients underwent eye debridement. It was found that patients developed symptoms 2-6 days after surgery. Also, the median time for onset of severe complications and death was shorter than other patients who had not undergone any surgical procedure. 15 of these 34 patients needed ICU care and mortality was 20.5%. Most common complication in non-survivors was ARDS, shock, acute cardiac injury and arrhythmia. Thus, it was concluded that surgery may accelerate and exacerbate disease progression of COVID-19. Although no co-relation was done for type of surgery with outcome.

A study published in China assessed the magnitude of mental health outcomes and associated factors among health care workers treating patients of COVID-19 in China[16]. It was a cross sectional study of 1257 health care workers in 34 hospitals with fever clinics and wards for patients with COVID-19 across China. A considerable proportion of health care workers reported symptoms of depression, anxiety, insomnia and distress; especially women, nurses, those in Wuhan and front line workers directly engaged in diagnosing, treating or providing nursing care to patients with suspected or confirmed COVID-19. This suggests that psychological support interventions may be required for front line workers with higher associated risk factors.

This also suggests that these factors may also cause psychological impact on ophthalmologists. A patient might seek consultation for ophthalmic complaint while being in incubation period and this may cause depression, distress or anxiety amongst treating consultant. In long course, this can also cause economical impact.

AAOhas issued Interim guidance for triage of ophthalmology patients [12]

S. No.	Clinical Situation	Patient management/ Precautions
1.	Routine ophthalmic issues and previously scheduled appointments	• Routine problems should be deferred and previously scheduled appointments to be cancelled • Appointments should be rescheduled only upon clearance from public health authorities • Refill all necessary medications
2.	Urgent ophthalmology appointment for a patient with no respiratory illness symptoms, no fever and no COVID-19 risk factors	• Standard precautions • Added precautions of not speaking during slit-lamp examination • Use of surgical mask and eye protection in setting of adequate PPE supplies for clinician and patients may reduce pre-symptomatic transmission
3.	Urgent ophthalmic problem in a patient with respiratory illness symptoms, but no fever or other COVID risk factors	• Can be seen in eye clinic • Place in an examination room immediately with door closed with a surgical mask. • Treating ophthalmologist and other personnel require surgical mask at minimum. • Gown, gloves, surgical mask and eye protection are recommended for the clinician. An N-95 mask should be worn if a procedure is planned that will result in aerosolized virus. • The examining room must be disinfected after examination
4.	Urgent ophthalmic problem in a patient who is at high risk for COVID-19	• The patient is best sent to the ER or other hospital-based facility equipped to evaluate for and manage COVID-19. • If the patient has an urgent eye problem based on screening questions, the facility should be one that is equipped to provide eye care in the hospital setting. • If SARS-CoV-2 infection is confirmed, CDC (or hospital) guidelines for care of suspected COVID-19 patients should be followed for health care facility preparation and infection control.

		• Eye care is best provided in the hospital setting. Transmission precautions‡ for treating ophthalmologists include wearing a surgical mask, gown, gloves and eye protection (face shield or goggles, if available).
5.	Urgent ophthalmic problem in a patient with documented COVID-19 (or person under investigation [PUI])	• The patient should remain in the hospital setting if possible. • Determine whether the eye problem is urgent based on screening questions, and if so, evaluation and management should be in the hospital setting. • If the patient is not hospitalized at the time of referral, the patient is best referred to the ER or other hospital-based facility equipped to manage both COVID-19 and eye care. • CDC or hospital guidelines should be followed for care of COVID-19 patients. • Transmission precautions† for treating ophthalmologists include wearing an N-95 mask, gown, gloves and eye protection (face shield or goggles, as above).

‡Standard (Universal) Precautions: Minimum infection prevention precautions that apply to all patient care, regardless of suspected or confirmed infection status of patient, in any health care setting (e.g., hand hygiene, cough etiquette, use of PPE, cleaning and disinfecting environmental surfaces).

*** Supply permitting, tight-fitting goggles may be preferable to face shields for eye protection.*

Thus, Ophthalmologists may be the first health care providers to evaluate patients potentially infected with nCOVID 19. Hence, the proximity between ophthalmologists, health care provider and patients during examination, evaluation and treatment procedures may pose a direct risk of cross infection to other patients as well as to health care workers. The risk is higher with unsuspected asymptomatic patients with subclinical infection.[17] Routine aerosol generating procedures like non-contact tonometry should be avoided and tonometry tip should be cleaned after each case.[18] It has been suggested to avoid general anesthesia, but if unavoidable, it is advised to use PPE during the procedure.[19] To lower the risk of droplet transmission, a protective shield should be installed on slit-lamps.[20] Equipment like slit-lamps, ophthalmoscopes, computers and doorknobs that are frequently touched by the staff should be disinfected as per local disinfection guidelines.[18] Personal meetings should be deferred wherever possible and replaced by virtual communications. The staff should be instructed to wash hands frequently as per hand hygiene guidelines recommended by WHO.[20]

Hence, it is imperative that understanding of ocular manifestations of COVID by ophthalmologists may facilitate early diagnosis and prevention of transmission of the disease.

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Answer to Quiz No.3

Foram Desai, MS

1. Located in periphery of iris
2. Associated with Vitamin A defieciency
3. Feature of CRAO
4. Accumulation of axoplasmic material in nerve fibre layer
5. Ischemic infarcts of choroid
6. Senile scleral plaque
7. Myopic retinopathy
8. Epithelial opacities anterior to suture line of corneal graft
9. Anterior remnant of hyaloid artery at posterior surface of lens
10. Seen on FFA
11. Retinal hemorrhage with pale centre
12. Associated with POHS

A	C	N	I	L	E	F	K	P	S	X	C	S	G	Q	L	Z	G
Y	H	Z	N	D	C	G	Y	H	Y	F	Q	O	D	W	R	F	Z
V	E	P	B	I	T	O	T	Z	N	W	N	E	Y	Z	S	I	N
U	R	A	X	L	Q	B	N	K	S	E	V	B	Q	U	T	S	U
G	R	I	B	N	J	F	D	B	L	H	M	O	Z	X	K	C	P
X	Y	H	Q	P	G	R	O	K	M	L	I	Z	A	M	I	H	J
X	R	K	I	J	B	T	G	J	Q	N	P	S	L	V	Y	E	F
T	E	L	S	C	H	N	I	G	A	T	Z	B	T	C	L	R	W
F	D	Y	M	B	R	L	Q	U	E	Y	D	H	M	O	K	K	I
O	T	O	Q	L	E	K	V	X	Z	A	U	J	Z	T	X	H	D
C	L	M	I	T	T	E	N	D	O	R	F	B	V	T	S	U	K
R	C	W	H	D	X	O	R	S	K	Q	O	P	S	O	G	N	R
W	M	E	O	M	E	M	Y	H	I	M	S	T	Y	N	Y	T	H
P	D	L	J	R	L	Z	G	P	F	W	T	X	H	W	R	X	S
S	Q	A	D	B	H	R	M	F	L	K	E	M	T	O	V	M	K
L	M	N	E	O	R	L	E	O	P	A	R	D	C	O	W	T	P
H	F	U	R	I	S	U	T	W	N	Z	F	H	R	L	U	Q	G
R	M	K	A	Y	E	P	H	T	E	L	U	S	F	Y	X	Z	L
O	P	I	L	Z	X	O	M	L	Q	N	C	Z	O	T	F	N	X
U	N	P	T	D	Z	V	B	R	U	S	H	F	I	E	L	D	Y

Corona – The Testing Conundrum

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Right since the time Corona has emerged on the global scene there is one thing which has been discussed time and again; how much to test for Corona.

Currently the Govt of India (GOI) is being consistently blamed for testing less.

To understand the rationale of how much to test we will have to understand how this testing actually works at the Community level.

Before looking for options in testing we must considerthe fundamental concept that,

There is no perfect Test.

You can have a test that is accurate to a very high degree but "never 100% accurate".

So inevitably every test we will do will have a certain percentage of,

1. False Positives – test showing the case as diseased where disease is absent and

2. False Negatives – test showing the case as free from disease where it's actually present

Another concept which must be understood is that of "Prior Probability" or "Prevalence".

How accurate or reliable a test isalso highly dependent on the prior probability that someone being tested actually has the disease.

This is such a fundamental concept in Medicine that it is safe to say that,

All tests are meaningless without a fair degree of suspicion for the presence of a disease.

Ok, so enough of concepts.

Now let's do some number crunching.

If we take a random personin an area and decide to test him, the "Prior Probability" that he has the disease is the overall incidence of that disease in the region defined as "Prevalence". Let's assume for now it's 1% which is of course a presumption on the higher side for an early stage of an Epidemic.

Let's assume we have a very highly accurate test too. We assume that this Test will have just 0.1% False Positive and 0.1% False Negative Results.

Meaning that such test will have 99.9% accuracy or it will detect 999 out of 1000 cases meaning thereby only 1 in 1000 with the disease will be marked asnot having the disease.This is its False Negative Rate.

Being very accurate let's also assume thatthe test will showonly 1 in 1000 as falsely having disease where they are actually free from it. This is its False Positive Rate.

Now let's see what happens if we use this test on a community.

Random Testing

Let's start with 100,000 random people. Statistically, 1000 of them have the disease as Prevalence of disease is 1%.

Now out of these 1000 positive cases,

This test will mark 999 as "having the disease" but 1 also as "having no disease". This is False Negative Error.

Among the other 99,000 Negative cases,

This test will mark 99 as "having the disease" and the rest as "having no disease". This is False Positive Error.

So if the test says "Positive for disease", what is the likelihood that the tested person actuallyhas the disease?

It will be 999 / (999 + 99).

Or 10/11

Or91%

So when you test "randomly", 1 in 10 people you find positive are actually not positive for the disease. And please note that this happens with a highly accurate test.

Focused Testing

What if we were to test more carefully and become more selective?

What if we test only population who have higher "Prevalence"?

I.e., Populations of hotspots or thedirect contacts of known infections or those having respiratory infections (like SARI testing done by ICMR).

Let's assume a Prevalence of 10% in a population of 100,000.

Now, out of our population of 100,000, people having the disease will be 10,000.

Out of these 10,000 Positive cases,

This Highly Accurate Test will mark 9990 as "having the disease" and 10 as "having no disease".False Negative Error.

Of remaining 90,000 Negative Cases,

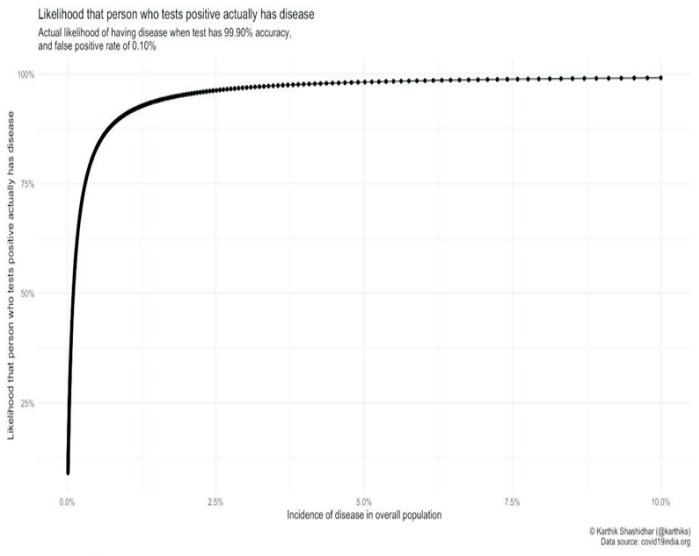
Test will mark 90 as "having the disease" and 89910 as "having no disease".False Positive Error.

So if the test says "having the disease", what is the likelihood that the tested person is actually having the disease?

9990/ (9990+90) or 99.1% of people marked out by the test as "Positive for disease" will actually have it.

And these results are with the assumption that the Test is highly accurate (1 in thousand errors, positive or negative). Graph in Figure 1 shows the likelihood of person actually having the disease is a function of the prior probability of having the disease in a given population being tested.

Figure 1



It can be clearly seen that the accuracy of final results are highly sensitive to the prior probability of having the disease.

Higher the Prevalence of the disease, the higher is the final accuracy of the test.

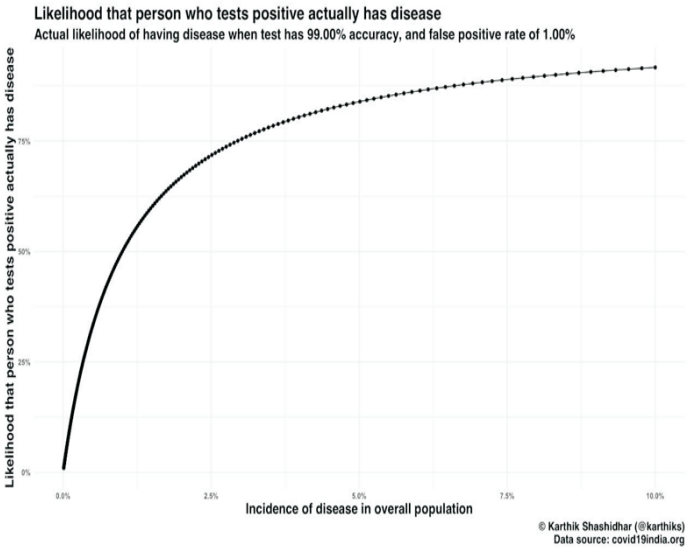
Now the problem is that we do not know the actual prevalence of the disease especially in the beginning of an Epidemic. (PROBLEM 1)

What Happens If The Test Is Less Accurate?

Now let's assume the test is not that accurate. Let's assume it is 99% accurate or wrong once every 100 times or 1% False Negative. Let's also assume a 1% False Positive rate.

The curve now looks very different.

Figure 2



We can see that final results become even less reliable.

Now another problem is that we also don't know the exact accuracy of the tests for Covid-19. (PROBLEM 2)

It's impossible to put a number on it since it's a new disease. We are reasonably certain of the accuracy of the PCR testing but that of Antibody tests are anybody's guess.

Infact it can be shown that if we keep the numbers realistic and assume that False Positive Rate of the Test is 1% and the Prevalence of the disease is 0.05%, as would be the case in early phase of Epidemic, the Test will be Wrong 95% times!

And this will give us a massively wrong picture.

So the correct strategy in this case is to test where the prior probability is already highand with your best possible test. This will give us the most accurate picture of the disease in the society.

GOI is thus using, PCR Test for COVID-19 and testing only those,

Who have travelled abroad

Who have come in contact with infected people

Who have respiratory illnesses

Who havetravelled to Delhi in a certain religious congregation.

And the criteria are being consistently expanded.

Knowledge regarding COVID-19 is being gained very fast. New tests are coming up but releasing these tests on the population without exactly knowing their fallacies would cause mayhem.

This is also the reason why all agencies whether in US or Europe or in India are taking so much time to validate newer tests.

Hence we can very safely say that, This idea of Test, Test and Test is not without its pitfalls.

And we must trust the ICMR/GOI/Other Regulatory agencies which are trying to find the best possible way out of this testing conundrum.

Credits: Data has been taken from different Books, websites,Mr Karthik Shashidhar's graphs which are based on data fromwebsite www.covid19india.org, and material and news available onMainstream and Social media.

Review on Covid-19-A Novel Virus-Ocular Implications

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Abstract: In 1960 human coronaviruses was discovered.1First study was from human patients with the common cold, and later was known as human coronavirus 229E and human coronavirus OC43.2]Corona virus causes respiratory infection including pneumonia, cold, sneezing and coughing while in animal it causes diarrhoea and upper respiratory diseases. Transmission of corona virus is from human to human or human to animal via airborne droplets. In human cell through membrane ACE-2 exopeptidase receptor enters corona virus. CoVs known to cause various ocular infections in animals. Clinical entities such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis have been documented in feline and murine models. WHO has advised to avoid public place and close contact to infected persons and pet animals. Corona virus (2019-nCoV) was isolated from Wuhan market China at 7 Jan. 2020.

Keywords: Corona virus, COVID-19, MERS-CoV, SARS-CoV, Wuhan

History and Origin

Corona virus first case was identified as cold in 1960. In Canadian study 2001, approximately 500 patients were identified as Flu-like system. 17-18 cases of corona virus strain was confirmed as infected by polymerase chain reaction. Till 2002 Corona was considered to be as simple non fatal virus. Various reports were published in 2003 with the proofs of spreading the corona to many countries such as United States America, Vietnam, Singapore, Hong Kong, Thailand and in Taiwan. In 2003, several cases of severe acute respiratory syndrome was caused by corona and more than 1000 patient mortally was reported. This was the black year for microbiologist. When microbiologist was started focus to understand these problems. In 2004, "state emergency"was declared by World health organization and centers for disease control and prevention[3-5]. In 2012, Saudi Arabian reports were presented several infected patient and deaths. COVID-19 was first identified and isolated from pneumonia patent belongs to Wuhan, china.[6–7]

Microbiology

Corona virus is spherical or pleomorphic, single stranded, enveloped positive sense single stranded RNA and covered with club shaped glycoprotein. Corona viruses are four sub types such as alpha, beta, gamma and delta corona virus. Each of sub type corona viruses has many serotypes. Some of them were affect human of other affected animals such as pigs, birds, cats, mice and dogs.[8-12]

Mode of Spreading

Peoples can get the infection through close contact with a person who has symptoms from the virus includes cough and sneezing. Generally corona virus was spread via airborne zoonotic droplets. Virus was replicated in ciliated epithelium that caused cellular damage and infection at infection site.

According to a study published in 2019, Angiotensin converting enzyme 2 (ACE.2), a membrane exopeptidase in the receptor used by corona virus in entry to human cells.[12-14]

Characteristics

Corona virus infected patient have many common features such as fever, cough, and fatigue while diarrhea and dyspnea were found to be as uncommon feature report published on 24 jan 2020. Bilateral abnormalities were reported in many patients. In china in 2020 Corona virus was isolated from bronchoalvelor lavage fluid. It is also detected in blood samples. Till now, corona virus was not confirmed in feaces and urine sample of patent.[15-17]

Ocular Implications in Humans and Animals

World Health Organization (WHO) on 30th January has declared a public health emergency of international concern (PHEIC).[18] On the experience of MERS-CoV and SARS-CoV a set of recommendations for personal protective equipment (PPE) based have been released.[19] This set of recommendation includes wearing goggles or face shield for protection against ocular transmission of the CoV. Evidence of ocular transmission has still not been well studied. On the other hand, CoV ocular infection has been well established in various animals. In some cases, such as CoVs which affect the murine and feline orders, they can cause sight-threating ocular complications. The feline CoV (FCoV) is an Alpha corona virus that affects both domestic and wild cats. The murine CoV mouse hepatitis virus (MHV) is a collection of strains that demonstrate very different organ tropisms. Such evidence suggests that CoVs can shed and even infect ocular issues. To

understand the ocular manifestation of human CoVs more research has to be done.

Health-care professionals are of great concern who has highlighted the presence of SARS-CoV RNA in tears. In 2004, tear samples were collected from suspected SARS-CoV patients and were sent for RT-PCR for the SARS-CoV. The findings of this study suggested that SARS-CoV can be present in tears and emphasized the need for appropriate precautions to prevent transmission through ocular tissues and secretions.[20] However, up till today, it is still unclear how SARS-CoV can end up in tears. Proposed theories include the conjunctiva being the direct inoculation site of SARS-CoV from infected droplets, the migration of upper respiratory tract infection through the nasolacrimal duct or even hematogenous infection of the lacrimal gland. Furthermore, the results were inconsistent across studies. Another study that assessed both tears and conjunctival scrapings from 17 patients with confirmed SARS-CoV infection did not yield any positive result from RT-PCR. The authors attributed the findings to three possibilities. Firstly, the RT-PCR was not sensitive enough to pick up small quantities of SARS-CoV RNA. Secondly, the sample collection was a one time process, which may have missed the window if viral shedding in ocular tissue only lasted for a short period of time. Finally, there is also the possibility that the SARS-CoV did not exist in ocular tissue. However, as the SARS-CoV epidemic died down, these crucial questions were left unanswered.[21,22]

Clinical Progression-Diagnosis

Human CoVs leads to cold-like upper respiratory infection and self-limiting lower respiratory infection before SARS-CoV cases . By the isolation of SARS-CoV from a patient with pneumonia in China the first death due to coronaviruses was reported. Similarities present in the clinical aspects of COVID-19 infections as observed in other respiratory infected viruses and previous beta-CoV, it is known that clinical picture varies from simple respiratory infection findings to septic shock. Similar to SARS CoV and MERS CoV that caused epidemics in the past years, the first symptoms are commonly defined as fever, cough, shortness of breath. [23] Intestinal symptoms were rarely reported in patients with COVID-19 and diarrhea was observed in about 20-25% of patients with MERS-CoV or SARS-CoV infection . On X-rays or thorax CT imaging of the examined patients, unilateral or bilateral involvement compatible with viral pneumonia was found, and bilateral multiple lobular and subsegmental consolidation areas were observed in patients hospitalized in the intensive care unit.[24]

Lab Diagnosis

Throat-swab and Nasopharyngeal specimens from the upper respiratory tract were obtained from all patients at admission/suspected were collected in viral-transport medium whose temperature should be maintained between 2-8℃. These samples are triple layered packed in thermocol box . 2019-nCoV was confirmed by real-time RT-PCR using the protocol of ICMR. The sample then sent to nodal center KGMU for testing of Covid-19.

Prevention

According to WHO, separate the infected patient from other family member to single room, implementation of contact and droplet precaution, airborne precaution etc. European Centre for Disease Prevention and Control (ECDC) also published the information leaflet to peoples i.e. Avoid contact with sick people, in particular those with a cough. Avoid visiting markets and places where live or dead animals are handled, Wash your hands with soap and water or use an alcohol based disinfectant solution before eating, after using the toilet and after any contact with animals, Avoid contact with animals, their excretions or droppings.[25,26]

Conclusion

Corona virus spreads in human to human transmission by close contact via airborne droplets generating by coughing, sneezing, kissing and smooching. Such activities should be avoided with infected partners and family members. Corona virus may transmit through pet animals such as dog, cat, pig, cow, turkeys. So avoid contact and separate them if observed any infection activities like diarrhea, cold, fever. Avoid contact with sick person and also avoid the market or public place as per possible as per WHO and ECDC guideline . There are no anti corona virus vaccine to preventor treatment but some supporting therapy work. As CoVs can cause ocular infection across different animals, the possibility of SARS-CoV-2 having ocular implications cannot be ignored. However, the examples in animals also highlight that CoVs are a heterogeneous group of viruses that can cause ocular implications through a wide variety of mechanisms. Some of these mechanisms are extremely different from those adopted by human CoVs. CoVs are responsible for producing a wide spectrum of ocular manifestations from anterior segment pathologies like conjunctivitis and anterior uveitis to sight-threatening conditions like retinitis and optic neuritis. It may also be prudent to recognize that CoVs can also develop in-vivo mutations which drastically alter the manifestations of the disease. Ophthalmologists and other health-care workers should continue to prevent the possible transmission of CoVs through ocular tissue. Future research needed to fight with corona virus. Till then only 'Distance is rescue'.

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Revisiting Ocular Effects of Hydroxychloroquine

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Hydroxychloroquine (HCQS), the antimalarialdrug is an invaluable drug used for the management of chronic rheumatic disease. The active component of drug is the quinoline alkaloids quinine and quinidine obtained from the bark of cinchona tree. The therapeutic efficacy of this drug for arthritis was confirmed during the time of World War II.[1] Recently, HCQS has been approved by the US Food and Drug Administration for the treatment of systemic lupus erythematosus (SLE), polymorphous light eruption, and rheumatoid arthritis.[2]

The adverse effects of HCQScan range from neuromyotoxicity, cardiotoxicity and ocular toxicity. Ocular toxicity can manifest as a non-significant keratopathy to a potentially blinding retinopathy.[3,4] Ocular toxicity was first reported by Cambiaggi in 1957[5] in a patient with SLE who was on treatment with chloroquine. The earlier reported prevalence of retinal toxicity was 1-3% using visual fields and fundoscopy as the diagnostic tools. However, with the advancement of the new diagnostic tools such as multifocal electroretinography (mfERG), optical coherence tomography (OCT), and fundus autofluorescence (FAF), the early changes can be detected often before the patient's symptoms. Therefore, the recent literature reported the prevalence of toxicity to be 7.5% in patients who were on HCQS for at least 5 years.[6]

Mechanism Of Ocular Toxicity:

The mechanism of HCQS toxicity is not well known. The slow and chronic damage caused by HCQS toxicity is still under research. HCQS bind to melanin in RPE leading to prolonged toxicity. However, clinically the primary site of damage is photo receptors followed by secondary disruption of RPE. The parafoveal and extramacular localization of damage could not be related to any anatomic pattern of retina. HCQS and chloroquine have bioavailability of approximately 70%. They are deposited in the tissues; which may persist for up to 5 years.[7]

Clinical Presentation:

Commonly affected ocular structures with HCQS include the cornea and retina.

Cornea: Corneal verticillata is more common with chloroquine than HCQS at recommended doses and is directly related to higher dosage. Patient may complaint of halos and photosensitivity with the corneal deposits all of which are reversible upon discontinuation of the drug.

Retina: The most dreaded complication however is the retinopathy which can result in permanent visual loss.[8] The patient is asymptomatic initially with no detectable fundal abnormalities. Initial screening tests i.e. visual fields examination may show decrease retinal sensitivity in central 10 degree area with perifoveal thinning of outer retinal layers on OCT suggestive of early retinopathic changes. In cases where initial screening tests are doubtful, the gold standard objective test mfERG may aid in early diagnosis. Characteristic findings include decreased photoreceptor function in a ring shaped pattern around the fovea.[9]

The advanced form of HCQS toxicity is characterized by a classical bilateral 'Bull's-eye maculopathy', an appearance caused by a ring of parafoveal RPE depigmentation that spares a foveal island. Attenuation of retinal arterioles and optic disc pallor may be evident in advanced cases.

The earliest functional changes occur paracentrally. As such the central vision is not affected so the patient is asymptomatic. The damage is progressive and irreversible; thus persisting even after the discontinuation of the drug[6]. However, the Asian population may not present with the classic bull's eye pattern of para central visual field loss. Visual field changes in these patients may extend beyond the central 10degree, thus emphasizing on the need of wider range of visual field testing.[10]

Dosage And Duration:

The daily dose recommendation for HCQS treatment of rheumatic diseases has recently changed from 6.5mg/kg lean body weight to 5 mg/kg total body weight for patients without additional risk factors, with a maximum of 400mg during the first 5 years of treatment.[6]

However, there has been a debate whether to use ideal or real body weight for calculation of the HCQS dose. Because HCQS distributes poorly in fatty tissues,[11] the initial literature shows that the risk happened to be much greater in thin/lean individuals whenever calculated with the ideal body weight. Thus, later it was suggested that the dosage should be calculated by ideal body weight to reduce the theoretical risk of

overdosing obese patients. Melles and Marmor in their case series showed that the risk at a given dose per kilogram was actually more closely correlated with actual weight than ideal weight.[6] According to their observation, the prevalence of retinal toxicity in relation to milligrams per kilogram of actual bodyweight was essentially independent of body habitus, whereas the risk multiplied in thin individuals if the dose was calculated using ideal body weight. Their study also concluded that there was an increased risk of developing retinal toxicity if the average daily dose exceeded 5mg/kg.

Risk Factors:

Since HCQS is excreted through the body majorly by kidneys, renal insufficiency accounts for the most important risk factor for increasing the ocular toxicity[12]. Melles and Marmor reported twice the risk of retinopathy in individuals who had glomerular filteration rate (GFR) of less than 50%.6 A multivariate analysis by a french PLUS study13 also showed a statistically significant lower blood concentration of HCQS in patients with higher Creatinine clearance (CrCl) as opposed to patients with renal insufficiency having low CrCl.

Tamoxifen, a selective estrogen receptor modulator(SERM) commonly used in the treatment of breast cancer has been known to cause central macular changes in dose dependent pattern.[14] HCQS if prescribed to a patient on treatment with tamoxifen can significantly increase the risk of retinopathy by their synergistic action on retinal cells.[15]

Pre-existing retinal and macular disease may impede early detection of the retinopathy thus increasing the risk of toxicity. However there is no conclusive evidence to suggest the increase risk of toxicity in these patients. Therefore, these patients should be screened more frequently.[6]

Screening Tools:

According to the current guidelines from the American Academy of Ophthalmology for screening patients on HCQS, the patient should be screened using one objective test in addition to visual field testing (subjective test), because recent literature shows that the central visual fields defects can present before any evidence of structural abnormalities.[16-17]

- Amsler Grid: Use of a red Amsler grid or red target for visual field testing is recommended for initial screening.

- HVF:The most sensitive and commonly used subjective test for monitoring HCQ toxicity is Automated Humphry visual field (HVF) testing using central 10-2 protocol.

The patient may show a paracentral scotoma early or a ring scotoma in advanced cases. As mentioned previously, a wider testing field using HVF 30-2 or 24-2 should be used in Asian population. Since visual field testing is a subjective test, the findings must be corroborated with an objective test.[18]

- SD-OCT: The most commonly used objective test is Spectral-domain OCT (SD-OCT) which enables early detection of the structural abnormalities by providing the cross-sectional images of the macula. Characteristics findings include parafoveal changes and thinning or loss of photoreceptor layers, a "preclinical" stage where the photoreceptor inner segment-outer segment (IS/OS) junction appears "moth-eaten" due to preferential loss of cone photoreceptors.[19]

'Flying saucer sign', has also been described as preservation of the outer retinal structures in the central fovea, perifoveal loss of the photoreceptor IS/OS junction, and outer retinal thinning.

A wide field SD-OCT should be used for screening the Asian population to detect the extramacular changes.

- mfERG : The most sensitive objective test for detecting the early HCQ retinopathy even before visual field changes is mfERG. It measures bioelectric signals from photoreceptors to elaborate depressed retinal sensitivity. It is now considered the gold standard for confirming HCQretinopathy in patients showing abnormal findings on other screening tests.[20]

Fundus auto flourescence (FAF): FAF is another objective test which can be used for screening.21An increased ring of signal within the parafoveal and perifoveal regions, which is indicative of photo receptor dysfunction and RPE abnormalities is noted on FAF.

Why To Screen?

HCQS is a widely used drug for various autoimmune and inflammatory conditions with fewer side effects than its available counterparts. The ocular damage caused by HCQS is irreversible even if the drug is discontinued. However, if the retinopathy is recognized at an earlier stage before RPE damage has occurred, the progression can be limited by discontinuing the drug and hence loss of visual acuity can be prevented. Thus the pattern of damage should be recognized at the earliest and verified either by different or repeated testing of the same screening modality.

Screening Guidelines:

The following screening guidelines should be followed as proposed by American Academy Of Ophthalmology in their 2016 revised guidelines[6] :

1. The patient should be screened within one year of starting HCQS to establish a baseline testing results using HVF and SD-OCT and any pre-existing retinal and macular diseases should be excluded after thorough fundus examination.

2. In high risk patients such as those with renal disease, Tamoxifen, pre-existing macular disease or daily dose greater than 5mg/kg of total body weight screening should be done annually.

3. In low risk patients, annual screening is recommended only after 5 years of HCQS usage.

Should Screening Be Continued After Cessation Of HCQS?

At present there are no accepted guidelines for screening in patients who have discontinued HCQS after diagnosis of retinal toxicity has been made. A study recommended an initial follow up after 3 months of diagnosis of HCQS retinopathy followed by annual screening.22In the absence of an established protocol it is generally recommended that a close surveillance should be kept of all such cases.

Management:

At present no medical or surgical treatment has been proven to be effective in treating or reducing the risk of HCQS retinopathy. Even after the stoppage of drug, the retinopathy continues to progress. However, the progression can be limited if retinopathy can be recognized before the damage to RPE cells. Once the diagnosis of retinopathy has been established, the decision to stop the drug should be taken in conjunction with the treating physician after weighing against the medical risks.

Similarly, there are no evidence based guidelines for dose reduction in patients with renal insufficiency and pre-existing macular pathology. Hence, newer methods for surveillance in the future are required to aid in safe usage of HCQS.

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Minimally Invasive Glaucoma Surgery (MIGS)

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Introduction

Glaucoma is the leading cause of irreversible blindness worldwide. Trabeculectomy is still the "gold standard" in glaucoma surgery. However it is associated with significant morbidity such as hypotony and bleb related complications[1], This has warranted a quest for alternate safer procedures ensuring better IOP control and QoL (quality of life).[2,3] This has led to the advent of Minimally Invasive Glaucoma Surgeries (MIGS). These procedures aim at either overcoming the resistance at the juxtacanalicular meshwork, increasing uveoscleral outflow via suprachoroidal pathway or by creating a subconjunctival drainage pathway.[4]

MIGS procedures are usually indicated in eyes with primary open angle glaucoma and are generally performed in combination with cataract extraction as safer and less invasive means of reducing IOP

INDICATIONS	CONTRAINDICATIONS
Primary Open angle glaucoma	Primary and Secondary Angle Closure Glaucomas
Pigmentary glaucoma ,Pseudoexfoliation glaucoma and other secondary open angle glaucomas	Advanced Glaucomas
Mild to moderate disease	Previous Glaucoma surgery
Glaucoma with co existing cataract	Need for lower target IOP

Classification of MIGS

1. Procedures increasing trabecular outflow by bypassing the juxtacanalicular trabecular meshwork (TM)

- Trabectome
- Excimer Laser Trabeculotomy (ELT)
- iStent
- Hydrus
- Gonioscopy-assisted Transluminal Trabeculotomy (GATT)

2. Subconjunctival drainage pathway

- XEN Gel Stent

3. Procedures increasing uveoscleral outflow via suprachoroidal pathway

- CyPass Micro- Stent (withdrawn)

Trabectome

Trabectomeis US Food and Drug Administration (FDA) approved high frequency (550 kHz) bipolar electrocautery with a 19.5 gauge disposable hand piece with an insulated foot plate containing electrocautery, irrigation and aspiration functions. It ablates a strip of Trabecular Meshwork (TM) and inner wall of Schlemm's Canal (SC) without affecting the surrounding areas. It removes the area of greatest resistance to the aqueous outflow and reestablishes access to the eyes natural drainage system. Itcan be performed simultaneously with cataract surgery.[5] It is recommended to not use viscoelastic during procedure as it can produce optical blur or can interfere with electrocautery. About 90 – 120 degree area can be treated through a single incision under direct gonioscopic visualization. IOP spikes and hyphema are known complications. Various trials have shown significant IOP reduction with trabectome.[6,7] However multicentre systematic data is awaited

Excimer Laser Trabeculotomy (ELT)

ELT (Excimer Laser Trabeculotomy) is done using 308 nm Xenon Chloride pulsed excimer laser which delivers photoablative energy to create micro perforations in the TM and inner wall of Schlemm's Canal. Healing response can be minimized by avoiding trauma to the outer wall of SC which contains fibroblasts. The laser device either uses a gonioscopy lens to visualize the TM or comes with an endoscopic laser probe for direct visualization.[9-10] laser burns are placed over 90 degrees. Microperforations and reflux of blood is considered to be an end-point of treatment. No serious adverse effects have been recorded. As per recent studies ELT lowers IOP and reduces AGM simultaneously for up to 5 years. ELT combined with phacoemulsification is more effective than ELT alone. It is also documented to be more effective in eyes with higher baseline IOP.[8]

iStent

The iStent is the first ab internoimplant designed for the treatment of mild to moderate glaucoma. It bypasses the outflow resistance at the trabecular level by creating a direct communication between the anterior chamber and Schlemm's canal. The procedure can be done de-novo or simultaneously with cataract surgery.

Figure 1a : Design of an iStent Fig 1b: Picture showing the actual size of istent. Image courtesy – Arvind Neelkantham , Glaucoma Centre of Texas

iStent is a FDA approved heparin coated, non-ferromagnetic implant made of surgical grade titanium. It has a ridged, snorkel design with 3 retention arches on its outer surface for secure placement (Figure a). A second-generation model called the iStent inject (Figure 3) has been available and the inserter comes preloaded with two stents allowing the injection at the same time without exiting the eye. The device is injected into the Schlemm's canal under gonioscopic view (Fig 3). Transient IOP elevation , intra operative blood reflux from Schlemm's canal, Stent malposition and obstruction are some of the reported complications.[9] A recent meta – analysis noted that there was a significantly greater IOP reduction after the use of two first-generation stents compared to one, irrespective of phacoemulsification status. For the first generation stent, combined phaco-iStent provided a greater level of IOP reduction and reduction in the number of medication classes relative to phacoemulsification alone[10].

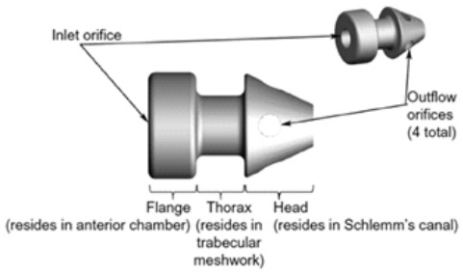

Figure 2 :Design of Istent inject

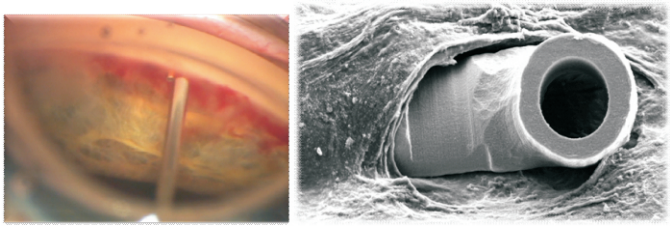

Figure 3 : iStent Snorkel sits parallel to the iris plane and iStent rails are seated against scleral wall of Schlemm's canal.Image Courtesy: Arvind Neelakanthan, Glaucoma Centre Of Texas

Schlemm's Canal Scaffold (Hydrus)

Hydrus Microstent (Ivantis, Inc, Irvine, CA, USA) is a crescent shaped implant made of ninitol. It bypasses the trabecular meshwork and dilates & supports the Schlemm's canal. The scaffold design helps to keep the collector channel accessible allowing greater flow of aqueous from the anterior chamber. The rationale behind dilating Schlemm's canal lies in the previous findings that elevated IOP actually causes the canal to collapse, leading to lasting changes in the TM and adjacent Schlemm's canal.[11] The device spans to three clock hours once inserted into Schlemm's canal under direct gonioscopic view. It dilates the canal by four to five times the natural width. Transient IOP spike, intra operative blood reflux from Schlemm's canal, Stent malposition and obstruction and focal peripheral anterior synechiae are some of the reported complications.

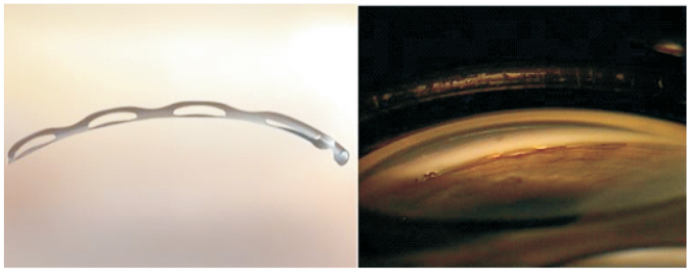

Figure 4a : Design of Hydrus implant and gonioscopic image showing hydrus implant insitu. Image courtesy –Brandon Lorry & Glen Burgess, Ivanti,Inc.

The FDA approval of hydrus was procured on the basis of 24 month results of the HORION trial where 556 mild to moderate glaucoma patients were randomized to 2 groups – cataract surgery with or without the microstent. More than 77% of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58% of the control group . No major adverse events were reported in the microstent group.[12]

Gonioscopy- assisted Transluminal Trabeculotomy (GATT)

GATT is a minimally invasive , conjunctiva sparing approach which cleaves the trabecular meshwork, thereby improving the normal conventional outflow pathway. A goniotomy is made in the nasal quadrant under gonioscopy lens. Schlemm's canal is cannulated 360 degrees using 5-0 prolene suture / microcatheter. Once the distal tip has circumnavigated the entire canal, it is retrieved and externalized. Gentle traction is applied to the externalized trailing end, creating a constricting loop, that gradually cleaves the entire TM and thus, creating a 360 degrees trabeculotomy ab interno. If cataract surgery is also planned, the GATT procedure is performed first followed by cataract surgery. Hyphaema and IOP spike can be seen post operatively. As per current data this technique is quite effective in primary and secondary open angle glaucomas and selected cases of anterior segmented dysgenesis in children.[13]

XEN Gel Stent/Aquesys

XEN gel stent (Aquesys) is FDA approved 6mm long , soft , permanent , non migrating device made of porcine gelatin cross linked with glutaraldehyde.It shunts aqueous from anterior chamber to subconjunctival space. When hydrated, it becomes compressible and tissue conforming. It comes in three different lumen sizes of 45, 65 , 140 micron. The implant comes with an injector, preloaded within a 27-gauge needle. As per Poiseulilles law of laminar flow , the length of the tube and inner diameter of the tube determine the rate of flow of aqueous. A preloaded injector is introduced in the anterior chamber through a clear cornea incision and is advanced till it reaches the opposite TM under direct gonioscopy (Figure 5a). The needle is inserted through the TM to create a scleral channel. It is further advanced till the bevel of the needle is seen in the subconjunctival space 3mm away from the limbus (Fig 5b) and the stent is released into the subconjunctival space (Fig 5c). A low lying ab interno bleb is formed immediately (Fig 5d) . Newer studies propose subconjunctival Mitomycin C use intra operatively or post operatively to reduce the subconjunctival fibrosis. It can also be combined with cataract surgery.

Figure 5 : XEN gel implant connecting the anterior chamber to the sub conjunctival space.Image Courtesy - Allergan

Figure 5a | Figure 5b | Figure 5c | Figure 5d

of implant has been reported. IOP spike in early postoperative period has been reported. As the procedure leads to bleb formation, subconjunctival fibrosis can occur requiring needling with antimetabolites. Few reports of internal ostium occlusion and corneal erosion have been noted.

The results of the AqueSys XEN 45 Glaucoma Implant in Refractory Glaucoma trial reported ≥ 25% reduction in mean IOP in 80.8% of eyes at 1 year follow up, but 32.3% eyes required needling with anti metabolites in the postoperative period.[14]

A recent study documented complete success in 80.4% and a qualified success in 97.5% of cases subjected to Xen stent implantation in conjunction with cataract surgery.[15] Xen implant has been noted to be effective in uveitic glaucoma.[16]

Suprachoridal Microstent (CyPass)

CyPass Micro-Stentwas devised as a flexible implant to be inserted into the supraciliary space from anterior chamber thus increasing the physiological uveo-scleral outflow. It got the FDA approval in 2016 for use in conjunction with cataract surgery in patients with mild to moderate open angle glaucoma based on results of 2yearCOMPASS study.A statistically significant reduction in intraocular pressure at two years post-surgery was noted in patients implanted with the CyPass Micro-Stent at the time of cataract surgery, as compared to subjects undergoing cataract surgery alone. At two years post-surgery, there was little difference in endothelial cell loss between the CyPass Micro-Stent and cataract surgery-only groups.

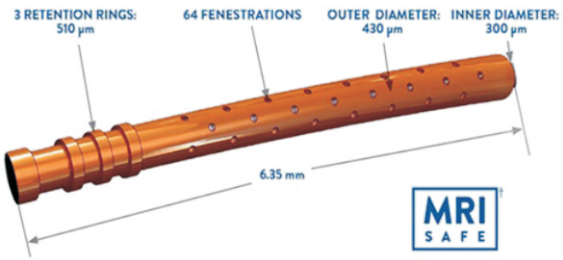

Figure 6: Cypass Microstent

The COMPASS-XT study was designed to collect safety data of the subjects who participated in the COMPASS study17for an additional three years, with analysis of the completed data set at five years post-surgery. At five years, the CyPass Micro-Stent group experienced statistically significant endothelial cell loss compared to the group who underwent cataract surgery alone. Endothelium cell loss was correlated with stent position within

the angle and with the number of retention rings noted on gonioscopy, particularly with two or more retention rings visible. Following these results , the stent was voluntarily withdrawn by the company in August 2018. Sufficient data on removal or trimming of stent is not available.

Conclusion

MIGSthus reduce the need for topical anti glaucoma medications in cases of mild to moderate glaucoma thereby minimizing patient adherence problems, increasing quality of life and potentially reducing lifetime costs of medications. 25Also the conjunctiva is spared for more invasive glaucoma surgeries in the future if required and reducing the bleb related complications.

However, the role of MIGS is reserved to mild to moderate glaucomas. These procedures alone are not adequate to achieve low target IOP needed for advance glaucomas

Other limitations of MIGS are lack of studies determining the longterm efficacy and safety of these procedures , lack of data pertaining to cost-effectiveness of the devicesand incomplete knowledge of ideal patient selection. In assessing current MIGS data, because most trials have included cataract surgery, it is important for clinicians to recognize the IOP-lowering ability of cataract surgery alone[17].

If supported longterm by studies , MIGS holds the potential to emerge as safer, minimally invasive and less morbid treatment option. Considering the ceaseless ongoing research and rapidly evolving technology, the field of glaucoma surgery might witness a drastic change in practice patterns in near future.

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What's New in Medical Retina?

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It is said that things move fast in the world of modern medicine. The field of medical retina appears to be no exception, with numerous developments taking place, such as introduction of new drugs, new treatment modalities and imaging techniques. While a detailed description is out of the scope of this article, we hope to give you a glimpse into what is new in the world of medical retina.

Newer Imaging Modalities: We describe a few imaging modalities that have become popular recently.

1. Wide-field Imaging: Conventional fundus imaging typically generates images with a 30 to 50-degree field of view, corresponding to approximately 5% to 15% of the retinal surface area. This allows for visualization of the posterior pole but not theretinal periphery. The Optos system (Optos, Dunfermline, Scotland), through the use of a large ellipsoid mirror with 2 focal lengths (allowing wide scanning angles) and an SLO, provides image capture with a 200 degrees internal field of view (approximately equivalent to 135 to 150 degrees external field of view).The system provides the ability to capture red and green reflectance imaging, as well as fundus autofluorescence, and fluorescein/indocyanine green angiography.[1] Ultra-Wide-field Angiography (UWFA) has been shown to demonstrate abnormalities in a variety of retinal conditions, including diabeticretinopathy, retinal vein occlusion, sickle cellretinopathy, uveitis, and pediatric retinal disease.[2,3]

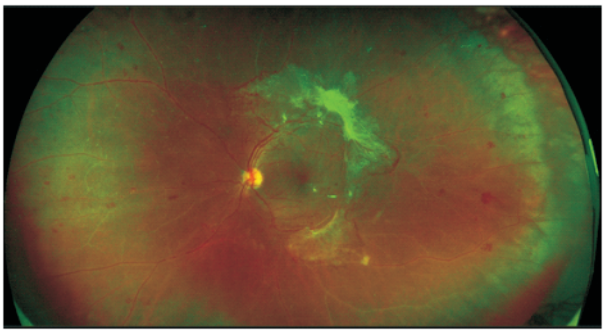

Figure 1 Wide-field Optos image of the left eye with advanced PDR showing extensive fibrovascular proliferation over the posterior pole and peripheral sclerosed vessels

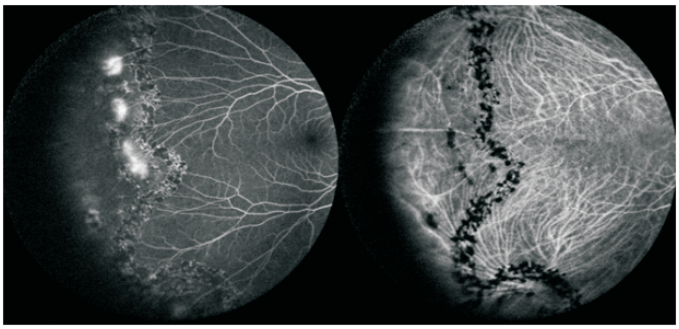

Figure 2 Wide field combined fundus fluorescein and indocyanine green angiography on the Spectralis platform in a 30-year-old male patient demonstrating peripheral vascular leak

2. Multi Color Imaging : Mult iColor scanning laser imaging is a new technology for fundus imaging offering detail and clarity not available from traditional fundus photography. Multi Color images are captured by simultaneously scanning with three individual laser wavelengths: blue, green, and infrared. The different wavelengths penetrate the tissue to different depths and therefore provide structural information from different depths within the retina.[4]

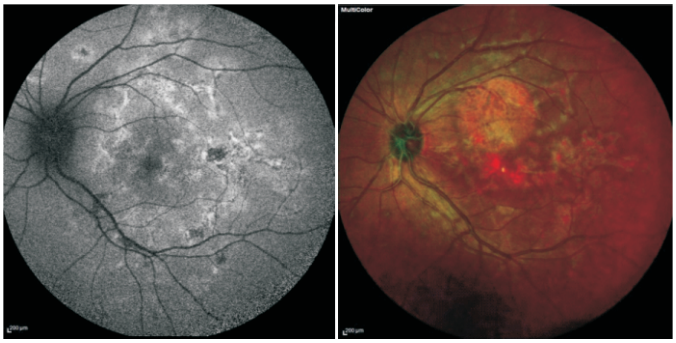

Figure 3Multicolor OCT image of the left eye showingserpiginous like choroiditis lesions in a 22-year-old male patient with the corresponding left eye autofluorescence image

3. Wide Field OCT : Optovue (Fremont, CA) Avanti RTVue-XR widefield system uses SD technology and can obtain 70,000 A-scans/second. The Avanti RTVue-XR can create 12 mm x 9 mm B-scans, and its active eye tracking enhances image stability. Wide field OCT can provide detailed information of the lesions that are present away from the arcade. These are very useful imaging modalities for conditions like choroidal tumors and peripheral lesions such as retinoschisis.[5-7]

4. Hand Held OCT: Spectral-domain OCT systems (Bioptigen EnvisuSDOIS; Bioptigen, Research Triangle Park, NC, USA) with handheld imaging probes connected to a table-topconsole by a 1.3-m-long cable is a device which has now been used widely in imaging pediatric disorders. It has been proven particularly useful in neonatal populations for the study of ocular development and for diseases such as retinopathy of prematurity.[8]

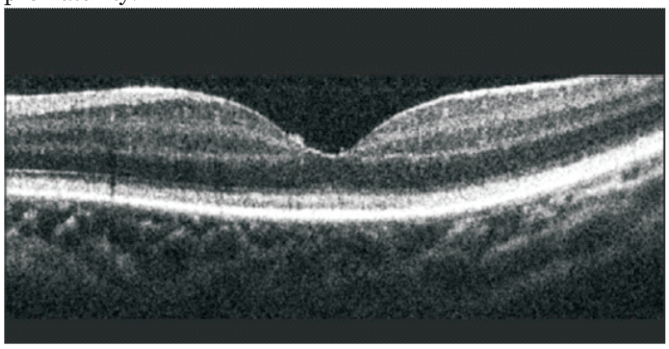

Figure 4A spectral domain-optical coherence tomography image using the Envisu 2300 (Bioptigen Inc., Research Triangle Park, NC, USA) of a 1-year old female child with a cone-rod dystrophy demonstrating an absent foveal tent and an irregularly thickened and hyper-reflective layer of cone outer segment tips

5. Adaptive optics: Optical retinal imaging modalities rely on the optical elements of the eye itself (mainly the cornea and lens) to produce retinal images. As a results of imperfections in these structures, aberrations are introduced to the imaging light and image quality is degraded. To compensate for these aberrations, adaptive optics (AO) along with optical coherence tomography (OCT) have been utilized.[9] This enabled for the first time invivo volumetric retinal imaging with high isotropic resolution. Using adaptive optics, photo receptor loss/changes can be imaged.[10,11]

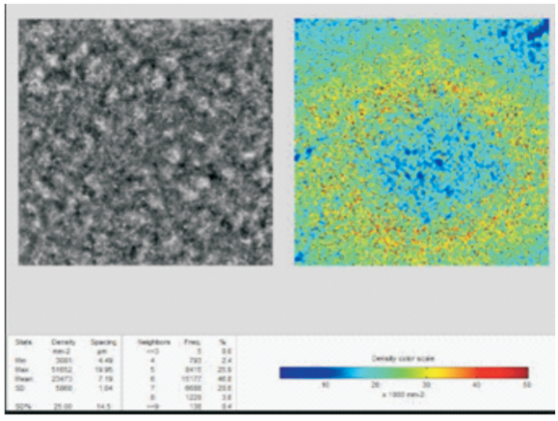

Figure 5 Adaptive optics imaging of the left eye fovea of a healthy 25-year-old male showing normal average cone count and distribution

6. Optical coherence tomography angiography (OCTA): OCTAis a new non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating angiographic images in a matter of seconds. OCTA compares the decor relation signal (differences in the back scattered OCT signal intensity or amplitude) between sequential OCT b-scans taken at precisely the same cross-section in order to construct a map of blood flow. The two main types of OCTA instruments are spectral-domain OCTA (SD-OCTA) and swept-source OCTA (SS-OCTA). Both use Fourier domain detection techniques, but the SD-OCT instruments use a broadband near-infrared super luminescent diode as a light source, currently with a center wavelength of approximately 840 nm, with a spectrometer as the detector, while SS-OCT devices use a tunable swept laser while SS-OCT devices use a tunable swept laser, currently with a center wavelength of approximately 1,050 nm, with a single photodiode detector. The main advantage of SS-OCTA imaging over SD-OCTA is a faster scanning speed, which allows for denser scan patterns and larger scan areas than SD-OCTA scans for a given acquisition time. Another advantage of the current SS-OCTA technology is that it uses a longer center wavelength that can reduce sensitivity roll-off of the signal under the RPE, which results in enhanced light penetration into the choroid and better detection of signals from the deeper layers. [12,13]

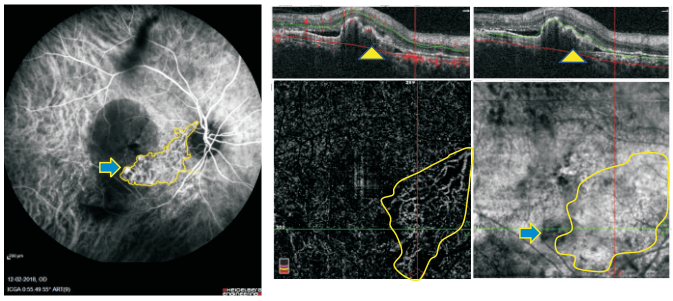

Figure 6A Indocyanine greenangiography of the right eye of a 55-year-oldmale patient, demonstrating a branched vascular network with hypercyanacent lesions at their terminal ends suggestive ofpolyps (highlighted).

Figure 6B SD OCTA image of the same eye delineating the outline of the branched vascular network.

New treatment options:

Age Related Macular Degeneration (AMD)

While tremendous progress has been made in the field of wet AMD, there still appears to be no treatment for dry AMD. Here, we take a look at some treatment options which may become viable in the near future

1. Photo biomodulation involves application of visible to near-infrared light to cells to produce beneficial effects. A recent study on 42 patient with dry AMD showed that application of multi-wavelength light composed of yellow (590 nm), red (670 nm) and near-infrared (790 nm) for a period of 3 weeks resulted in significant improvement in BCVA, contrast sensitivity, and the drusen size.[14]

2. Brimonidine is a selective alpha-2 receptor adrenergic agonist with additional neuroprotective properties[15]. Phase II clinical trial to evaluate the safety and efficacy of a brimonidine tartrate intravitreal implant (Brimo DDS, Allergan)in patients with dry AMD showed that Brimo DDS reduced the rate of progression at 1 year.[16]

3. Minocycline is a tetracycline derivative with neuro protective properties. Presently, there are ongoing phase II trials that are evaluating the effects of oral minocycline (100 mg, twice daily) and doxycycline (40 mg, daily) in the treatment of AMD patients with geographic atrophy.[17, 18]

4. Anti Inflammatory agents:

a. CLG561 is an inhibitor of properdin. It acts by destabilizing the alternative pathway. A phase 2 study of 114 participants evaluated the safety and efficacy of 12 (every 28 days) intravitreal injections of CLG561 as a monotherapy and in combination with LFG316(Tesidolumab) which is a complement factor C5 inhibitor as compared to sham in subjects with GA [19]. Results have yet to be published.

b. APL-2 is a synthetic cyclic peptide that binds specifically to C3, effectively blocking all three pathways of complement activation: classical, lectin, and alternative. DERBY and OAKS studies compared efficacy and safety of APL-2 (15 mg/0.1 ml) intravitreal injection monthly or once every other month for 24 month with sham injections. The primary endpoint was change in total area of GA from baseline measured by FAF. Results are still awaited.[19]

c. Zimura (Ophthotech) completed patient recruitment for its phase 2b clinical trial of Zimura (avacincaptad pegol), a complement factor C5 inhibitor. A total of 286 patients have been enrolled into this randomized, double-masked, sham controlled multicenter clinical trial. This clinical trial is designed to assess the safety and efficacy of various Zimura dosing regimens over 12 months. Results are awaited.[19]

5. Anti-oxidative stress agents: Risuteganib (ALG-1001) is an integrin inhibitor and thus down regulates oxidative stress response and restores retinal homeostasis. Currently, a phase 2 clinical trial designed to evaluate the safety and efficacy of Risuteganib (1.0 mg) in patients with intermediate non-exudative AMD is underway.[20]

6. Amyloid Beta Targets (MRZ-99030) : Amyloid protein has been identified as a primary component of drusen in patients with AMD. Amyloid Beta Targets is an Aβ aggregation modulator, previously reported to prevent the formation of soluble toxic oligomeric Aβ species. Amyloid beta target is a dipeptide administered as intravenous injection. It promotes the formation of large, amorphous/globular Ab species when present at a 10:1 stoichiometric excess to Ab. Phase one studies have been completed involving this agent.[21]

7. Visual cycle modifying agents:ALK-001 modulates vitamin A metabolism, by decreasing toxic vitamin A aggregates. Phase 2 Study of ALK-001 in Geographic Atrophy (SAGA) is still going on. One of the earliest changes in the retina that precede symptoms of AMD is the formation of toxic vitamin A dimers. Replacing the retina's vitamin A with ALK-001 slows the formation of toxic vitamin A dimers. To date, ALK-001 is the only small molecule designed to prevent the dimerization of vitamin A that has demonstrated functional preservation of visual function in animal models. The central hypothesis of this work is that retarding vitamin A dimerization will slow the development and/or progression of AMD.[22]

8. Choroidal blood flow enhancing agents: Alprostadil is a naturally occuring Prostaglandin E1.Phase 3 study proved that Alprostadil infusion was superior to placebo treatment in patients affected by dry AMD. Patients treated with Alprostadil showed a BCVA greater than 0.94 lines compared with patients treated by placebo after 3 months, increasing to 1.51 lines at 6-month follow-up.[23]

9. Newer Anti VEGF agents

a. Conbercept consists of the VEFG binding domains of human VEGFR-1 and VEGFR-2 combined with the Fc portion of the human immunoglobulin G. It binds VEGF A,VEGF B and Placental growth factor[24]. Hundred and twenty two patients with exudative AMD were randomized 1:1 to receive either 0.5 mg or 2.0 mg conbercept for 3 consecutive monthly doses. After the third dose, subjects were again randomized to either monthly or as-needed (PRN) therapy, without changing the dose of conbercept that they were receiving. At the third month, mean BCVA improvement was there in both the groups.

b. Faricimabis the first bispecific antibody to simultaneously bind and neutralise both angiopoietin-2 and VEGF-A. In nAMD, Ang-2 works synergistically with VEGF to drive pathologic blood vessel permeability and destabilisation. STAIRWAY is a phase II, multicentre, RCT, investigating the efficacy, safety and pharmacokinetics of faricimab administered with extended dosing regimens in 76 treatment-naive patients with nAMD.[25]

c. Brolucizumab is a humanized, single-chain antibody fragment inhibitor of VEGF-A.It inhibits all isoforms of VEGF-A including VEGF 165.Phase III of the HAWKstudy involved990 patientsover2-year to compare the efficacy and safety of Brolucizumab 3mg and 6 mg vs. Aflibercept 2 mg in subjects with nAMD. Results show noninferiority of Brolucizumabin BCVA vs aflibercept. More patients demonstrated sustained dryness for ≥2 and ≥3 consecutive visits. Superior anatomic results were seen for brolucizumab at Weeks 16 and 48. Overall ocular and nonocular adverse event rates for brolucizumab were comparable to aflibercept(26). HARRIER study, a phase IIIdouble-masked, multi-center, two-arm study comparing the efficacy and safety of brolucizumab vs. aflibercept in 660 subjects with nAMDover 2years. The study showed noninferiority as a majority of patients maintained BCVA on q12w intervaland superior anatomic results for brolucizumab at weeks 16 and 48.[26]

d. OPT-302is a soluble form of VEGF receptor 3 comprising the extracellular domains 1-3 of human VEGF receptor 3 and the Fc fragment of human IgG1. The VEGFR-3 or "trap" molecule blocks the activity of the proteins VEGF-C and VEGF-D.OPT-302 is used in combination with inhibitors of VEGF-A. Combination therapy of OPT-302 and a VEGF-A inhibitor achieves more complete blockade of members of the VEGF family. Phase 2 clinical trial enrolled 366 treatment-naive wet AMD patients who were randomized in a 1:1:1 ratio to receive one of the following treatment regimens administered every 4 weeks for 24 weeks: OPT-302 (0.5 mg) in combination with ranibizumab (0.5 mg); OPT-302 (2.0 mg) in combination with ranibizumab (0.5 mg); or sham in combination with ranibizumab (0.5 mg).Superior visual gains were noted in the combination therapy.[27]

Diabetic Macular Edema:

While there is no doubt that anti–VEGF-A monotherapy has revolutionized the treatment of diabetic macular edema (DME), there still remains a subset of patients who are non-responders. The unmet need presented by these patient forms the impetus for developingnew options for the treatment of DME. We enumerate a few that show promise

1. Next-generation anti–VEGF-A drugs

a. Conbercept is a recombinant human VEGF receptor-Fc fusion protein, which inhibits VEGF-A, VEGF-B, and placental growth factor (PlGF).The FRONTIER and SAILING studies showed improvement in visual acuity and concomitant decreases in retinal thickness on OCT in patients with DME.[28]

b. Abicipar Pegol belongs to the class of genetically engineered antibodymimetic proteins called designed ankyrin repeat proteins (DARPins). Results from the phase 2 PALM study showed that abicipar pegol, injected every 8 or12 weeks in patients with DME, offered functional and anatomic effects similarto those of ranibizumab injected monthly.[29]

2. Suprachoroidal corticosteroid: The injection of triamcinolone acetonide (CLS-TA; Clearside Biomedical) into the suprachoroidal space is a novel approach to the treatment of patients with DME.The HULK clinical trial examined suprachoroidal CLS-TAwith and without intravitreal aflibercept and showed signs of increased efficacyand durability with the investigational drug.[30]

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JOURNAL UPDATE

Repeat SLT can Provide Drop-free IOP Control for 18 Months

According to this post hoc analysis, repeat selective laser trabeculoplasty (SLT) offers effective IOP control in glaucomatous eyes requiring retreatment. The study included 115 treatment-naïve eyes with open-angle glaucoma or ocular hypertension undergoing 360° SLT twice within 18 months. Two months after the repeat procedure, participants showed a greater adjusted absolute IOP reduction than from the initial procedure. Approximately 67% of study eyes maintained drop-free IOP at 18 months, with no adverse events. Ophthalmology, April 2020

Optic Nerve Sheath Diameter in Glaucoma Patients and its Correlation with Intraocular Pressure

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Aim: To compare Optic Nerve Sheath Diameter (ONSD) in Primary Open Angle Glaucoma (POAG), Primary Angle Closure Glaucoma (PACG) and Normal Tension Glaucoma (NTG).

Material And Method: Patients with POAG (n≥38), PACG (n≥32), NTG (n≥18) and Controls (n≥48) underwent B-scan ultrasound and Computed Tomography Scan (CT scan) measurement of ONSD. Intraocular pressure (IOP) was measured in all groups and was correlated with ONSD.

Result: ONSD was significantly (p≥<0.001) increased in NTG patients (mean≥5.0mm ±0.48SD) compared with POAG (mean≥4.20mm±0.32), PACG (mean≥4.33mm±0.27) and control (mean≥4.21mm±0.31). ONSD showed correlation with IOP in PACG group (r≥0.392, p≥0.02) while it did not in other groups.

Conclusion: ONSD in a group of NTG patients were significantly increased compared with POAG, PACG and controls indicating the role of translaminar cribriform pressure gradient in NTG patients. Indirect measurement of ICP by assessment of ONSD may provide further insight into retrolaminar pressure component and pathophysiology of glaucoma.

Introduction

Glaucoma is the leading cause of irreversible blindness affecting more than 60 million people worldwide.[1] Glaucoma is a chronic progressive optic neuropathy that is recognised by the appearance of characteristic cupping of optic disc associated with corresponding visual field defects. The disease is characterised by progressive loss of retinal ganglion cells(RGCs)& their axons associated with tissue remodelling of the optic nerve head(ONH).

A sustained increase in Intraocular Pressure (IOP) may be due to increased formation of aqueoushumor, poor drainage or raised pressure in the episcleral veins. Of these first & last rarely occurs and it follows that raised IOP is essentially due to an increased resistance to its drainage through angle of anterior chamber.

The optic nerve is derived from an out-pouching of the diencephalon (optic stalk) during embryonic development. As a consequence, the fibres of the optic nerve are covered with myelin produced by oligodendrocytes, rather than Schwann cells of the peripheral nervous system, and are encased within the meninges. The optic nerve is ensheathed in all three meningeal layers (dura, arachnoid and pia mater). Its diameter increases from about 1.6 mm within the eye to 3.5 mm in the orbit to 4.5 mm within the cranial space. The optic nerve component lengths are 1 mm in the globe, 24 mm in the orbit, 9 mm in the optic canal, and 16 mm in the cranial space before joining the optic chiasm.[2]

The optic nerve sheath is an anatomical extension of the duramater and so the subarachnoid space around the optic nerve is continuous with the intracranial subarachnoid space. The optic nerve is separated from its sheath by a fluid layer of cerebral spinal fluid (CSF), which is in continuity with the rest of the central nervous system. The lamina cribrosa is a trabecular structure of several layers and pores of different sizes through which the optic nerve fiber bundles pass, and it is a continuation of the inner layer of the posterior sclera. These are well known facts. The sieve like structure, lamina cribrosa acts as a pressure barrier between the intraocular space and the retrobulbar space of the optic nerve. Increase in intra cranial pressure (ICP) lead to an increase in the volume of the fluid layer, thereby increasing optic nerve sheath diameter (ONSD) as measured in the retrobulbar portion of the optic nerve trajectory. Dilatation of the optic nerve sheath has been shown to be a much earlier manifestation of ICP rise.[3,4] The pressure gradient between the anterior force of IOP and posterior force of CSF-p within the orbit is also known as Translaminar Cribriform Pressure Difference(TLCPD)

TLCPD = IOP – CSF-p

The TLCPD depends on the IOP and the retrobulbar CSF pressure. The basic hypothesis has been that increased TLCPD

is detrimental to the axons of the optic nerve via a mechanical insult and/or through a disturbed axoplasmic transport, which then causes edema. A change in either IOP or ICP may affect the homeostasis of the ONH. In the last decade, it has also been postulated that possible low ICP in normal-tension glaucoma. The fact that dilated onh is due to raised ICP. If ICP is low in NTGs why are we getting dilated ONH in ntg? Dilated ONH means raised ICP and so less TLCPD.[5] Morgan et al. (2016) has discussed the possible influence of orbital pressure on the pressure in the optic nerve subarachnoid space (ONSAS) and that it might buffer large TLCPD effects when ICP is very low. They hypothesized that low orbital pressure and decreased elasticity of the pia mater could lead to increased transfer of low pressures from the orbit and the ONSAS to the retrolaminar optic nerve.[6] No significance noted in present context. The ability of lamina cribrosa to withstand pressure gradient without deformity is dependent on its thickness, the rigidity of extracellular matrix and peripheral sclera tension. The lamina cribrosa's ability to maintain shape is important in protecting structures that pass through it. Increased TLCPD could cause bowing of the lamina cribrosa. Such deformity may damage optic nerve ganglion cells via mechanical compression or ischaemia as the vessels pass through the lamina cribrosa.[7] CSF-P and IOP have equivalent effects on TLCPD and optic disc surface movement. Wostyn et al. suggested an alternative explanation for NTG development—the low ICP may be due to CSF circulatory failure which causes disturbed neurotoxin clearance along the optic nerve.[8] This has been supported by findings of lower CSF flow-range ratio in the ONSAS of NTG patients.[9] Furthermore, a hypothesis that high ICP fluctuations, i.e., rhythmic oscillations in ICP, may be an independent risk factor for glaucoma has also been presented.[10] Re-write in your own words. Copying exactly word by word is not to be done.

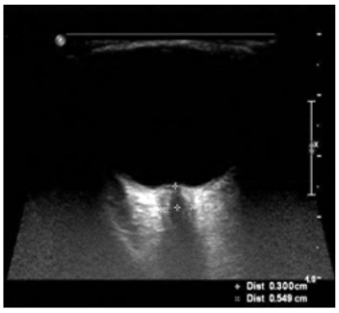
An interesting new concept is the postulated presence of a perivascular transport system for waste clearance in the eye and the brain, i.e., the “glymphatic system” which is another means to move extracellular fluid.[11,12,13] A reason why high TLCPD could be detrimental to the axons of the optic nerve could therefore be that it causes a restriction of normal glymphatic flow, leading to accumulation of toxic substances around axons and consequently damage to the axons of the optic nerve.[14]

The ideal method to measure CSF pressure is lumbar puncture but it is an invasive modality with increased risk with various life threatening complications. It has been found that raised CSF pressure causes increased ONSD and vice versa[13,4]. Therefore, measuring ONSD can be surrogate method to measure the CSF pressure and can throw some light in pathophysiology of various types of glaucoma. The optic nerve sheath is fairly easy to visualize by ultrasonography by insonation across the orbit in the axial plane. A-mode ultrasonography was used to view the optic nerve sheath more than four decades ago; B-mode scanning was performed subsequently to assess intraocular lesions[15]. Evolution of ultrasound technology and the development of high frequency (> 7.5 MHz) linear probes with improved spatial resolution have enabled excellent views of the optic nerve sheath. The ONSD, measured at a fixed distance behind the retina has been evaluated to diagnose and measure intracranial hypertension in traumatic brain injury and intracranial haemorrhage.[1,17] Ultrasound-based assessment of the ONSD is a validated method for indirect measurement of the ICP.[17,18,19] ONSD is much easier to measure on Computed Tomography scan (CT scan) than with sonography due to the good reproducibility of CT and the lack of a learning curve.

Objectives : The objective of the study is to study Optic Nerve Sheath Diameter in patients of POAG , PACG and NTG and to correlate it with IOP

Materials And Methods

Study Design



It is a hospital based cross sectional study.

Three cohorts of individuals over 18 years old were recruited for the study from department of Ophthalmology LLR hospital Kanpur: patients with POAG (n≥38),PACG (n≥32), NTG(n≥18) and they were compared with healthy control (n≥42). Glaucoma patients were defined on basis of intraocular pressure, having characteristic optic disc damage and visual field loss as has been described previously in the literature.[20,21] The healthy volunteers were screened by experienced ophthalmologists. Those with a family history of glaucoma, or an increased or asymmetrical cup/disc ratio or any other optic disc structural change (notching, disc hemorrhage), or an IOP above 21mmHg, were excluded as possible glaucoma suspects. Patients with a history of ocular trauma or eye disease (except glaucoma) that could not be

accounted for by refractive error were excluded. Patients on antiglaucoma drugs or with any known neurological disorder was also an exclusion criterion.

The study was approved by the ethical review committee (Institutional Review Board) of our own institution and was conducted in accordance with Good Clinical Practice within the tenets of the Helsinki's agreement. Each patient/subject was required to sign an informed consent statement before being enrolled into the study and prior to any study measurements being taken.

Measuring Devices

IOP was measured with the Goldmann applanation tonometer (GAT). Central corneal thickness (CCT) was measured using a pachymeter (Pachscan, Sonomed, and U.S.A). Angle of anterior chamber was assessed by 4 mirror goniolens. Visual fields were assessed by Humphrey's Perimeter (Zeiss, Germany). Disc photograph was taken by Fundus camera (Zeiss VisucamLite, Germany). Measurement of the ONSD was performed with a B-scan ultrasound probe (Sonomax, Montreal, Canada) and CT scan (Siemens, Germany).

Experimental Design

During the study visit, the following examinations were be performed in the same order : BCVA using the Snellen's chart placed in the same location at the same distance from the patient under the same illumination for all subjects, IOP measurement by Applanation tonometer, Angle of anterior chamber, Disc photo, Visual field, and finally ONSD measurements. Later was performed by an observer masked to the patients' diagnosis. The patient was made to lie in the supine position with the head in a neutral position and both eyes closed and in primary gaze position. After application of coupling gel the insonation depth was set to 5–8 cm, the transducer was softly placed over the upper eyelid in an axial plane. This sonographic section provides a transverse view of the globe and the structures of the retrobulbar area . The ONSD was calculated perpendicular to the vertical axis of the scanning plane 3mm behind the globe, where the optic nerve sheath structure is more prone to expansion due to increase in ICP[22] probably due to a decrease in sheath thickness in that retrobulbar segment of the optic nerve[14, 23] . Only one eye per patient was included in the study. The eye with greater glaucomatous damage was selected in the glaucoma patients.

Brain CT scan was performed with a series of millimetre slices (one slice every 0.6 mm). As for ultrasound, ONSD was measured at a distance of 3mm behind the eyeball, immediately below the sclera.[16,24] ONSD was measured transversely as a section through the centre of the optic nerve.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM SPSS Inc., Chicago, IL, USA) for Windows statistical package. The Mann-Whitney test was used to compare between two variables. The Kruskal-Wallis test was used to compare variables between four diagnostic groups. Spearman's correlation coefficient was used to study association between variables. Probabilities were two-tailed and considered statistically significant if $p<0.05$.

Results

Table : Demography & ONSD in study participants

VARIABLE	POAG	PACG	NTG	CONTROL
Number	38	32	18	48
AGE(in years)	50.50±6.49	50.94±7.35	56.4±10.4	50.23±6.48
VA (log MAR)	0.44±0.32	1.76±0.26	1.13±0.55	0.06±0.09
Mean IOP (in mmHg)	27.29±3.45	49.75±11.13	16.72±3.84	15.19±2.51
CCT(in µm)	527.60±10.26	543.19±8.24	504.83±14.27	520.1±13.66
MD	-6.17±2.14	-11.35±2.02	-5.11±0.94	0.39±0.65
ONSD on USG (in mm)	4.20±0.32	4.33±0.27	5.0±0.48	4.21±0.31
ONSD on CT (in mm)	4.23±0.33	4.35±0.26	5.01±0.5	4.20±0.27

VA – Visual Acuity ; IOP – Intra ocular pressure ; CCT – Central Corneal Thickness ; MD – Mean Deviation ; ONSD – Optic Nerve Sheath Diameter

In our study, a total of 136 patients were included out of which 66(48.53%) were in 41-50 years age group whereas 60(44.12%) were in 51-60 years and 10 (7.35%) in > 60 years age group. Overall affected males were 84(61.76%) and females were 52 (38.24%). Males outnumbered females in all the groups except in PACG group where females outnumbered males (20,i.e.,62.5% females; 12,i.e.,37.5% males).

In our study ONSD was significantly increased in Normal Tension Glaucoma (5.0±0.48; p≥0.001) compared to other groupsbutno significant correlation was found between IOP and ONSD in NTG group and POAG group($r\geq-0.209$, $p\geq 0.406$; $r\geq0.141$, $p\geq 0.398$ respectively) while in PACG group there was mild positive correlation between IOP and ONSD which was significant($r\geq0.392$, $p\geq0.02$). The graph below shows increased ONSD both on USG and CT in NTG group as compared to other groups.

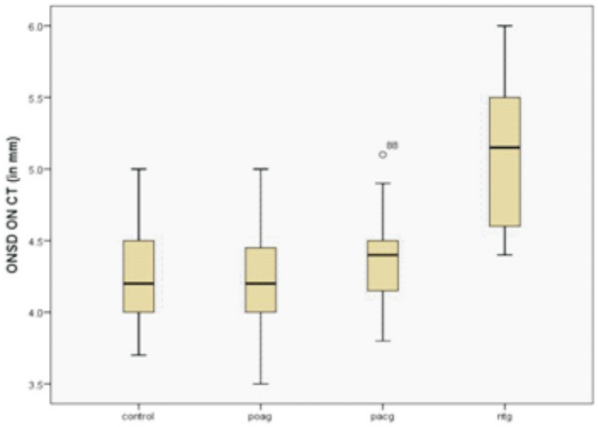


Figure 1 : Box Plot showing Mean of ONSD in CT

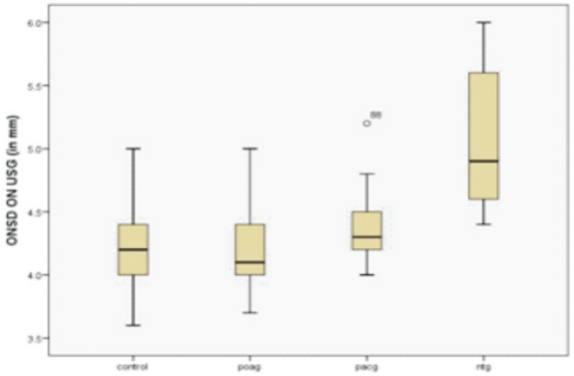


Figure 2 : Box Plot showing Mean of ONSD in usg

Discussion

The present study was conducted to evaluate the relevance of studying ONSD in glaucoma patients, and to study whether this indirect measurement of ICP correlates with IOP in these patients.

In the present study the ONSD in NTG Indian patients measured significantly (P≥0.00) larger diameters compared to controls without ON diseases. The findings of larger ONSDs in NTG patients are in accordance with measurements in a study from Jaggi et al(7.9±0.9mm)[25] and A Pircher et al (6.4±0.9mm)[26] who showed that ONSD in NTG patients was significantly increased (p<0.001) and contradictory to Abegao Pinto et al[127]who did not find any significant difference in ONSD among NTG , POAG and Control (p≥0.08)which may be due to difference in the methodology used or difference in head position scanning between these two groups.

The TLCPD is not the only factor affecting optic nerve head but it is also the thickness of the wall separating these compartments i.e. lamina cribrosa. An abnormally thin sclera has been seen in NTG patients[28] which results in increased stress on optic nerve in these patients.

Two mechanisms explain the enlarged ONSDs in NTG patients. First a localized CSF-Pressure elevation behind the globe due to impaired CSF outflow might lead to increased radial stress to the optic nerve sheath and thereby stretching the optic nerve sheath. Second, an accumulation of proteins of different biological functions[29].

In our study no significant correlation was found between IOP and ONSD in NTG group and POAG group(r≥-0.209, p≥ 0.406; r≥0.141, p≥ 0.398 respectively) while in PACG group there was mild positive correlation between IOP and ONSD which was significant (r≥0.392, p≥0.02) whereas study conducted by Abegao Pinto L et al[20] showed that OSND did correlate with IOP in NTG patients (r≥0.53; p<0.001) but not in POAG patients and healthy controls (p≥0.46 , P≥0.86). The difference in Pinto et al study from our study may be because diurnal variation of IOP was not taken in to consideration. Since no study has been conducted regarding ONSD in PACG group hence, result cannot be compared.

Limitations of Study

Our work has several limitations. A direct measurement of intracranial pressure was not included, thus, intracranial pressure was presumed to be normal by taking history, so, there is possibility of contamination of the experimental groups by individuals with a yet undiagnosed neurological clinical condition. The sample size in NTG group was very small compared to other groups so further studies with larger sample size is required to confirm our results. In some patients, changes due to diurnal variation in IOP could give different results.

Conclusion

It is the trans-lamina cribrosa pressure difference (and not the transcorneal pressure difference, i.e. the so called intraocular pressure) which is of importance for the physiology and pathophysiology of glaucoma.Indirect measurement of ICP by assessment of ONSD may provide further insight into retrolaminar pressure component and pathophysiology of glaucoma. ONSD measurement can be used as a useful tool for diagnosing NTG in early stage as ONSD greater than 5 mm is might be indicator of greater glaucomatous damage in NTG patients. ONSD measurement through USG-B scan and CT scan being a non invasive procedure can be used as an alternate method of measuring CSF-pressure in glaucoma patients as well as in other neurological diseases.

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NEOPLASTIC MASQUERADE SYNDROME

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Introduction

Neoplastic masquerade syndrome can be defined as neoplastic or proliferative lesions that cause intraocular infiltration of cells, simulating immune-mediated uveitis. The term "masquerade syndrome" is used in ophthalmology to describe conditions that are characterized by intraocular infiltration of inflammatory cells, simulating immune-mediated uveitis.[1,2] The neoplastic entities can be divided into lymphoid and non-lymphoid malignancies within either the retina or the uvea.[2,3] The lymphoid malignancies and non-lymphoid malignancies occurring in the eye are further subdivided as shown in Table 1. In this article we would discuss the relevant features of various Neoplastic Masquerade Syndromes.

	Type	**Anatomical involvement**
1.	Primary Intraocular Lymphomas	Retina and Vitreous
2.	Primary Uveal Lymphomas	Choroid and Iris
3.	Secondary Intraocular Lymphomas	Mainly choroidal involvement of systemic lymphoma
	CLASSIFICATION OF NON-LYMPHOID MALIGNANCIES OF THE EYE	
1.	Amelanotic Melanoma	
2.	Metastatic Tumor to the Choroids and Retina	
3.	Non-Neoplastic Proliferative Diseases of the Uvea, such as Juvenile Xanthogranuloma	

Lymphoid Malignancies

Primary Intraocular Lymphoma

Primary intraocular lymphoma (PIOL) is a high-grade malignant non-Hodgkin's lymphoma (NHL), arising in the retina with involvement of the vitreous and, occasionally, optic nerve. It is the most common "masquerader" according to investigators. PIOL is considered to be a subtype of the primary central nervous system lymphoma (PCNSL), and when occurring simultaneously in patients with PCNSL, the entity is named "oculocerebral lymphoma".[1,2,4]

Most PIOL are of B cell origin, and can be subtyped as diffuse large cell B cell lymphomas (DLBCL), according to the updated World Health Organization (WHO) Lymphoma Classification.1 Intraocular lymphoma of T cell type is rare, although its existence is becoming increasingly recognized. Most reported cases of intraocular T cell lymphoma, however, represent a secondary manifestation of mycosis fungoides or of a systemic T cell lymphoma in conjunction with systemic leukemia and are associated with human T cell lymphotropic virus type-1 (HTLV1) infection or with acquired immunodeficiency syndrome.[2,3,4]

Although it has been described in some young patients, PIOL typically affects those between the fifth and sixth decades. PIOL may be either unilateral or bilateral on initial presentation; however, the vast majority of patients will ultimately develop a bilateral manifestation.4 Intracranial lymphoma develops in 60-85% of patients with initial ocular disease, usually within the first 2 years of diagnosis.5 In turn, approximately 15–25% of patients with PCNSL will develop ocular disease. Systemic spread outside the CNS or ocular tissues rarely occurs. An inexplicable increase in the incidence of PCNSL has been reported over the last 15 years in both immuno competent and immuno suppressed patients.[1,3,4]

Symptoms and Signs of PIOL

PIOL when occurring prior to CNS disease, frequently presents as bilateral idiopathic steroid-resistant chronic uveitis, possibly with accompanying vitritis. Involvement of the CNS by tumor cells causes nonspecific symptoms and signs with the most frequent single symptom being "behavioral change". The most common focal neurologic signs include hemiparesis in 40-50% and cerebellar signs (eg. ataxia) in 15–40%.1

Ophthalmological Findings of PIOL

Anterior Segment

Anterior segment findings are observed in up to 43% of patients with PIOL.[3,4] Common findings include corneal precipitates, mild anterior flare, and a pseudohypopyon. Most often the posterior segment changes precede the anterior segment findings; however, occasionally, anterior segment disease can be the initial presentation of PIOL. Secondary anterior segment changes include neova scularization of the iris and irido corneal angle with possible glaucoma. In rare circumstances, PIOL can cause a mass in the iris following secondary infiltration.

- **Posterior Segment**

Vitreous cells and haze ("vitritis") are typical findings, and are present in the majority of cases. The characteristic fundus lesion is a flat creamy orange-yellow subretinal mass. These lesions may be single or multiple, discrete or confluent. The

presence of multiple subretinal pigment epithelial masses is considered by some clinicians to be pathognomic of PIOL. Rarely, PIOL presents as a single solitary intraocular mass.[3,4]

Diagnostic Techniques

The diagnosis of PIOL can be suspected on fundoscopy when the above-described "classical" retinal or subretinal infiltrates are present. Additional examinations, such as ultrasonography, fluorescein angiography, and/or high-resolution neuroimaging of the CNS, are usually performed to support the diagnosis. Fluorescein angiography provides information with regard to the location of the infiltrative process (retina versus choroid), and demonstrates any retinal pigment epithelium (RPE) disturbance. The mixed picture of hyper- and hypofluore scence on fluorescein angiography can result in a "leopardskin" appearance, considered to be highly indicative of PIOL (Figure 1a and b).[2,5] Neuroimaging studies include computed tomography scans (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET).

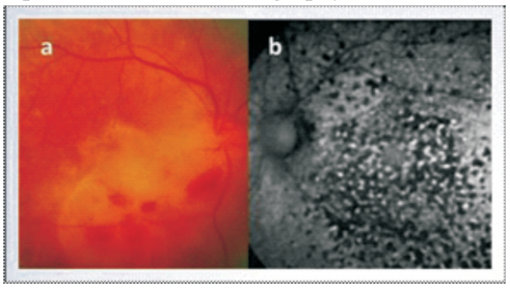

Figure 1: a- Primary Intraocular Lymphoma – Subretinal infiltrates with haemorrhages

b- "Leopard skin" appearance on fundus flourescein angiography

Cytological and Histological Diagnosis in PIOL

- **Vitreous Biopsy**

Cytological studies of vitreous biopsies remain the first line of investigation in the morphological diagnosis of PIOL.Vitreous specimens are obtained by fine needle aspiration, vitreal aspiration or via pars plana vitrectomy (PPV).[3,5,6] Vitreous aspirates in PIOL are mildly to moderately cellular, and comprise mature inflammatory cells such as macrophages, small lymphocytes with scattered large atypical lymphocytes and, possibly, fibrinous or necrotic material in the background (Figure 2). The neoplastic cells are usually pleomorphic showing hyperchromatic nuclei with irregular contours and prominent, sometimes multiple, nucleoli. The cytoplasmic rim is usually narrow or absent. Due to the fragility of neoplastic lymphocytes, a specimen may contain numerous lytic cells.The neoplastic cells are usually positive for B cell antigens, such as CD20, CD79α or PAX-5.[1,2]

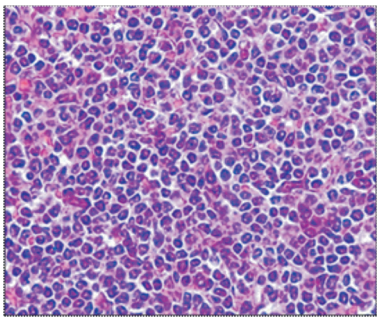

Figure 2: Histopathology of B cell lymphoma

- **Chorioretinal Biopsy**

If vitreous samples fail to demonstrate lymphoma cells, increasingly retinal and chorioretinal biopsies or subretinal aspiration are performed in patients with the subretinal infiltrates considered typical for PIOL.[5,6] Enucleation is unavoidable when a blind and painful eye develops due to secondary glaucoma and/or complete retinal detachment, and thus can lead to the diagnosis of malignant lymphoma.

- Biochemical and Molecular Analysis

In addition to cytomorphology and immunocytology, investigations such as flow cytometry, determination of cytokine concentrations, particularly interleukin-10 (IL-10), polymerase chain reaction (PCR) examining for monoclonal rearrangements of immmunoglobulin heavy (IgH) or light (IgL) chains in B cell lymphoma, or T cell receptor genes in T cell lymphoma, as well as determination of CDR3 (complementary determining regions) polymorphisms in the variable region of the immunoglobulin gene, are done[1,4,6].

Treatment of PIOL

The treatment recommendations for PIOL with or without CNS disease remain controversial. Radiotherapy alone to the eyes and CNS was the main form of treatment for PIOL/PCNSL, due to the sensitivity of lymphoma cells to radiation. Most patients usually succumbed to recurrent disease. Furthermore, ocular radiation was associated with delayed toxicity, including radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, and loss of limbal stem cells, cataracts, and glaucoma.[1,2,3] With multimodality therapy, including a boosted radiation dose to the spinal cord and intrathecal methotrexate, vision could be improved and life prolonged. Recent innovations in treatment include multi-agent primary chemotherapy. The regimen included methotrexate and procarbazine, or vincristine, thiotepa, or both vincristine and cytarabine. Other alternative therapies that require further assessment include intravitreal methotrexate and trofosfamide.[5,6] The management of patients with intraocular lymphoma only is also controversial. Localized radiation to one or both eyes is usually performed. Promising results for PIOL were obtained with high-dose chemotherapy followed by autologous bone marrow.[6]

Primary Uveal Lymphomas

Primary uveal lymphomas are probably the rarest intraocular

lymphomas. It either arises from the choroid or iris[1,2].

1. Primary Choroidal Lymphoma

They are considered to be tumors with their origin in the choroid, due to the absence of systemic disease at the time of diagnosis, and to their unilaterality in most patients. Most primary choroidal lymphomas are low-grade and are clinically indolent. Consequently, they have been termed "pseudotumors" and "reactive lymphoid hyperplasia" of the uvea in the past and usually occur unilaterally in men in the fifth decade of life.[5-7]

Typical presenting symptoms include recurrent episodes of blurred vision, painless loss of vision as well as metamorphopsia subsequent to secondary serous detachment of the macula. The signs of primary choroidal lymphoma include the creamy choroidal infiltrates on fundus examination with low echogenicity on ophthalmic ultrasound (Figure 3). There may be an initial response to steroid therapy. Ultimately, a diffuse thickening of the uveal tract becomes obvious on fundoscopy and, in some patients, subconjunctival or episcleral extension may occur.[5,6,7]

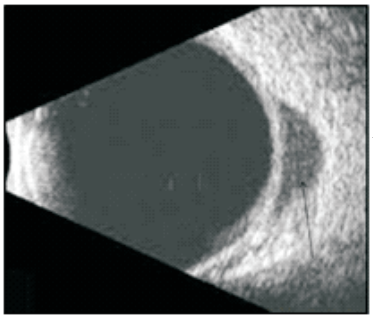

Figure 3: B scan appearance of Primary Uveal Lymphoma

On the basis of morphological features and immunopheno type, the primary choroidal lymphoma can be subtyped as "extranodal marginal zone B cell lymphomas" (EMZL) of mucosa-associated lymphoid tissue (MALT) type, according to the WHO Classification.[1,8]

Treatment of Primary Choroidal Lymphoma

Prior to any commencement of therapy in patients with primary choroidal lymphoma, a complete lymphoma "staging" investigation is essential. If no systemic disease is found, local treatment is appropriate and can include excisional biopsy of any epibulbar mass, cryotherapy, as well as low-dose irradiation in divided doses[2,4,7]. Occasional patients with primary choroidal lymphoma have been reported to have developed systemic disease following treatment. Involvement of the central nervous system by primary uveal lymphoma is exceptionally rare.

2. Primary Iridal Lymphoma

Those lymphomas occurring primarily in the iris are exceptionally rare. The typical presenting symptoms of primary iridal lymphoma include a painful eye, photophobia, and sometimes decreased vision.The clinical signs reported in the literature include uveitis of uncertain nature, nodular or diffuse iridal precipitates, iris discoloration with heterochromia and anisocoria, iridal swelling as well as hyphema or pseudohypopyon.[4,7,8] On ultrasound examination, ill-defined tumors of low reflectivity can be observed. Paracentesis from the anterior chamber and/ or iris biopsy with subsequent cytological and histological examinations respectively are the two methods employed, which usually lead to the establishment of a definitive diagnosis. Low-dose irradiation or systemic chemotherapy is the treatment of choice.

Secondary Intraocular Lymphoma or Leukemia

Leukemic involvement of the ocular tissues is the most common form of intraocular lymphomatous proliferation. At least 65% of cases of leukemia were seen to have involvement of the eye at autopsy. Ocular manifestations are rarely the first sign of disease in malignant lymphoma/leukemia, and have been reported in up to 80% of patients at some stage of their disease.[6,8] They usually occur in the choroid, and less often in the iris. Exceptionally rarely, intravascular lymphoma (also known as neoplastic angioendotheliomatosis) has also been reported to affect the eye.

Post-transplantation Lympho Proliferative Disorder

A well-known complication of solid organ transplantation is the occurrence of lymphoproliferations, such as the post-transplantation lymphoproliferative disorder (PTLD). This is considered a particular disease entity, most often caused by a chronic Epstein Barr virus (EBV) infection[6,8,9]. Some forms of PTLD undergo a malignant transformation with development of a malignant lymphoma. The risk of developing PTLD appears to be dependent upon the duration of immuno suppression. PTLD rarely affects the eye.

Non-Lymphoid Malignancies

Uveal Melanoma

Uveal melanoma is the most frequent primary intraocular tumor in white adults with an incidence of 0.7 per 100,000. These neoplasias, particularly the diffuse form, may present with clinical features suggestive of intraocular or orbital inflammation. Approximately 4.9% of patients with uveal melanoma present with symptoms such as episcleritis, anterior and/or posterior uveitis, endophthalmitis or panendophthalmitis.[10,11] The use of ocular echography has increased the diagnostic accuracy of uveal melanoma; however, unusual presentations of uveal melanoma may still perplex the clinician, masquerading as other entities.

Retinoblastoma

Retinoblastoma is the most common intra ocular tumor in childhood occurring in 1 in 17,000 to 24,000 live births and may occur either as a hereditary or as a sporadic tumor. Typically, retinoblastoma presents with leucocoria or

strabismus; in very rare cases, it may present as an inflammation. In particular, the rare variant of a diffuse infiltrating retinoblastoma, leading to conjunctival chemosis, pseudohypopyon and/or vitritis, can present with inflammatory signs.[1,9,10] Imaging studies – particularly with the presence of dystrophic calcification – are the most reliable in establishing the diagnosis; aqueous or vitreous biopsies are generally not recommended due to the considerable risk of tumor spread.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma is a rare idiopathic cutaneous granulomatous disorder usually occurring in young children. The cutaneous lesions are orange-red papules or macules, predominantly occurring over the face, neck, and upper trunk. Ocular involvement usually affects the anterior segment, particularly the iris where it presents as a yellow nodule.6,8,11 Complications of iridal juvenile xanthogranuloma are recurrent hemorrhage, and possibly the development of glaucoma. Occasionally, the posterior segment is involved and can be complicated by retinal hemorrhage, detachment, and blindness.Several treatment modalities have been used, including corticosteroids, low-dose radiotherapy, and surgical excision. With uveal juvenile xanthogranuloma, however, nonsurgical therapy is recommended due to the risk of severe bleeding.[10,12]

Metastatic Tumors

Uveal Metastases

The most common metastases to the uvea are bronchial cancer in men and breast cancer in women.These may present with pale white to yellow lesions on fundoscopy under a serous detachment without involvement of the retina, superficially representing primary uveal lymphoma.[13,14]

Retinal Metastases

These are exceptionally rare.In patients where no primary malignancy is known, a vitreous aspiration or retinal biopsy may be required to establish the diagnosis.[15,16]

Points To Ponder

Primary intraocular (retinal) lymphoma is considered a subset of primary central nervous system lymphoma, with the majority of the lymphomas being high grade malignant B cell lymphomas.

Multiple yellow-orange subretinal lesions, with the corresponding "leopard skin" appearance on fluorescein angiography, are considered to be pathognomic for PIOL.

Vitreous biopsy remains the first line of investigation in PIOL diagnosis establishment.

Before commencement of treatment of all PIOL patients, extensive "staging" examinations should be performed to determine the extent of disease (i.e. CNS involvement) and to exclude a secondary ocular involvement of a previously unknown systemic lymphoma.

Although the prognosis of patients with PIOL/PCNSL is generally poor, newer therapies provide optimism in prolonging their life expectancy.

Primary choroidal lymphomas are usually low-grade B cell lymphomas of MALT type.

The majority of primary iridal lymphomas are high-grade lymphomas, either of B or of T cell type.

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Scleral Foreign Body Mimicking Episcleritis

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Case 1: A 28 year old male, presented with complaints of localised area of redness in the palpebral conjunctiva of left eye associated with foreign body sensation since one month. Visual Acuity in both eyes was 20/20 with brisk pupillary reaction in both eyes. Slit lamp examination of left eye showed a well defined subconjunctival nodule measuring 5mmx3mm in the superonasal quadrant (Figure 1a). Anterior chamber was quiet. Posterior segment evaluation was normal. Right eye examination was WNL. There was no history of trauma. A provisional diagnosis of episcleritis was made. Complete blood count with ESR, chest x-ray and Mantoux test were done to rule out tubercular infection. The patient was started on low dose topical steroids. No decrease in size of nodule was observed after 2 weeks. On repeat evaluation there was a high suspicion of an occult foreign body. X-ray orbit revealed a linear opacity in the superonasal quadrant. On repetitive questioning, patient gave history of some foreign body falling in left eye, one month ago. CT Scan was done and foreign body was confirmed lying in the superficial ocular coat in the superonasal quadrant (Figure 1b). On globe exploration (Figure 1c) an iron piece was found embedded deep in sclera. A 5mmx3 mm iron foreign body was removed (Figure 1d) and scleral suturing was done with 8-0 nylon. Post operatively patient was given topical steroids and antibiotics. Follow-up was uneventful.

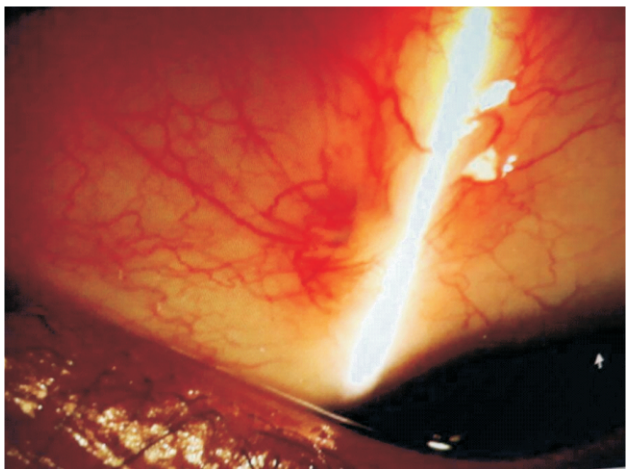

Figure 1a

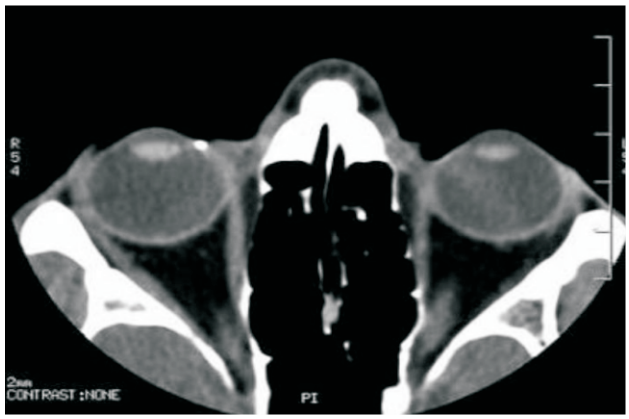

Figure 1b

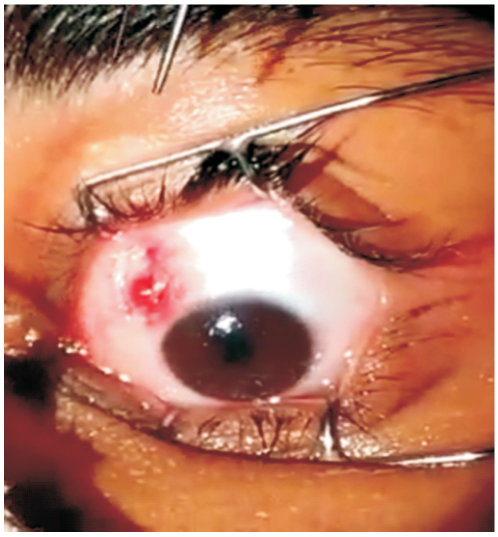

Figure 1c

Figure 1d

Case 2: A 13 year old male presented with localised swelling in the left eye associated with pain since one month. Visual Acuity

in both eyes was 20/20. Slit lamp examination showed a painless, paralimbal swelling temporally at 3'o clock. Anterior chamber was quiet and rest of the examination was within normal limits. Right eye examination was WNL. A provisional diagnosis of nodular episcleritis was made and the patient was started on low dose topical steroids. Complete blood count with ESR, chest x-ray and Mantoux test were done to rule out tubercular infection.No relief of symptoms was observed after 2 weeks. All the investigations were within normal limits. A suspicion of foreign body was made and ultrasound biomicroscopy (Figure 2a) was done which revealed a subconjunctival hypo echoic lesion with hyper echoic centre in outer scleral layers. CECT brain was ordered to rule out neurocysticercosis, but scans had no significant findings. On persistent questioning, to revise the diagnosis, patient gave history of trauma with wooden pencil one month ago. Globe exploration was done (Figure 2b, 2c). We removed a wooden foreign body 4mmx2mm in size, partially embedded in the scleral coats from the superotemporal quadrant (Figure 2d). Follow-up was uneventful.

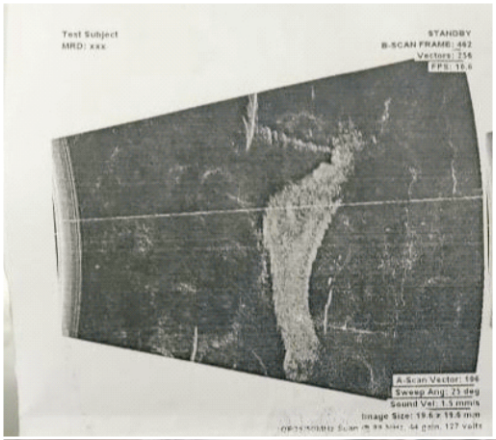

Figure 2a

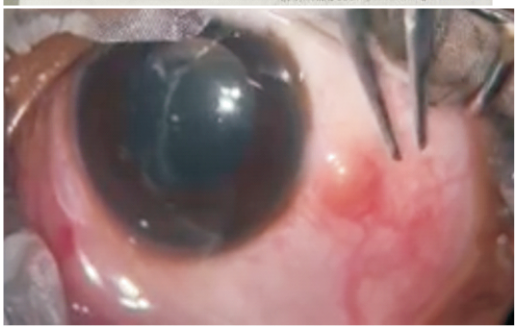

Figure 2b

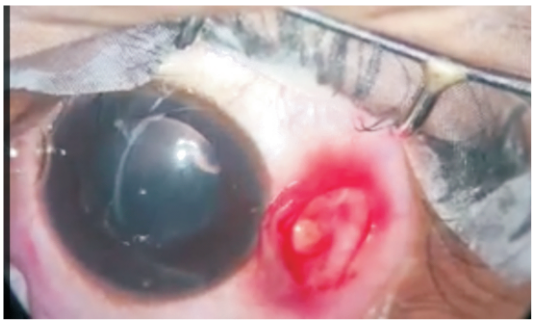

Figure 2c

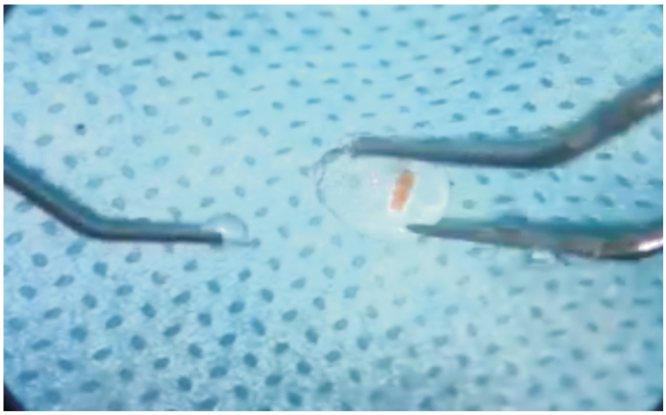

Figure 2d

Discussion:

Episcleritis is a benign, recurrent condition affecting females predominantly, presenting as diffuse or nodular form, with common complaints of redness, pain, foreign body sensation, lacrimation and with or without nodule formation. Visual acuity is usually maintained.[1,2] It is usually self limiting and mostly idiopathic in nature but can be an indicator of underlying systemic disease (autoimmune).Redness can be diffuse or localised depending on the type of episcleritis with a well circumscribed, elevated, mobile lesion in the cases of nodular episcleritis.[3,4] Differential diagnosis includes conjunctivitis, phlycten, foreign body granuloma, scleritis etc.

The reported cases highlight the importance of a thorough history taking and retrograde analysis of diagnosis and treatment, especially if the patient's response to the medication is unsatisfactory. A meticulous slit lamp examination can be helpful in directing a localized sign, in presentations with multiple differential diagnoses, towards a particular diagnosis. As in our cases, a partially embedded foreign body in the coats of the eye can easily mimic the presentation of nodular episcleritis. Hence, it is important to consider even if, in the initial history the patient negates any trauma. Episcleritis normally responds to the treatment in 2-21 days[5] but in cases where the response is poor, one should consider foreign body as a strong differential and proceed with other ancillary investigations to rule out this possibility.

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How to Become the Best Doctor & How to Build The Best Medical Practice?

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The Art is long, Life is Short. -Hippocrates

The current practice of medicine faces many opportunities and challenges going forward. There are many forms of clinical Practice today, including Solo Practice, Group Practice, Corporate Practice, Institutional Practice and newer forms of Practice Consolidations and Mergers. There are also newer challenges (clinical establishment act, generic drugs, possible price cap on devices, Goods and Services Tax, etc), which have an impact on the way we practice medicine, and it is in our best interests to stay ahead of the challenges posed by these policy changes. With decreasing reimbursements, increasing cost of equipments and a changing economy, it may become increasingly difficult to stay afloat and flourish.

In this write-up, we share valuable pearls for the young doctors to overcome these challenges—from personal enrichment to building a practice and dealing with increasing patient loads and the eventual difficult patient.

What are qualities of best doctor to build best medical practice?

A good doctor needs to be a people's person at heart. Someone who enjoys interacting with all sorts of people. He/ she needs to be truly skilled in art and science of medicine and surgery, as modern medical science has really evolved to a very high level of precision over the last few years, and therefore the patient expectations have also risen dramatically. However, in this competitive and demanding world, both the science and technique as well as the art are important. And therefore, while it is quite enough to be a good surgeon and give good results, to excel, one has to learn good communication skills, strive constantly to give the best surgical results, as well as the best overall experience to the patients.

How young doctor(s) can imbibe these qualities?

Young doctors first and foremost need to learn and fine tune their surgical skills as best as they can, and the earlier, the better. At a young age, without the additional responsibilities of family and children, it is possible to travel to different cities and countries, and get the best possible training. Good surgical training is the bedrock, that no one can do without in today's age. Along with this, young doctors should also make it a habit to observe their seniors interacting with patients, particularly difficult and demanding patients. If you have plans of having your own practice, then you need to know the basics of financial planning and administration. Observe the facilities that are provided in good practices, and the small things that can make a significant difference to the overall patient satisfaction.

How these qualities can help young doctor to start and run a new medical practice?

By default, even today most young doctors end up starting their own practice, though the practice patterns are now changing rapidly, with more emphasis on group practices, shared facilities etc. When one starts a new practice, often they realize that the residency training has not prepared them for this at all. When managing a new medical practice, the doctor needs to go beyond clinical medicine to truly satisfy and manage a patient, and beyond patient management to run an efficient, financially viable growing medical practice. Someone said that "The education of the doctor which goes on after he has his degree is the most important part of his education". At this stage, we need to keenly and quickly learn the basics of practice management, in terms of staffing, administration, providing the right ambiance, marketing, communication and patient handling skills etc. in short, while we need to hone our surgical skills during training, we must also focus on our soft skills if we want to run a successful practice.

How to manage high volume patient workload in medical practice?

If you are fortunate enough to have a high volume patient workload in your practice, it often becomes a challenge to give enough time to each patient and fully satisfy them. Here effective communication skills become very important, where you can give all the necessary and relevant information in a

short time, and utilize your chair time with the patient most efficiently. However, despite all this, there will be patients and attendants who need repetitive explanations and guidance, and here the role of well trained staff, and particularly counselors becomes very important. We must utilize the services of well trained and groomed staff and counselors who can take over the work of explanations and can give the patients more time, thereby reassuring them and satisfying all their queries. Depending on the workload and the practice setting, we can delegate many other tasks to the staff members. For example our high volume ophthalmic practice, optometrists do more than half the work, and trained ophthalmic technicians perform investigations etc. However, it is important to keep motivating the staff regularly to provide their best services to the patients.

How to handle unsatisfied patients?

This is becoming an increasingly difficult but necessary art to master. We must take part of the blame for raising the patient expectations so high, that they have become very difficult to satisfy. A lot of aggressive advertising, tall claims and high surgical costs have convinced the patients that surgery (in branch like ophthalmology-for example cataract and refractive surgery) is a ten minute wonder, where nothing can go wrong, and the patient will get "super-vision". In this scenario, the first thing is to have good counselling for all surgical patients. Adequate chair time needs to be given so that the patient expectations are realistic, and there is no mismatch between their expectations and what can be delivered. Despite these efforts, if a patient ends up dissatisfied with the results, the first thing is to give a patient hearing. Many irate patients often cool down enough with a felling of having been heard and understood. Never try to brush aside their complaint, even if they seem insignificant to you. Patients will seldom create much trouble if the doctor is respectful and sensitive and hears them out, but with become increasingly aggressive of they get the impression that the doctor makes them feel inferior or is too rushed to listen to them. Also, it goes without saying that we must do the best that we can to solve the cause of their dissatisfaction, and be financially considerate while doing so to minimize patients to take course of consumer court.

How to market yourself early on for successful medical practice?

Marketing and image building is an essential part of practices today, and is no longer considered a unhealthy word in medicine. However, marketing in medicine bears a greater responsibility to be ethical and appropriate. We owe it to the dignity of our profession to ensure that our marketing is not in poor taste. Marketing is not synonymous with advertising, and aggressive advertising is still controversial among medical circles. Subtle marketing on the other hand is less expensive, often more effective and also acceptable. But with the increasing presence of corporate sector in the medical profession, advertising is here to stay. Marketing in the medical field can initially be cold call type like newspaper advertisements, billboards etc., where we make unsolicited contact with a wide audience. For a new practitioner, this is necessary as he needs to inform the widest possible audience in his area of practice about his services and expertise. Later, one can progress to inbound marketing using the internet and social media for potential customers, giving them a platform to ask queries and know you and your services before they choose you and in-house advertising, where the services available in your practice are prominently displayed in your own premises with clear information and staff is willing and capable to answer any queries related to these services. For a young practitioner, it is important to control the finances in marketing, and after the initial few cold calls, turn to more focused marketing and do not try to "outdo" competitors in advertising. It is also a good idea to organize educational awareness activities and camps at sites of public gatherings, which is a cheap and effective way to market yourself. Finally, you must aim for a scenario, where your satisfied patients become your best marketing tools, because this word of mouth publicity is the strongest and most convincing to potential customers.

How young doctors can take leadership role- e.g. presenting their in conferences and as office bearers of medical societies?

To grow professionally among peers, one needs to have good oratorical as well as public relation (PR)/communication skills. Start by attending the meetings of the medial societies in your area and offer to organize one or two activities at special occasions, where you can display your organizational as well as presentation skills. Societies always need young, dynamic people willing to take on responsibilities, without displaying any ego. Remember not to get involved in factional politics, and be respectful to all seniors.

How to grow medical practice?

If you can provide good services, the work is bound to grow. You need to ensure that you deliver not only good surgical results, but also ensure an overall good experience for your patient. This would mean that you focus on all services provided in your practice right from the ease of paring near your practice to the reception, waiting time, comfort in the waiting hall, adequate facilities for drinking water, toilets, refreshments, if needed, reading material to keep them busy while waiting, professional reasonable

quick service, cheerful and cooperative staff and an adequate explanation of fall their queries and concerns. Of course, the satisfaction provided by the doctor would be the main driver, and you need to develop your own soft skills and communication skills so that the patients feel reassured on

meeting you, and you can inspire confidence in them. Learn to connect with your patients and empathize with their concerns. As you grow, try to provide more services (like cornea and retina etc. in ophthalmology) depending on the financial viability.

How to manage the team of doctors, managers and other staff members?

If you have other doctors and managers/staff members working for you, it is crucial and often difficult to keep them satisfied and motivated. One crucial factor is opportunities for financial and/ or professional growth. Also, be accessible to listen to genuine problems of your staff and give them a patient hearing. Just like your patients, the staff also wants to feel heard and understood. Do small activities (for example we celebrate birthday of every staff member at our practice), to foster the team spirit among all the members, and make them feel valued. At the same time, also let it be known that you observe everything, and any misdemeanors will be strictly acted upon.

Managing yourself- How to work efficiently managing a busy practice and how to achieve work life balance?

In a busy practice, efficiency is important to ensure that the patients are seen quickly, and your working time also doesn't overstretch. Learn to delegate all except the core work. Develop a good team and employ good quality staff that can take off some of your burden. Have enough staff to guide the patients and answer their queries and develop effective communication skills yourself, so that you can give a quick yet comprehensive explanation to the patient about his/ her condition. If your practice is managed efficiently, this will leave you time for your family. However, the most important factor for achieving a good work life balance is to firstly recognize its need and importance. Remember that your work is just one aspect of your life, which cannot replace the equally or often more important aspects like health and family. Ambition is an endless race, and therefore work to satisfy yourself and not get ahead of others.

Violence Against Doctors: What Doctors can Do to overcome this Frightening New Epidemic?

There is increasing trend of violence against the doctors in India and it has become a frightening new epidemic. Almost every week, there is an incidence of violence against doctor or hospital. In today's world, sadly doctors do not hold the same place of respect as they did 15-20 years back and there is a steadily declining mutual trust and erosion of the doctor patient relationship. As a responsible member of medical fraternity, it is our duty to strengthen doctor-patient relationship and follow measure to prevent or minimize violence against doctors. Small and medium healthcare establishments are vulnerable and there are increasing incidence of violence against doctors. All the members of medical fraternity need to remain alert about violence and aggression against doctors. It is advisable to look for indicators of violent behavior such as staring and eye contact, tone and volume of voice, anxiety, mumbling and pacing (STAMP).

Violence and aggression against doctors can be minimized by following P.S.M.

P: Prevent or restrict entry of public. At no stage hordes of relatives should be allowed at the patient's bedside. Entry should be strictly by passes and this must be implemented through good security, preferably by ex-army personnel. Security guards and good quality CCTV cameras must be placed outside as well as inside the hospital at sensitive areas like ICU, Operation theater and casualty.

S: Strengthen Doctor patient relationship by Communication: As mentioned earlier, much needs to be done to improve doctor-- patient relationship. This must begin by the doctor informing the relative of what is going on. Always inform about the cost of the treatment, prognosis, need of repeat surgery and regular follow up, etc.

M: Medical Unity and Media: Last but not the least, medical community need to be united to handle the crisis of violence against doctors, especially by forming an whats-App group (Rush to Stop Violence against Practicenor: RSVP). United medical fraternity can also build pressure on Govt. to bring and implement tough law to protect medical professionals. The Prevention of Violence Against Medicare Persons and Institutions Acts, which have been notified in 19 states in the past 10 years, have failed to address the issue. To prevent violence against doctors, government spending on healthcare must be increased and the Indian Penal Code should be changed to provide for a tougher penalty that could act as a deterrent to violence against doctors. Also doctors need to ensure to publish their version in media so the balanced view can be published.

Take Home message for Young Doctors –

Young doctors can select their career path carefully. If they decided to pursue private practice keeping in mind that running your own practice is a huge work and responsibility. Think well before you choose what exactly you want to do. If you feel you are not cut out to handle all the responsibility (including clinical, financial, administrative etc.), choose another option like working in hospital or a shared facility.

If you do choose to have your own practice, the initial few years are very crucial and remember to focus only on patient satisfaction at this time. Also, remember to be strong even if there are minor setbacks. Keep the big picture in mind, and do not fret over small things. In the end, remember that the ultimate aim of life is to be happy and professional success is just one means of achieving that along with many other things.

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